Official Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Demonstrate the Effects of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes, Cardiovascular Risk Factors and Moderately Impaired Renal Function

NCT Number: NCT03315143

Document Date: Protocol Version 1: 29-August-2018

AMENDED CLINICAL TRIAL PROTOCOL 01

COMPOUND: sotagliflozin/SAR439954

A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Demonstrate the Effects of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes, Cardiovascular Risk Factors and Moderately Impaired Renal Function

STUDY NUMBER: EFC14875

STUDY NAME: The SCORED Trial

Version Number:	1	EudraCT IND Number WHO universal trial number	2017-002644-32 [redacted] U1111-1187-8703
Date:	29-Aug-18	Total number of pages:	133

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 01	India only	29-Aug-18, version 1 (electronic 1.0)
Amended Clinical Trial Protocol 01 CA and US	Canada and United States of America only	12-Jan-18, version 1 (electronic 1.0)
Protocol Amendment 01 CA and CA	Canada and United States of America only	12-Jan-18, version 1 (electronic 1.0)
Original Protocol		07-Sep-17, version 2 (electronic 3.0)

Amended protocol 01 (29-Aug-18)

OVERALL RATIONALE FOR THE AMENDMENT

In order to meet the requirements of the health authority of India, the study protocol is being amended to exclude patients with HbA1c greater than 10% at Screening and to add rescue criteria for patients with uncontrolled hyperglycemia.

Please note that this protocol amendment is applicable to the following country only: India.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary (Study population), 7.2 Exclusion criteria, 10.1.1.1 On-site Visit 1	Update exclusion criteria with upper limit of HbA1c	To comply with an Indian health authority requirement
8.8.1 Antihyperglycemic concomitant medication	Add rescue criteria for patients with uncontrolled hyperglycemia	To comply with an Indian health authority requirement
Appendix F Country-specific requirements	Add an appendix documenting country-specific requirements	To comply with a process change at Sanofi
Appendix G Protocol amendment history	Add an appendix documenting protocol amendment history	To comply with a process change at Sanofi

CLINICAL TRIAL SUMMARY

COMPOUND: sotagliflozin/SAR439954	**STUDY No.:** EFC14875 **STUDY NAME: SCORED**
TITLE	A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Demonstrate the Effects of **S**otagliflozin on **C**ardi**o**vascular and **R**enal **E**vents in Patients with Type 2 **D**iabetes, Cardiovascular Risk Factors and Moderately Impaired Renal Function. The **SCORED** trial.
INVESTIGATOR/TRIAL LOCATION	Multinational, multicenter
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVES	**Primary objectives:** The 2 primary objectives of this study are to demonstrate that, when compared to placebo in patients with type 2 diabetes (T2D), cardiovascular (CV) risk factors, and moderately impaired renal function, sotagliflozin: • Is non-inferior to placebo on the composite endpoint of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke (3-point major adverse CV events [MACE]) • Reduces the composite endpoint of CV death or hospitalization for heart failure (HHF) **Secondary objectives:** • The secondary objectives of this study are to demonstrate that, when compared to placebo in patients with T2D, CV risk factors, and moderately impaired renal function, sotagliflozin: - Reduces the composite endpoint of CV death, non-fatal MI or non-fatal stroke (3-point MACE) - In patients with Baseline estimated glomerular filtration (eGFR) ≥30 mL/min/1.73 m^2, reduces the composite renal endpoint of sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days) - In patients with Baseline eGFR ≥30 mL/min/1.73 m^2 and Baseline urinary albumin-to-creatinine-ratio [UACR] ≥300 mg/g (34 mg/mmol), reduces the composite renal endpoint of sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days) - Reduces the composite endpoint of CV death, HHF, or urgent heart failure (HF) visit (defined in Appendix E), - Reduces CV death - Reduces all-cause mortality • To assess the safety and tolerability of sotagliflozin in patients with T2D, CV risk factors, and moderately impaired renal function

	Other: • To demonstrate that, when compared to placebo in patients with T2D, CV risk factors, and moderately impaired renal function, sotagliflozin: - In patients with Baseline eGFR ≥30 mL/min/1.73 m^2, reduces the composite endpoint of sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days), or CV or renal death - Reduces the composite endpoint of CV death, non-fatal MI, non-fatal stroke, or unstable angina requiring hospitalization (4-point MACE) - In patients with Baseline eGFR ≥30 mL/min/1.73 m^2, reduces the composite renal endpoint of worsening nephropathy, defined as: new onset or progression to macro albuminuria (≥300 mg/g [34 mg/mmol]) accompanied by a UACR value increase of ≥30% from Baseline, sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, need for renal transplant, eGFR <15 mL/min/1.73 m^2 (for ≥30 days), or renal death • To compare sotagliflozin versus placebo with respect to change from Baseline to 6 months, 12 months, and 24 months in the following endpoints: - Hemoglobin A1c (HbA1c) - Body weight - Blood pressure (BP) - Urinary albumin-to-creatinine ratio - Estimated glomerular filtration rate - Hematocrit - Hemoglobin - Albumin - Total protein • To compare sotagliflozin versus placebo with respect to change from Baseline to 6 months and 12 months in the following endpoints: - N-terminal pro-B-type natriuretic peptide (NT-proBNP) - High-sensitivity troponin T (hsTnT) - High-sensitivity C-reactive protein (hsCRP) • To compare sotagliflozin versus placebo with respect to change from Baseline in the following endpoints: - Proportion of patients not taking insulin at baseline who start insulin during the study
STUDY DESIGN	This study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in approximately 10,500 patients with T2D, CV risk factors, and moderately impaired renal function. The study will consist of 3 periods: a Screening period of 1 to 4 weeks, a randomized, Double-blind Treatment period, and a Post-treatment period. The dose of sotagliflozin or matched placebo should be increased from 200 mg to 400 mg in the first 6 months of the randomized Double-blind Treatment period, if tolerated. Patients who meet all eligibility criteria at Screening (Visit 1) will come back for the Randomization Visit (Visit 2) between 7 and 28 days later and, if they are still eligible for the study, they will be randomized 1:1 to sotagliflozin or placebo. Patients will start sotagliflozin 200 mg or matching placebo at Visit 2 after Randomization. Randomization will be stratified by region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) and by HF-related criteria (Yes/No).

	HF-related criteria is 'Yes' when a patient meets at least 1 of the following major CV risk factors: 1. Ejection fraction (EF) ≤40% documented within the past year 2. Hospitalization for HF during the previous 2 years At Week 4 (Visit 3), clinical safety and tolerability will be assessed (including vital signs and collection of adverse events [AEs], including events of special interest [EOSIs], adverse events of special interest [AESIs] and serious adverse events [SAEs]). If in the opinion of the Investigator the patient's clinical condition is satisfactory and the patient has tolerated the investigational medicinal product (IMP) well without evidence of dehydration, symptomatic hypotension (eg, dizziness, lightheadedness), or other AEs intolerable to the patient such as severe polyuria or nocturia, the dose will be increased to 400 mg of sotagliflozin or matching placebo. If the dose is not up-titrated for safety reasons, all attempts will be made to up-titrate the dose at 1 of the next 2 subsequent visits: Visit 4 (Week 8) or, if not Visit 4, then Visit 5 (Week 26). The 400 mg dose (or 200 mg in those who cannot tolerate up-titration by Visit 5) will be maintained for the duration of the remaining double-blind study treatment period. If, at any time during the study, a patient does not tolerate 400 mg, the dose of sotagliflozin or matching placebo may be down titrated to 200 mg once daily (qd) or temporarily discontinued, or if medically necessary, permanently discontinued. All IMP discontinuation should initially be considered as temporary unless permanent discontinuation is mandated by the protocol. The study is event driven. Therefore, it will continue until approximately 844 events of CV death or HHF and approximately 1189 3-point MACE are positively adjudicated. All randomized patients will be asked to return to the study site for a Study Closeout Visit once the date the required number of events are projected to be positively adjudicated has been determined. The timing and window of this visit will be communicated to sites. All randomized patients will be followed from Randomization until their Follow-up Visit (or Study Closeout Visit, for patients who prematurely permanently discontinued from IMP) or death, whichever comes first. Patients will continue taking IMP after a CV or renal endpoint occurs unless they have prematurely permanently discontinued treatment or the criteria for permanent treatment discontinuation have otherwise been met. Patients with a suspected renal event (reduction of eGFR) should be brought in for an unscheduled visit and have a repeat assessment of renal function 30 to 45 days following the onset of the event to confirm it is sustained. If acute renal failure is suspected, further clinical evaluation should be performed as per local standard of care, including confirmation of renal laboratory parameters, and consideration should be given to a nephrology referral. A dual-energy X-ray absorptiometry (DXA) sub-study will be performed at participating sites in a subset of approximately 190 patients and will compare sotagliflozin and placebo for changes from Baseline to end of treatment in bone mineral density (BMD) and markers of bone and calcium metabolism. **Premature Treatment Discontinuation** All IMP discontinuation should initially be considered as temporary unless permanent discontinuation is mandated by the protocol. If a patient prematurely permanently discontinues treatment with IMP, the patient will be asked to undergo a premature End-of-Treatment (pEOT) Visit as soon as possible. Subsequently, every effort will be made to have the patient return to the site/be reached by phone at the time corresponding to their scheduled visits, until the end of the study. Patients will continue to be followed after a CV or renal endpoint occurs.

	If a patient refuses to continue in the study after premature IMP discontinuation, and the pEOT Visit is <10 days after the last IMP administration, then **every effort** should be made to secure a follow-up contact is performed at least 14 days (±4 days) after the last IMP intake with procedures normally performed at the Follow-up Visit. If the patient does not agree to on-site visits, he/she will be contacted by telephone to inquire about safety status (including hospitalizations and endpoints). Every effort should be made to collect endpoint information and vital status at least once a year and at the time of Study Closeout. **End of study** All randomized patients will be asked to return to the study site for a Study Closeout Visit when approximately 844 primary CV events of CV death or HHF and approximately 1189 3-point MACE are positively adjudicated. The timing and window of this visit will be communicated to sites. For patients who previously prematurely permanently discontinued IMP, the Study Closeout Visit will be the final study visit and no further visits are planned. Patients still taking the IMP at the time of the Study Closeout Visit (ie, who have not prematurely permanently discontinued IMP) will have their final study visit (Follow-up Visit) 14 days (±4 days) after their Study Closeout Visit. Patients who have withdrawn from the study cannot be rerandomized in the study.
STUDY POPULATION **Main selection criteria:**	**Inclusion criteria:** **Mandatory Inclusion Criteria (all 4 criteria are necessary)** I 01. Signed written informed consent I 02. Type 2 diabetes with HbA1c ≥7% (53 mmol/mol) at Screening (central laboratory) I 03. Estimated glomerular filtration rate ≥25 and ≤60 mL/min/1.73 m^2 by the 4 variable Modification of Diet in Renal Disease (MDRD) equation (at Screening, based on central laboratory) I 04. Patients either: - Age ≥18 years with at least 1 (one) of the major CV risk factors listed below **OR** - In the absence of a major CV risk factor, age ≥55 years with at least 2 (two) of the minor CV risk factors listed below In order to be considered eligible to participate in the study, patients must meet all 4 (four) of the mandatory criteria. Patients can be eligible if they have both major and minor CV risk factors, as long as 1 of the 2 conditions in Inclusion Criterion Number 4 is met. Major and minor CV risk factors are listed below. **Major CV risk factors (at least 1 criterion to fulfill Inclusion Criterion Number 4)** A) Hospitalization for HF during previous 2 years B) Ejection fraction (EF) ≤40% *Documented within the past year by previous imaging modality (such as echocardiogram, MUltiple Gated Acquisition (MUGA) scan, Magnetic Resonance Imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), left ventricular (LV) angiography)* ***Note:** An echocardiogram to assess EF at the time of Screening MUST be performed in all patients if an assessment of EF has not been documented within 1 year prior to Screening* C) Diagnosis of left ventricular hypertrophy *By either electrocardiogram (ECG) or echocardiogram*

	D) Coronary artery calcium (CAC) score ≥300 Agatston Units *Documented by coronary artery CT scan* ***Note:** a coronary artery CT scan **MAY** be performed to measure the CAC score if required for eligibility **if not previously documented*** E) N-terminal pro-B-type natriuretic peptide ≥400 pg/mL (47 pmol/L) *At Screening, based on central laboratory* F) High-sensitivity troponin T >15.0 pg/mL (0.015 µg/L) for men and >10.0 pg/mL (0.010 µg/L) for women *During Screening period, based on central laboratory* G) High-sensitivity C-reactive protein >3 mg/L (28.6 nmol/L) *At Screening, based on central laboratory, if the Investigator does not consider the elevation to be due to an acute inflammatory condition (eg, acute infection)* H) Urinary albumin-to-creatinine ratio ≥300 mg/g (34 mg/mmol) *At Screening, based on central laboratory* **Minor CV risk factors (if no major CV risk factors, at least 2 criteria to fulfill Inclusion Criterion Number 4)** I) Body mass index ≥35 kg/m^2 at Screening J) Dyslipidemia despite maximally-tolerated statin therapy: - Low-density lipoprotein cholesterol >130 mg/dL (>3.36 mmol/L) Or - High-density lipoprotein cholesterol <40 mg/dL (<1.03 mmol/L) for men or <50 mg/dL (<1.29 mmol/L) for women *Based on the last measured and documented laboratory measurement in the previous 6 months* K) Currently smoking tobacco *Consumes an average of at least 1 cigarette, pipe, or cigar per day, at Screening* L) Coronary artery calcium score >100 and <300 Agatston Units *Documented by coronary artery CT scan* ***Note:** a coronary artery CT scan **MAY** be performed to measure the CAC score if required for eligibility **if not previously documented*** M) Urinary albumin-to-creatinine ratio ≥30 mg/g and <300 mg/g (3 and 34 mg/mmol) *During Screening period, based on central laboratory* N) Systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg despite antihypertensive therapy at the Screening Visit O) Family history of premature coronary heart disease (defined as MI or coronary revascularization procedure) in a first degree relative *In a male relative <55 years or in a female relative <65 years* **Exclusion criteria:** E 01. History of diabetic ketoacidosis or nonketotic hyperosmolar coma within 3 months prior to the Screening Visit or between Screening and Randomization E 02. Antihyperglycemic treatment (if applicable) has not been stable in the 12 weeks prior to Screening or between Screening and Randomization, in the opinion of the Investigator

	E 03.	Patients who are planning to start a sodium-glucose linked transporter-2 (SGLT2) inhibitor (other than study drug) during the study. This includes patients who, **in the opinion of the Investigator**, based on their comorbid profile, are likely to receive an SGLT2 inhibitor (other than study drug) during the study
	E 04.	Any SGLT2 inhibitor <1 month prior to the Screening Visit, or between Screening and Randomization
	E 05.	Lower extremity complications (such as skin ulcers, infection, osteomyelitis, and gangrene) identified during the Screening period, and still requiring treatment at Randomization
	E 06.	Any allergic reaction to any SGLT2 inhibitor or sotagliflozin
	E 07.	Blood pressure ≥180 mmHg (systolic) or ≥110 mmHg (diastolic) at both the Screening and Randomization Visits
	E 08.	Hospitalization for hypertensive emergency within 3 months prior to Randomization
	E 09.	End-stage HF: requiring LV assist device, intra-aortic balloon pump (IABP), or any type of mechanical support at the time of Screening
	E 10.	Planned coronary revascularization procedures, electrophysiologic device implantation, cardiac mechanical support implantation, or other cardiac surgery after Randomization
	E 11.	History of dialysis within 1 year prior to Randomization
	E 12.	History of solid organ transplant
	E 13.	Serum creatinine altering drugs ≤30 days before Screening, or between Screening and Randomization (trimethoprim, cimetidine, cephalosporins, probenecid, aminoglycosides, ketoconazole). *Please note that diuretics are allowed within 30 days of Screening*
	E 14.	Clofibrate, fenofibrate, dronedarone, or ranolazine treatment that has not been at a stable dose in the 30 days prior to Screening or between Screening and Randomization or a dose adjustment is expected during the study based on the judgement of the Investigator
	E 15.	Use of systemic glucocorticoids (excluding topical application or inhaled forms) for more than 10 consecutive days within 3 months prior to Screening Visit or for more than 10 consecutive days between Screening and randomization
	E 16.	Digoxin plasma level >1.2 ng/mL (in a patient treated with digoxin at Screening, based on local laboratory*)
	E 17.	Use of any investigational drug(s) within 5 half-lives prior to the Screening Visit or between Screening and Randomization
	E 18.	Severe disease or short life expectancy making implementation of the protocol or interpretation of the study results difficult (CV disease [including congestive HF New York Heart Association IV], respiratory, hepatic, neurological [including stroke in 3 months prior to Screening], psychiatric, or active malignant tumor (except for non-melanoma skin cancers, which are not exclusionary) or other major systemic disease [including any diseases with evidence of malabsorption or severe anemia])
	E 19.	Presence of any other conditions (eg, geographic, social) actual or anticipated, that the Investigator feels would restrict or limit the patient's participation for the duration of the study
	E 20.	Patient is the Investigator or any Sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol

	E 21. Any country-related specific regulation that would prevent the patient from entering the study (eg, individuals committed to an institution by virtue of an order issued either by the judicial or the administrative authorities) E 22. Pregnant (demonstrated by serum pregnancy test at Screening) or breastfeeding women E 23. Women of childbearing potential not willing to use a highly-effective method(s) of birth control during the study treatment period and the follow-up period, or who are unwilling or unable to be tested for pregnancy (see contraceptive guidance in Appendix A), during the study E 24. Laboratory findings at the Screening Visit: - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of the normal laboratory range (ULN) (1 repeat is allowed)* - Total bilirubin >1.5 times the ULN (except in case of Gilbert's syndrome) - Specific to India: HbA1c >10% (86 mmol/mol) (central laboratory); see Appendix F One time rescreening is allowed at the Investigator's medical judgment for any manageable reasons that caused the Screening failure and if the patient is likely to be eligible before the enrollment completion. *If a patient meets exclusion criteria E 16 or E 24, a one-time repeat testing is allowed for digoxin level, ALT, or AST without the need to rescreen the patient. Further eligibility criteria for inclusion in the DXA sub-study are detailed in Appendix B.
Total expected number of patients:	10,500
Expected number of sites:	Approximately 900 sites
STUDY TREATMENTS	
Investigational medicinal products	Sotagliflozin and placebo
Formulation:	Oral tablet
Route of administration:	by mouth
Dose regimen:	**Sotagliflozin:** **From Visit 2 to Visit 3**: Sotagliflozin 200 mg administered as 1 (one) 200-mg tablet qd before the first meal of the day **From Visit 3, as tolerated**: Sotagliflozin 400 mg administered as 2 (two) 200-mg tablets qd before the first meal of the day **Placebo:** **From Visit 2 to Visit 3**: Placebo administered as 1 (one) placebo tablet (identical to sotagliflozin 200-mg tablets in appearance) qd before the first meal of the day **From Visit 3, as tolerated**: Placebo administered as 2 (two) placebo tablets (identical to sotagliflozin 200-mg tablets in appearance) qd before the first meal of the day
Noninvestigational medicinal products	There are no noninvestigational medicinal products in this study.

ENDPOINTS	**Primary efficacy endpoints:** • Time to the first occurrence of any of the following clinical events: - Cardiovascular death - Non-fatal MI - Non-fatal stroke • Time to the first occurrence of any of the following clinical events: - Cardiovascular death - Hospitalization for heart failure **Secondary efficacy endpoints:** • Time to the first occurrence of any of the following clinical events in patients with Baseline eGFR ≥30 mL/min/1.73 m^2: - Sustained ≥50% decrease in eGFR from Baseline (for ≥30 days) - Chronic dialysis - Renal transplant - Sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days) • Time to the first occurrence of any of the following clinical events in patients with Baseline eGFR ≥30 mL/min/1.73 m^2 and Baseline UACR ≥300 mg/g (34 mg/mmol): - Sustained ≥50% decrease in eGFR from Baseline (for ≥30 days) - Chronic dialysis - Renal transplant - Sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days) • Total number (ie, including recurrent events) of the following clinical events: - Cardiovascular death - Hospitalization for heart failure - Urgent HF visit (defined in Appendix E) • Time to CV death • Time to all-cause mortality **Other efficacy endpoints:** • Time to the first occurrence of any of the following clinical events in patients with Baseline eGFR ≥30 mL/min/1.73 m^2: - Sustained ≥50% decrease in eGFR from Baseline (for ≥30 days) - Chronic dialysis - Renal transplant - Sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days) - Cardiovascular death - Renal death • Time to first occurrence of any CV death, non-fatal MI, non-fatal stroke, or unstable angina requiring hospitalization • Time to worsening nephropathy in patients with Baseline eGFR ≥30 mL/min/1.73 m^2, defined as: new onset or progression to macro albuminuria (≥300 mg/g [34 mg/mmol]) accompanied by a UACR value increase of ≥30% from Baseline, or sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), or need for renal transplant, chronic dialysis, eGFR <15 mL/min/1.73 m^2 (for ≥30 days), or renal death

	• Changes from Baseline to 6 months, 12 months, and 24 months in: - Hemoglobin A1c - Body weight - Blood pressure - Urinary albumin-to-creatinine ratio - Estimated glomerular filtration rate - Hematocrit - Hemoglobin - Albumin - Total protein • Changes from Baseline to 6 months and 12 months in: - N-terminal pro-B-type natriuretic peptide - High sensitivity troponin T - High sensitivity C-reactive protein • Proportion of patients who start insulin (who are not taking insulin at baseline) **Safety endpoints:** • All AEs, including AESIs, EOSIs, and SAEs • Severe hypoglycemia (also an EOSI) • Clinical laboratory results and vital signs (including heart rate, BP) • For patients in the DXA sub-study, change from Baseline in: - Bone mineral density - The following markers of bone and calcium metabolism: serum and urinary calcium; serum 25-hydroxyvitamin D; serum 1,25 dihydroxyvitamin D; serum and urinary phosphorus; serum parathyroid hormone (PTH); serum N telopeptide of type 1 collagen (NTX); serum β-C-terminal telopeptide of type 1 collagen (β CTX 1); serum N-terminal propeptide of type 1 procollagen (P1NP); serum magnesium
ASSESSMENT SCHEDULE	See Section 1.1 and Section 1.2
STATISTICAL CONSIDERATIONS	**Sample size determination:** The study is powered based on the endpoints of time to CV death or first HHF and time to 3-point MACE, based on the following trial design assumptions: • A recruitment period of approximately 24 months with approximately 3.6%, 20.0%, 36.5%, and 39.9% of patients recruited during each of the 4 (four) 6-month periods; • Approximately 27 months of follow-up after the last patient is randomized, with treatment duration ranging from 27 to 51 months • 2% annual censoring rate It is estimated that approximately 10,500 patients are needed to obtain approximately 844 positively-adjudicated CV deaths and HHF assuming a 3.5% annual event rate in the placebo group and a risk reduction of 20% (Hazard Ratio=0.8) and 1189 3-point MACEs assuming a 4.5% yearly event rate in the placebo group and a risk reduction of 15% (hazard ratio=0.85) comparing sotagliflozin versus placebo. This will provide: • 99% power to demonstrate non-inferiority on 3-point MACE • 90% power to demonstrate the superiority in CV death/HHF • 80% power to demonstrate the superiority in 3-point MACE

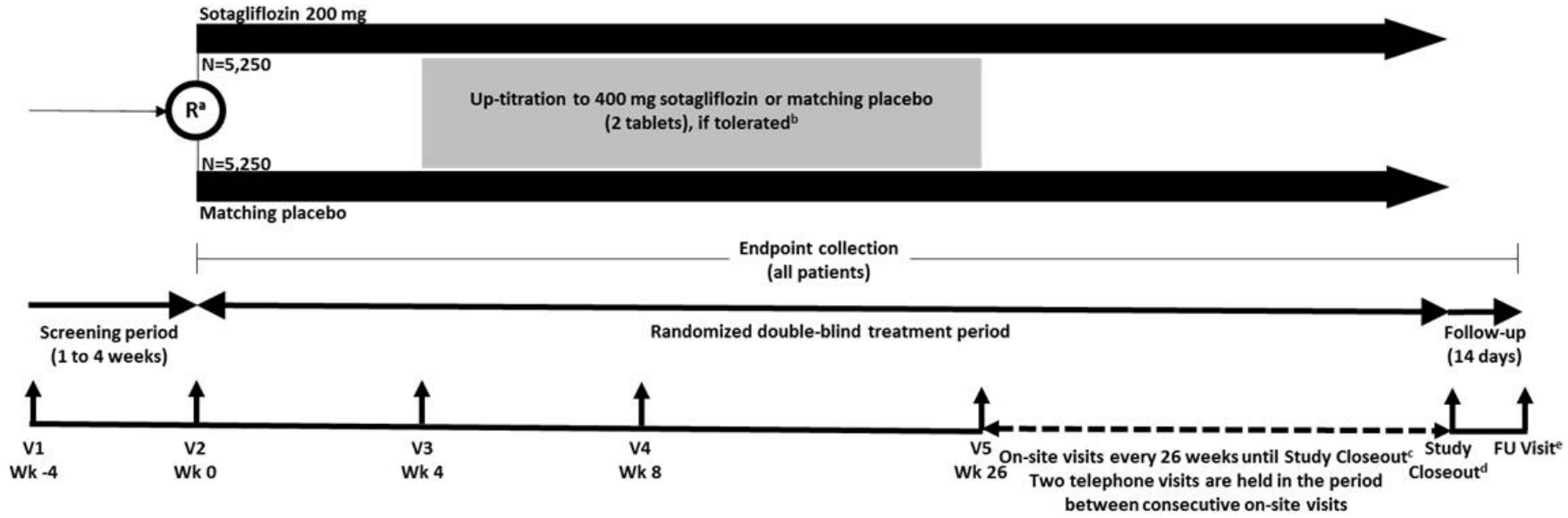
	The study is event driven. Therefore, it will continue until approximately 844 positively-adjudicated CV death or HHF events will have occurred (ie, number of patients with CV death or at least 1 HHF) and approximately 1189 3-point MACEs (ie, number of patients with at least one 3-point MACE) have occurred. **Analysis population:** The primary analysis population will be the intent-to-treat (ITT) population that includes all randomized patients irrespective of compliance with the study protocol and procedures. The safety analysis will be conducted on the safety population that includes all randomized patients who have received at least 1 dose of double-blind treatment. **Analysis of the primary endpoints:** 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 Cox proportional hazards model with treatment (sotagliflozin, placebo), region, and HF-related criteria (Yes/No) as the factors. The hazard ratio between sotagliflozin and placebo will be estimated along with the associated 2-sided 95% confidence interval (CI). Non-inferiority will be claimed if the upper bound (UB) of the 2-sided 95% CI is less than 1.3 (as specified in the *2008 Food and Drug Administration [FDA] Guidance for Industry: Diabetes Mellitus- Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*). Kaplan-Meier curves of the cumulative incidence rate will be provided by treatment groups. The time to the first event of CV death or HHF will be analyzed using the same Cox proportional hazards model described above with treatment (sotagliflozin, placebo), region, and HF-related criteria (Yes/No) as the factors. The hazard ratio between sotagliflozin and placebo will be estimated along with the associated 2-sided 95% CI. The stratified log-rank test will be used to compare the time-to-first-event curves. Kaplan-Meier curves of the cumulative incidence rate will also be provided by treatment groups. All randomized patients will be followed from Randomization until their Follow-up Visit (or Study Closeout Visit, for patients who prematurely permanently discontinued from IMP) or death, whichever comes first. The primary analysis will be based on the ITT approach that includes events occurring from Randomization to the Follow-up Visit (or Study Closeout Visit, if no Follow-up Visit is available), even after the patient has discontinued the study treatment. In the ITT approach, all randomized patients will be included and analyzed as randomized. **Analysis of the secondary endpoints:** Secondary endpoints will be analyzed using the same Cox proportional hazards model described above with treatment (sotagliflozin, placebo), region and HF-related criteria (Yes/No) as the factors. The hazard ratio between sotagliflozin and placebo will be estimated along with the associated 2-sided 95% CI. The stratified log-rank test will be used to compare the time-to-first-event curves. Kaplan-Meier curves of the cumulative incidence rate will also be provided by treatment groups. The total number (ie, including recurrent events) of events of CV death, HHF or urgent HF visit will be analyzed using extended Cox proportional hazards model for recurrent events with treatment (sotagliflozin, placebo), region and HF-related criteria (Yes/No) as factors.

	Multiplicity adjustment To control the family-wise Type-1 error rate at 0.05 (1-sided alpha=0.025), a fixed-sequence testing procedure will be applied to the primary endpoints. The hierarchy will be: 1. Non-inferiority of sotagliflozin versus placebo on 3-point MACE 2. Superiority of sotagliflozin versus placebo on time to first event of CV death or HHF If the hypotheses above are met, the family-wise Type-1 error rate at 0.05 (1-sided alpha=0.025) will be controlled by the Hochberg procedure for the first 2 secondary endpoints listed below: • Superiority of sotagliflozin versus placebo on 3-point MACE • Superiority of sotagliflozin versus placebo in patients with Baseline eGFR ≥30 mL/min/1.73 m^2 on a composite renal endpoint of sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days) If the hypotheses above are statistically significant, a fixed-sequence testing procedure will be applied to the other secondary endpoints listed below. The hierarchy will be: 1. Superiority of sotagliflozin versus placebo in patients with Baseline eGFR ≥30 mL/min/1.73 m^2 and Baseline UACR ≥300 mg/g (34 mg/mmol) on a composite renal endpoint of sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days) 3. Superiority of sotagliflozin versus placebo on the composite endpoint of CV death, HHF, or urgent HF visit (defined in Appendix E) 4. Superiority of sotagliflozin versus placebo on CV death 5. Superiority of sotagliflozin versus placebo on all-cause mortality **Interim Analysis** If a CV meta-analysis of the other sotagliflozin Phase 3 studies does not meet the 1.8 boundary (as specified in the *2008 FDA Guidance for Industry: Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*), an interim analysis will be conducted in this trial. Details will be described in a dedicated CV safety Statistical Analysis Plan. **Analysis of other endpoints** The analysis of other time to event endpoints will be analyzed using the same Cox proportional hazards model as for the primary endpoints, with treatment (sotagliflozin, placebo), region and HF-related criteria (Yes/No) as the factors. Analysis of other endpoints will be descriptive with no formal testing. Summary statistics at scheduled visits using observed cases will be provided by each treatment group. Graphical presentations will also be used to illustrate trends over time. **Analyses of Safety Data** All safety summaries will be descriptive; no statistical significance tests will be performed on safety data. These analyses will be based on the Safety Population, which is defined as all randomized patients who receive at least 1 dose of double-blind treatment, regardless of the amount of treatment administered. Patients will be analyzed for safety analyses according to the treatment actually received.

DURATION OF STUDY PERIOD (per patient)	All patients will have a Screening period of 1 to 4 weeks. The study is event driven, therefore the duration of the randomized, Double-blind Treatment period for each patient (unless they discontinue IMP prematurely) will be determined when approximately 844 positively-adjudicated primary events of CV death or HHF and approximately 1189 positively-adjudicated 3-point MACEs have occurred. The estimated study treatment duration for a given patient will be approximately 27 to 51 months, assuming approximately 24 months of recruitment, and approximately 27 months of follow-up after the last patient is randomized. Patients still taking the IMP at the time of the Study Closeout Visit (ie, who have not prematurely permanently discontinued IMP) will have their final study visit (Follow-up Visit) 14 days (±4 days) later.
STUDY COMMITTEES	**Executive Committee:** ☒ Yes ☐ No **Steering Committee:** ☒ Yes ☐ No **Data Monitoring Committee:** ☒ Yes ☐ No **Adjudication Committee:** ☒ Yes ☐ No

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



a: The Randomization Day is always Day 1. The Randomization is stratified by region and heart failure-related criteria (see Section 6.1.2).

b: At Visit 3 (Week 4), the dose of IMP will be increased to 400 mg or matching placebo (2 tablets) unless, in the opinion of the Investigator, up-titration is not appropriate for safety reasons. If up-titration does not occur at Visit 3 for safety reasons, all attempts will be made to up-titrate at Visit 4 (Week 8) or Visit 5 (Week 26). The 400 mg dose (or 200 mg in those who cannot tolerate up-titration by Visit 5) or corresponding matching placebo will be maintained for the duration of the remaining Double-blind Treatment period.

c: The study is event driven. Therefore, the study will continue until approximately 844 positively-adjudicated primary CV events of CV death or HHF and approximately 1189 positively-adjudicated 3-point MACEs have occurred.

d: **All** randomized patients will be asked to return to the study site for a Study Closeout Visit when approximately 844 primary CV events of CV death or HHF and approximately 1189 3-point MACE are positively adjudicated. Patients who prematurely permanently discontinue IMP will also attend a pEOT Visit as soon as possible after the last dose of IMP and will then continue study visits as per the original study schedule. Patients will continue to be followed after a CV or renal endpoint occurs irrespective of whether they are receiving IMP. If the patient does not agree to site visits, he/she will be contacted by telephone to inquire about safety status (including hospitalizations and endpoints).

e: A FU Visit will take place 14 days (±4 days) after the Study Closeout Visit for patients who do not prematurely permanently discontinue IMP.

CV cardiovascular; FU follow-up; HHF hospitalization for heart failure; IMP investigational medicinal product; MACE major adverse cardiovascular event; pEOT Premature End-Of-Treatment; R Randomization V visit; Wk week.

1.2 STUDY FLOW CHART

	Screening	Randomized Double-blind Treatment period										Patients who prematurely permanently discontinue IMP		Patients who do not prematurely permanently discontinue IMP	
Visit	1	2	3	4	5	6/7[a]	8	9/10[a]	11/17/23	12/13/15/16/18/19/21/22/24/25/27/28[a]	14/20/26				
Month		0	1	2	6	8/10	12	14/16	18/30/42	20/22/26/28/32/34/38/40/44/46/50/52	24/36/48	pEOT[b]	Study Closeout Visit[c]	Study Closeout Visit[c]	FU Visit[d]
Week	-1 to -4	0	4	8	26	35/44 ☎	52	61/70 ☎	78/130/182	87/96/113/122/139/148/165/174/191/200/217/226 ☎	104/156/208				
Day (Window [days])	-7 to -28	1	28 (±3)	56 (±7)	182 (±10)	245/308 (±10)	364 (±10)	427/490 (±10)	546/910/1274 (±10)	609/672/791/854/973/1036/1155/1218/1337/1400/1519/1582 (±10)	728/1092/1456 (±10)	*b*	*c*	*c*	Study Closeout +14 (±4)
Informed consent	X														
Inclusion/exclusion criteria	X	X													
Demographics	X														
Patient contact information to be collected/updated	X	X	X	X	X	X	X	X	X	X	X	X		X	
Medical/surgical history	X														
Medication history	X														
Body weight, height[e]	X	X	X	X	X		X		X		X	X	X	X	X
Vital signs[f]	X	X	X	X	X		X		X		X	X	X	X	X
Physical Exam	X						X				X	X	X	X	
IRT contact	X	X			X		X		X		X	X	X	X	X
Randomization		X													
Dispense IMP		X			X		X		X		X				

	Screening	Randomized Double-blind Treatment period										Patients who prematurely permanently discontinue IMP		Patients who do not prematurely permanently discontinue IMP	
Visit	1	2	3	4	5	6/7[a]	8	9/10[a]	11/17/23	12/13/15/16/18/19/21/22/24/25/27/28[a]	14/20/26				
Month		0	1	2	6	8/10	12	14/16	18/30/42	20/22/26/28/32/34/38/40/44/46/50/52	24/36/48	pEOT[b]	Study Closeout Visit[c]	Study Closeout Visit[c]	FU Visit[d]
Week	-1 to -4	0	4	8	26	35/44 ☎	52	61/70 ☎	78/130/182	87/96/113/122/139/148/165/174/191/200/217/226 ☎	104/156/208				
Day (Window [days])	-7 to -28	1	28 (±3)	56 (±7)	182 (±10)	245/308 (±10)	364 (±10)	427/490 (±10)	546/910/1274 (±10)	609/672/791/854/973/1036/1155/1218/1337/1400/1519/1582 (±10)	728/1092/1456 (±10)	*b*	*c*	*c*	Study Closeout +14 (±4)
IMP accountability and compliance			X	X	X	X	X	X	X	X	X	X		X	
Concomitant medication[g]	X	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG		X[h]										X	X	X	
LABORATORY TESTING[i]															
HbA1c and hematology	X				X		X		X		X	X	X	X	X[j]
Chemistry, eGFR	X	X	X	X	X		X		X		X	X	X	X	X[j]
Lipids		X					X				X	X		X	
Pregnancy (WOCBP)[k]	X	X	X	X	X		X		X		X	X	X	X	
Urinalysis and UACR[l]	X	X	X	X	X		X		X		X	X	X	X	
24-hour urine albumin and creatinine[l]	X														
NT-proBNP, hsTnT, and hsCRP[m]	X				X		X[m]					X[m]			

	Screening	Randomized Double-blind Treatment period										Patients who prematurely permanently discontinue IMP		Patients who do not prematurely permanently discontinue IMP	
Visit	1	2	3	4	5	6/7[a]	8	9/10[a]	11/17/23	12/13/15/16/18/19/21/22/24/25/27/28[a]	14/20/26				
Month		0	1	2	6	8/10	12	14/16	18/30/42	20/22/26/28/32/34/38/40/44/46/50/52	24/36/48	pEOT[b]	Study Closeout Visit[c]	Study Closeout Visit[c]	FU Visit[d]
Week	-1 to -4	0	4	8	26	35/44 ☎	52	61/70 ☎	78/130/182	87/96/113/122/139/148/165/174/191/200/217/226 ☎	104/156/208				
Day (Window [days])	-7 to -28	1	28 (±3)	56 (±7)	182 (±10)	245/308 (±10)	364 (±10)	427/490 (±10)	546/910/1274 (±10)	609/672/791/854/973/1036/1155/1218/1337/1400/1519/1582 (±10)	728/1092/1456 (±10)	*b*	*c*	*c*	Study Closeout +14 (±4)
ADDITIONAL TESTING TO MEET INCLUSION CRITERIA															
Cardiac CT for calcium score[n]	X														
Echocardiogram[n]	X														
OTHER TESTING															
DXA scan, 25-hydroxyvitamin D and markers of bone and calcium metabolism (subset of patients)[o]	X[o]	X[o]										X[o]		X[o]	
[redacted]															
Plasma digoxin (if applicable)[r]	X[r]		X[r]	X[r]	X[r]										
AEs/SAEs/AESIs/EOSIs/ severe hypoglycemia and endpoint events[s]	*Throughout the study*														

a Telephone visit.

b If a patient prematurely permanently discontinues treatment with IMP, the patient will undergo a pEOT Visit as soon as possible. Patients will then continue in the study with all study procedures/visits except those associated with IMP administration. Patients will continue to be followed after a CV or renal endpoint occurs irrespective of their treatment status. If the patient does not agree to site visits, he/she will be contacted by telephone to inquire about safety status (including hospitalizations and endpoints).

c **All** randomized patients will be asked to return to the study site for a Study Closeout Visit when approximately 844 primary CV events of CV death or HHF and approximately 1189 3-point MACE are positively adjudicated. The timing and window of this visit will be communicated to sites. For patients who previously prematurely permanently discontinued IMP, the Study Closeout Visit will be the final study visit and no further visits are planned.

d Patients still taking the IMP at the time of the Study Closeout Visit (ie, who have not prematurely permanently discontinued IMP) will have their final study visit (Follow-up Visit) 14 days (±4 days) after their Study Closeout Visit.

e Height to be measured only at Screening.

f Vital sign measurements (BP and heart rate) should be measured in a seated position.

g The dose of any concomitant RAAS inhibitors and beta-blockers should be collected at Baseline and at all study visits. For patients receiving RAAS inhibitors and/or beta blockers, the Investigator will need to confirm that patient is receiving the optimal or maximally tolerated dose, or otherwise record the reason for taking a lower dose.

h The 12-lead ECG recording at Day 1 (Visit 2) should be obtained prior to first dose of double-blind IMP.

i All laboratory assessments performed at Day 1 (Visit 2) should occur prior to first dose of double-blind IMP.

j The following laboratory assessments will be performed at the Follow-up Visit: eGFR, hemoglobin/hematocrit, albumin, and total protein

k Serum pregnancy testing only at Screening; urine pregnancy testing subsequently. Any positive urine test results must be confirmed based on serum pregnancy test. The Investigator may perform additional tests at their discretion or as required by local regulations.

l A urine dipstick will be performed by the Central laboratory and includes assessment of specific gravity, pH, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase. If the dipstick is positive for nitrite and leukocyte esterase or blood, reflexive testing will be performed (see Section 9.2.2.1). Urinary albumin-to-creatinine ratio will also be performed. Screening UACR will be measured by spot urine. If the Screening UACR is <300 mg/g (34 mg/mmol), but >100 mg/g (11 mg/mmol) then a 24-hour urine collection for measurement of UACR will be performed.

m **ALL** patients **MUST** have NT-proBNP, hsTnT, and hsCRP assessed at Screening. Patients also have these biomarkers assessed at Visit 5 (Week 26) and Visit 8 (Week 52). If the patient prematurely permanently discontinues study treatment before attending Visit 8, NT-proBNP, hsTnT, and hsCRP should be assessed at the pEOT Visit.

n If a patient has a diagnosis of T2D, age ≥18 years, a HbA1c ≥7% (53 mmol/mol), and an eGFR ≥25 and ≤60 mL/min/1.73 m^2, and does not have either 1 major or 2 minor risk factors based upon available information, additional testing (echocardiogram and/or coronary artery CT scan) **MAY** be ordered. A Coronary artery CT scan **MAY** be performed to measure the coronary artery calcium score if required for eligibility if not previously documented. An echocardiogram will be performed at Screening in **ALL** patients who have not an ejection fraction documented ***within the past year.*** If both tests have not been documented and are needed to meet inclusion criterion 04, they can be ordered at the same time.

o Approximately 190 patients (95 females and 95 males) will be enrolled into the DXA sub-study. 25-hydroxyvitamin D will be drawn at the **Screening Visit** to allow assessment of eligibility for the sub-study. The DXA scan and 24-hour urine collection (for calcium, creatinine, and phosphorus) will be performed during the Screening period prior to Randomization for patients who sign the dedicated informed consent form and otherwise meet the eligibility criteria for the sub-study at the time of the Screening Visit; urine samples specific to the sub-study (see Appendix B) should be returned prior to or at Visit 2 (Randomization). Serum markers of bone and calcium metabolism will otherwise be performed at Day 1 (Visit 2). At the end of treatment (pEOT Visit for patients who prematurely permanently discontinue and the Study Closeout Visit for patients who completed treatment), a DXA scan, 24-hour urine collection and serum markers of bone and calcium metabolism will be performed. Specific to Canada and USA: Fasting serum markers (see Appendix F)

Markers of bone and calcium metabolism include: serum and urinary calcium, serum 25-hydroxyvitamin D, serum 1,25-dihydroxyvitamin D, serum and urinary phosphorus, serum PTH, markers of bone resorption (serum NTX, serum β-CTX-1), and bone formation (serum P1NP).

[redacted]

r In patients treated with digoxin, digoxin levels should be measured at Screening and at Visit 3 (Week 4). Digoxin levels should be reassessed 2 to 4 weeks after an up-titration has been implemented (at an unscheduled visit, if indicated). If no up-titration is implemented, there is no requirement for digoxin level assessment beyond Visit 3. Throughout the study, additional digoxin plasma level assessments to be performed as per Investigators' judgment. All digoxin levels will be performed as local laboratory measurements.

s All AEs, including AESIs, EOSIs, SAEs, and severe hypoglycemia will be collected starting with signing informed consent. The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until stabilization, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. Patients 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. If acute renal failure is suspected, further clinical evaluation should be performed as per local standard of care, including confirmation of renal laboratory parameters, and consideration should be given to a nephrology referral.

AE adverse event; AESI adverse event of special interest; β-CTX-1 beta carboxy-terminal telopeptide cross-linked type 1 collagen; BP blood pressure; CT computed tomography; CV cardiovascular; DXA dual-energy x-ray absorptiometry; DNA deoxyribonucleic acid; ECG electrocardiogram; eGFR estimate glomerular filtration rate; EOSI event of special interest; FU follow-up; HbA1c hemoglobin A1c; HHF hospitalization for heart failure; hsCRP high-sensitivity C-reactive protein; hsTnT high-sensitivity troponin T; IMP investigational medicinal product; IRT interactive response technology; MACE major adverse cardiovascular event; NT-proBNP N-terminal prohormone of brain natriuretic peptide; NTX N-terminal telopeptide; pEOT premature End-Of-Treatment; P1NP procollagen type 1 amino-terminal propeptide; PTH parathyroid hormone; RAAS renin-angiotensin-aldosterone system; SAE serious adverse event; T2D type 2 diabetes; UACR urinary albumin-to-creatinine-ratio; WOCBP women of childbearing potential.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

3 LIST OF ABBREVIATIONS

AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BMD:	bone mineral density
BMI:	body mass index
BNP:	B-type natriuretic peptide
BP:	blood pressure
CAC:	coronary artery calcium
CEC:	Clinical Endpoint Committee
CI:	confidence interval
CKD:	chronic kidney disease
CPK:	creatinine phosphokinase
CSR:	clinical study report
CV:	cardiovascular
CVD:	cardiovascular disease
CVOT:	cardiovascular outcomes trial
DB:	database
DBP:	diastolic blood pressure
DILIs:	drug-induced-liver injuries
DKA:	diabetic ketoacidosis
DKD:	diabetic kidney disease
DMC:	data monitoring committee
DRF:	discrepancy resolution form
DXA:	dual-energy X-ray absorptiometry
EC:	Executive Committee
ECG:	electrocardiogram
e-CRF:	electronic case report form
EF:	ejection fraction
eGFR:	estimated glomerular filtration rate
EMA:	European Medicines Agency
EOSI:	event of special interest
FDA:	Food and Drug Administration
GCP:	good clinical practice
GI:	gastrointestinal
GLP-1:	glucagon-like peptide – 1
GP:	general practitioner
HbA1c:	hemoglobin A1c
HF:	heart failure
HHF:	hospitalization for heart failure
HLGT:	high-level grouped term

HLT:	high-level term
hsCRP:	high-sensitivity C-reactive protein
hsTnT:	high-sensitivity troponin T
IABP:	intra-aortic balloon pump
ICF:	informed consent form
IEC:	independent ethics committee
IMP:	investigational medicinal product
INN:	international nonproprietary name
IRB:	institutional review board
IRT:	Interactive Response Technology
ITT:	intent-to-treat
LV:	left ventricular
MACE:	major adverse cardiovascular event
MDRD:	modification of diet in renal disease
MI:	myocardial infarction
NI:	non-inferiority
NT-proBNP:	N-terminal pro-B-type natriuretic peptide
NTX:	N telopeptide of type 1 collagen
P1NP:	N-terminal propeptide of type 1 procollagen
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
pEOT:	premature End-of-Treatment
PET:	positron emission tomography
P-gp:	P-glycoprotein
PI:	principal investigator
PPG:	postprandial glucose
PT:	preferred term
PTH:	parathyroid hormone
PYY:	peptide YY
qd:	once daily
RAAS:	renin-angiotensin-aldosterone system
SAE:	serious adverse event
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SC:	steering committee
SD:	standard deviation
SGLT1:	sodium-glucose linked transporter-1
SGLT2:	sodium-glucose linked transporter-2
SMQ:	standardized MedDRA query
SOC:	system organ class
SPECT:	single-photon emission computed tomography
SUSAR:	suspected unexpected serious adverse reaction
T1D:	type 1 diabetes
T2D:	type 2 diabetes
TEAE:	treatment-emergent adverse event
UACR:	urinary albumin-to-creatinine ratio

UB:	upper bound
UGE:	urinary glucose excretion
ULN:	upper limit of normal
WOCBP:	women of childbearing potential
β-CTX 1:	beta-C-terminal telopeptide of type 1 collagen

4 INTRODUCTION AND RATIONALE

4.1 BACKGROUND: DISEASE AND PRELIMINARY THERAPEUTIC OBSERVATIONS

Type 2 diabetes (T2D) is a growing epidemic worldwide that is associated with a high incidence of macrovascular and microvascular complications (1). Type 2 diabetes is associated with cardiovascular (CV) risk factors such as dyslipidemia, hypertension, and obesity (2). The Emerging Risk Factors Collaboration has recently reported that patients with T2D have a doubled risk of CV death compared to patients without diabetes (2). Although microvascular complications have been shown to be decreased by glucose-lowering therapies, the effect on macrovascular outcomes is not as clear (3, 4, 5, 6). Therefore, it is important to evaluate the CV safety of glucose-lowering drugs, as specified in the 2008 Food and Drug Administration (FDA) Guidance Document (Guidance for Industry: Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes; 7) and the 2016 European Medicines Agency (EMA) Reflection paper on assessment of cardiovascular safety of medical products (8).

The prevalence of T2D is increasing, and it is projected that 439 million individuals worldwide will be affected by 2030 (9). As the frequency of diabetes increases, so will its complications, including renal impairment, CV death, and heart failure (HF). Hence, the development of glucose-lowering therapies effective at decreasing the risk of CV death and HF and/or the progression of renal impairment is a growing unmet medical need.

In patients with diabetes the prevalence of HF is considerably higher compared to the general population and increases with age (10, 11, 12). One in 5 patients with diabetes aged over 65 years suffers from HF (12). In addition, several observational studies and clinical trials have shown that HF patients with diabetes have increased CV morbidity and mortality compared to HF patients without diabetes (12, 13, 14, 15).

Approximately 50% of patients with T2D have chronic kidney disease (CKD), defined as a persistent elevated urinary albumin excretion (urinary albumin-to-creatinine ratio [UACR] ≥30 mg/g [3 mg/mmol]), renal impairment (defined as a persistent reduction in estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), or both (16).

Recent data indicate that sodium-glucose linked transporter-2 (SGLT2) inhibitors may address the growing unmet medical need of treatment for prevention of CV death and HF and progression of renal impairment in patients with T2D (17). These antihyperglycemic agents lower blood glucose levels through the inhibition of renal glucose reabsorption thereby enhancing renal glucose excretion. In 2015, the EMPA-REG OUTCOME trial showed that empagliflozin, another SGLT2 inhibitor, when added to standard of care, reduced the risk of CV death (a component of the primary composite endpoint) and HF requiring hospitalization in patients with T2D and established CV disease (CVD), including 10% with HF at screening (18). In 2017, the CANVAS program showed that canagliflozin, when added to standard of care, reduced the risk of a composite outcome of CV death, non-fatal myocardial infarction (MI) or non-fatal stroke in patients with T2D and established CVD or at high risk for CV events (19). Of note, the FDA recently approved empagliflozin for reducing the risk of CV death in adult patients with T2D and established CVD (20).

The mechanisms supporting the CV benefit of empagliflozin have not been fully elucidated, but several experts have speculated that the hemodynamic effects of SGLT2-inhibition are the main driver (21, 22, 23). Empagliflozin may have affected volume status via either or both of the following mechanisms: a sodium and volume reduction, and/or a decrease in arterial pressure. The possible diuresis and beneficial effect on maladaptive renal arteriolar responses may have led to improvement in both systolic and diastolic function, thereby lowering HF hospitalization and sudden cardiac death. Empagliflozin induces a considerable diuresis with early loss of urinary glucose and sodium, resulting in an approximate 4% increase in the hematocrit. Diuretics are an essential treatment in HF because renal perfusion and neurohumoral activation lead to sodium and water retention, the hallmark of the HF syndrome. Patients with diabetes, subclinical cardiac dysfunction, and renal impairment may be especially sensitive to fluid retention. The cardiac function of the EMPA-REG OUTCOME study population was not characterized, but it has been suggested that a substantial proportion of the trial's population might have had mild HF or some form of preclinical HF or diabetic cardiomyopathy (23, 24). The beneficial CV effects of empagliflozin were consistent across subgroups including patients with versus without HF at baseline (24).

In addition to the hemodynamic hypothesis, there is another hypothesis: under conditions of mild, persistent hyperketonemia, such as those that prevail during treatment with SGLT2 inhibitors, b-hydroxybutyrate is freely taken up by the heart (among other organs) and oxidized in preference to fatty acids. This fuel selection improves the transduction of oxygen consumption into work efficiency at the mitochondrial level. In addition, the hemoconcentration that typically follows SGLT2 inhibition enhances oxygen release to the tissues, thereby establishing a powerful synergy with the metabolic substrate shift (25).

The SGLT2 inhibitors have complex renal effects and, despite their diuretic action, may suppress, rather than stimulate the renin-angiotensin-aldosterone system (RAAS), which would be beneficial in preventing and treating HF (26). Type 2 diabetes is associated with upregulation of the SGLT2 tubular transporters. Sodium-glucose linked transporter-2 inhibitors block tubular glucose reabsorption along with sodium reabsorption in the proximal renal tubules, leading to increased sodium delivery to the macula densa. Increased distal tubule sodium delivery results in tubuloglomerular feedback, afferent glomerular arteriolar vasoconstriction, and subsequent reduction in glomerular capillary pressure. The reduction in intraglomerular hypertension inhibits the hyperfiltration that is characteristic of both type 1 diabetes (T1D) and T2D and is responsible for the tubulointerstitial fibrosis that is postulated to be the major determinant of the progression of diabetic kidney disease (DKD).

In the EMPA-REG OUTCOME study, a pre-specified secondary endpoint was a composite of the following renal outcomes: progression to macroalbuminuria, doubling of serum creatinine, initiation of renal-replacement therapy, or renal death (hazard ratio=0.61; 95% confidence interval [CI]: 0.53 -0.70; p<0.001). A slower progression of kidney disease with empagliflozin was also observed in a post-hoc assessment of renal outcomes (progression to macroalbuminuria was excluded from the endpoint [27]). In CANVAS (19), a prespecified secondary outcome was progression of albuminuria (Hazard ratio=0.73; 95% CI: 0.67 to 0.79). However, since the hypothesis testing plan was hierarchical, superiority for the first secondary outcome (all-cause mortality) was not shown and therefore hypothesis testing was discontinued. A key prespecified exploratory composite outcome was: a sustained 40% reduction in the eGFR, the need for renal replacement therapy or death from renal causes (Hazard ratio= 0.60; 95% CI: 0.47 to 0.77).

4.2 BACKGROUND: SOTAGLIFLOZIN

Sotagliflozin, a potent, dual inhibitor of SGLT2 and sodium-glucose linked transporter-1 (SGLT1), is in clinical development for the treatment of T1D and T2D (28). Sodium-glucose linked transporter-1 is expressed predominantly in the gastrointestinal (GI) tract, and is responsible for the majority of glucose absorption by the small intestine. Inhibition of SGLT1 in the GI tract delays glucose absorption, and stimulates L cells in both the ileum and the colon to secrete glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), gut hormones involved in pancreatic beta-cell function and appetite control, respectively. Although a complete lack of functional SGLT1 may be associated with symptoms of glucose and galactose malabsorption (29), pharmacologic inhibition of SGLT1 by sotagliflozin has not produced these effects in preclinical models or patients with T1D or T2D.

Sotagliflozin may have unique effects on both CKD and on blood pressure (BP). Study LX4211.1-107 was a Phase 1 study performed in patients with T2D with moderate to severe renal impairment (defined as a Screening eGFR of 15 to 59 mL/min/1.73 m^2). In patients with an eGFR between 15 to <45 mL/min/1.73 m^2, no reduction in postprandial glucose (PPG) on Day 7 compared to Day 1 was seen. However, urinary glucose excretion (UGE) decreased by approximately 50% in these patients. This finding suggests that the PPG effect is not due only to SGLT2 inhibition. The study also showed a statistically significant increase of GLP-1 induced by sotagliflozin, consistent with SGLT1 inhibition, delayed glucose absorption, and L cell stimulation. These results indicate that sotagliflozin still enhanced glycemic control in patients with T2D and renal impairment, which was consistent with the mechanism of action of sotagliflozin as a dual inhibitor of SGLT1 and SGLT2. These results support the hypothesis that sotagliflozin has a potential to improve glycemic control in this population through clinically meaningful SGLT1 inhibition. In addition, UGE statistically significantly increased following sotagliflozin dosing compared to placebo, suggesting that inhibition of renal glucose reabsorption via SGLT2 inhibition was at least partially maintained for patients with moderate to severe renal impairment.

In addition, dual inhibition of the SGLT1 and SGLT2 receptors may be responsible for the potent antihypertensive effect of sotagliflozin, which appears to be substantially more pronounced than the effect reported with selective SGLT2 inhibition. Study LX4211.1-202 was a Phase 2b study in patients with T2D on the combination of sotagliflozin and metformin, with inadequate glycemic control on metformin monotherapy. A mean difference of change in systolic blood pressure (SBP) from baseline to Week 12 of -3.9, -5.7, and -4.5 mmHg for 200 mg once daily (qd), 200 mg twice daily and 400 mg qd of sotagliflozin, respectively, was seen. Sotagliflozin induces a dose-dependent reduction of SBP in hypertensive patients. In study LX4211.1 202 DM, a prespecified sub-analysis of patients with a baseline BP ≥130 mmHg showed that SBP decreased by 7 and 14 mmHg (placebo-subtracted), respectively, in the 200 mg qd and 400 mg qd groups. Blood pressure changes with treatment were of a magnitude comparable to approved antihypertensive agents, and they were obtained without hypotension in a population whose baseline mean SBP was 125 mmHg and whose baseline mean diastolic blood pressure (DBP) was 79 mmHg. While clinically meaningful changes in BP were demonstrated, the population was not selected for the presence of hypertension and severe hypertension was excluded. Concomitant antihypertensive medications were allowed and adjustments in their dose were permitted as needed. The BP reductions therefore reflect a real world practice setting. However, their time

course over the day, their potential impact on severe hypertension, and their influence or interaction with other medications, have yet to be determined. Therefore, based on its effect on plasma volume and renal hemodynamics, chronic treatment with sotagliflozin is expected to both reduce the CV risk and the progression of DKD in patients with T2D.

4.3 BENEFIT/RISK PROFILE

Sotagliflozin, a dual inhibitor of SGLT1 and SGLT2, is being developed for the treatment of T1D and T2D. Multiple-dose (up to 12 week) administration in patients with T1D and T2D produced improvements in several metabolic parameters, including levels of fasting glucose, hemoglobin A1c (HbA1c), PPG, GLP-1, and PYY. Sotagliflozin also enabled patients with T1D to control their daily glucose levels while decreasing their daily insulin doses in one of the Phase 1 studies implemented to date (28). These data suggest that sotagliflozin will be of therapeutic benefit to patients with T1D and T2D.

Although a complete lack of functional SGLT1 may be associated with symptoms of glucose and galactose malabsorption (29), pharmacologic inhibition of SGLT1 by sotagliflozin has not produced these effects in preclinical models or patients with diabetes evaluated so far. No significant safety concerns have been identified in the sotagliflozin clinical program, and sotagliflozin has been well-tolerated in all completed studies. Serious adverse events (SAEs) and discontinuations due to adverse events (AEs) have been uncommon and have been balanced between treatment and control groups. Suspected adverse reactions that have occurred in ≥3.0% of patients in sotagliflozin clinical studies include headache, nausea, and diarrhea, all of which occurred at a numerically greater rate in patients treated with sotagliflozin than with controls. However, these events have been infrequent, the majority were mild to moderate in intensity, with most resolving spontaneously. Overall, no imbalance was observed in the events of hypoglycemia in the sotagliflozin program.

Overall, the potential benefits of sotagliflozin therapy for patients with T1D and T2D, including improvement in glycemic control and the reductions in weight and BP, outweigh the potential risks. The favorable benefit-risk assessment to date supports the further development.

More information on the safety of sotagliflozin and on the clinical program can be found in the Investigator Brochure.

4.4 RATIONALE FOR CURRENT STUDY

This study is designed to demonstrate the CV and renal effects of sotagliflozin in patients with T2D, high CV risk, and moderate renal impairment. One of the major objectives of this study is to fulfill the regulatory mandate that any new therapy for T2D must demonstrate that its use does not result in an unacceptable increase in CV risk. In concordance with the 2008 FDA guidance document for new therapies for T2D, non-inferiority (NI) of sotagliflozin versus placebo with a 1.3 NI margin (upper bound [UB] of the 95% CI [CI of the estimated risk ratio <1.3]) will be assessed on 3-point major adverse CV event (MACE; CV death, non-fatal MI or non-fatal stroke) as the first primary objective.

The second primary objective of the study is to evaluate if sotagliflozin decreases the risk versus placebo of CV death or hospitalization for heart failure (HHF) in patients with T2D, high CV risk factors and moderate renal impairment.

Secondary objectives include assessment of superiority of sotagliflozin versus placebo on 3-point MACE and on the progression of CKD in patients with T2D, high CV risk factors, and moderate renal impairment.

4.4.1 Rationale for selection of dose

In healthy subjects, sotagliflozin was well-tolerated following single doses up to 2,000 mg, and in multiple doses up to 800 mg over 10 days. Furthermore, in a thorough QT study, single doses of sotagliflozin (800 mg and 2,000 mg) were well-tolerated and did not prolong the QT interval. Additionally, evaluation of metabolites in urine and plasma of healthy subjects resulted in no safety concerns following single doses of 400 mg sotagliflozin.

The starting dose of sotagliflozin (200 mg qd) and the maintenance dose (400 mg qd) were selected based on the results of the Phase 2b study LX4211.1 202 DM. In this study, doses of sotagliflozin 75 mg qd, 200 mg qd, 200 mg twice daily, and 400 mg qd were tested over a 12-week, double-blind period. At 12 weeks, the 200 mg qd and 400 mg qd doses lowered HbA1c by a mean of 0.52% and 0.92%, respectively ($p<0.001$ for both arms), while placebo lowered HbA1c by a mean of 0.09%. The overall incidence of AEs on sotagliflozin 200 mg qd and 400 mg qd doses was similar to placebo, hence the 200 mg dose was less effective than the 400 mg qd dose and did not present clear advantages in safety or tolerability. Both doses are currently undergoing further evaluation in phase 3 glucose-control studies.

Sotagliflozin induces an acute, but modest, decrease in eGFR. Since the study population consists of patients at increased risk of acute kidney injury (ie, patients with moderately impaired renal function), study treatment will begin with the low dose of sotagliflozin (200 mg qd) and will be increased to the maintenance dose of 400 mg qd, once tolerability of the low dose has been established by the Investigator.

Recent studies have demonstrated that SGLT2-inhibitors decrease the risk of CV death and hospitalization for HF in patients with T2D and high CV risk. The underlying mechanism(s) for the CV benefit are still under investigation, but the hemodynamic effects of SGLT2-inhibitors have been speculated to play a major role (21, 22, 23) since these compounds decrease plasma volume and reduce BP likely resulting in improved systolic and diastolic function. It should be noted that in EMPA-REG OUTCOME (18) an approximate 4% increase in the hematocrit was observed in the empagliflozin arm compared with the placebo arm, and a post hoc univariate analysis suggested that a change in hematocrit was the key mediator of the CV benefit (30). A strong correlation with the cardioprotective effect of empagliflozin was also shown for albumin and hemoglobin, collectively suggesting the importance of changes in plasma volume. Several other studies have indicated that a reduction in plasma volume in patients with HF is associated with improved outcome (31, 32, 33, 34).

In study LX4211.1 202 DM sotagliflozin induced a dose-dependent increase of hematocrit albumin, and hemoglobin. The mean change (standard deviation [SD]) in hematocrit from baseline to Week 12 was 0.9 (2.52), 2.0 (2.47), and 1.9 (2.78) % in patients receiving sotagliflozin 200 mg qd, 200 mg twice daily, and 400 mg qd, respectively, versus -0.5 (2.98) % in the placebo arm. The mean change (SD) in albumin from baseline to Week 12 (SD) was 0.0 (0.279) , 0.09 (0.243), and 0.12 (0.242) g/dL in patients receiving sotagliflozin 200 mg qd, 200 mg twice daily, and 400 mg qd, respectively, versus -0.04 (0.273) g/dL in the placebo arm. The mean change (SD) in hemoglobin from baseline to Week 12 (SD) was 0.29 (0.775) , 0.55 (0.688), and 0.60 (0.820) g/dL in patients receiving sotagliflozin 200 mg qd, 200 mg twice daily, and 400 mg qd, respectively, versus -0.19 (1.084) g/dL in the placebo arm. In addition, in the same study, a prespecified sub-analysis of patients with a baseline BP ≥130 mmHg showed that SBP decreased by 7 and 14 mmHg (placebo-subtracted), respectively, in the 200 mg qd and 400 mg qd groups.

Therefore, given the observed higher efficacy of the 400 mg dose on glycemic control, hemoconcentration, and BP reduction and given the potential benefit of these changes on CV outcomes, the dose of 400 mg was chosen as the proposed maintenance dose for the study.

4.4.2 Rationale for Study Design and Control Groups

This study is a pivotal, Phase 3, CV outcomes trial (CVOT); hence, it has been designed as a randomized, double-blind, event-driven study with external, blinded adjudication. The study will continue until approximately 844 positively-adjudicated CV death or HHF events and approximately 1189 positively-adjudicated 3-point MACE have occurred.

In order to demonstrate the effects of sotagliflozin on CV and renal outcomes, the patients will be randomized to sotagliflozin or placebo in addition to standard of care treatments. This approach will ensure the scientific rigor of the comparison. Patients with established CVD (eg, prior acute MI or coronary revascularization) will not be eligible for the trial if treatment with an SGLT2 inhibitor is planned during the course of the study.

5 STUDY OBJECTIVES

5.1 PRIMARY

- The 2 primary objectives of this study are to demonstrate that, when compared to placebo in patients with T2D, CV risk factors, and moderately impaired renal function, sotagliflozin:
  - Is non-inferior to placebo on the composite endpoint of CV death, non-fatal MI, or non-fatal stroke (3-point MACE)
  - Reduces the composite endpoint of CV death or HHF

5.2 SECONDARY

- The secondary objectives of this study are to demonstrate that, when compared to placebo in patients with T2D, CV risk factors, and moderately impaired renal function, sotagliflozin:
  - Reduces the composite endpoint of CV death, non-fatal MI or non-fatal stroke (3-point MACE)
  - In patients with Baseline eGFR ≥30 mL/min/1.73 m^2, reduces the composite renal endpoint of sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days)
  - In patients with Baseline eGFR ≥30 mL/min/1.73 m^2 and Baseline UACR ≥300 mg/g (34 mg/mmol), reduces the composite renal endpoint of sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days)
  - Reduces the composite endpoint of CV death, HHF, or urgent HF visit (defined in Appendix E)
  - Reduces CV death
  - Reduces all-cause mortality
- To assess the safety and tolerability of sotagliflozin in patients with T2D, CV risk factors, and moderately impaired renal function

5.3 OTHER

- To demonstrate that, when compared to placebo in patients with T2D, CV risk factors, and moderately impaired renal function, sotagliflozin:
  - In patients with Baseline eGFR ≥30 mL/min/1.73 m^2, reduces the composite endpoint of sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days), or CV or renal death

  - Reduces the composite endpoint of CV death, non-fatal MI, non-fatal stroke, or unstable angina requiring hospitalization (4-point MACE)
  - In patients with Baseline eGFR ≥30 mL/min/1.73 m^2, reduces the composite renal endpoint of worsening nephropathy, defined as: new onset or progression to macro albuminuria (≥300 mg/g [34 mg/mmol]) accompanied by a UACR value increase of ≥30% from Baseline, sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, need for renal transplant, eGFR <15 mL/min/1.73 m^2 (for ≥30 days), or renal death

- To compare sotagliflozin versus placebo with respect to change from Baseline to 6 months, 12 months, and 24 months in the following endpoints:
  - Hemoglobin A1c
  - Body weight
  - Blood pressure
  - Urinary albumin-to-creatinine ratio
  - Estimated glomerular filtration rate
  - Hematocrit
  - Hemoglobin
  - Albumin
  - Total protein
- To compare sotagliflozin versus placebo with respect to change from Baseline to 6 months and 12 months in the following endpoints:
  - N-terminal pro-B-type natriuretic peptide (NT-proBNP)
  - High-sensitivity troponin T (hsTnT)
  - High-sensitivity C-reactive protein (hsCRP)
- To compare sotagliflozin versus placebo with respect to change from Baseline in the following endpoints:
  - Proportion of patients not taking insulin at baseline who start insulin during the study

5.4 DUAL-ENERGY X-RAY ABSORPTIOMETRY SUB-STUDY

The primary objective of the sub-study is to assess the impact of sotagliflozin on bone and calcium metabolism and bone quality in patients with T2D, CV risk factors, and moderately impaired renal function. Additional details of the sub-study are presented in Appendix B.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This study is a Phase 3, multicenter and multinational, randomized, double-blind, placebo-controlled, parallel-group study in approximately 10,500 patients with T2D, CV risk factors, and moderately impaired renal function. The study will consist of 3 periods:

- A Screening period of 1 to 4 weeks
- A randomized, Double-blind Treatment period including up-titration (the dose of sotagliflozin or matched placebo should be increased from 200 mg to 400 mg in the first 6 months of the randomized Double-blind Treatment period, if tolerated)
- A 14-day Post-treatment period

Approximately 190 patients (95 females and 95 males) will participate in the dual-energy X-ray absorptiometry (DXA) sub-study at participating sites. Full details of the DXA sub-study are presented in Appendix B.

6.1.1 Screening period

The Screening period will last 1 to 4 weeks. The period must be long enough to collect the data required to establish whether the patient satisfies the inclusion/exclusion criteria.

At the Screening Visit after signing of the informed consent form (ICF), eligibility criteria will be assessed and Screening assessments will be performed.

The Interactive Response Technology (IRT; either Interactive Voice Response System or Interactive Web Response System) will be contacted at Visit 1 for notification of Screening and for patient number allocation.

6.1.2 Randomized Double-blind Treatment period

Patients who meet all eligibility criteria during the Screening period will come back for the Randomization Visit (Visit 2) between 7 and 28 days later and, if they are still eligible for the study, they will be randomized 1:1 to sotagliflozin or placebo.

Randomization will be stratified by region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) and by HF-related criteria (Yes/No).

HF-related criteria is ‘Yes’ when a patient meets at least 1 of the major CV risk factors:

1. Ejection fraction (EF) ≤40% documented within the past year
2. Hospitalization for HF during previous 2 years

Patients will receive 200 mg sotagliflozin (or matched placebo) from Randomization onwards. At Visit 3 (Week 4), if in the opinion of the Investigator the patient's clinical condition is satisfactory and the patient has tolerated the investigational medicinal product (IMP) well, the dose will be increased to 400 mg sotagliflozin or matched placebo as described in Section 8.1.1.1. If IMP dose is not increased at Visit 3 (eg, for safety reasons) it will be increased at Visit 4 (Week 8) or Visit 5 (Week 26), if possible. The 400 mg dose (or 200 mg in those who cannot tolerate up-titration by Visit 5) will be maintained for the duration of the remaining double-blind study treatment period.

Antihyperglycemic therapy should remain unchanged for the first 12 weeks after Randomization. However, in cases of medical necessity, addition of antihyperglycemic therapy, dose adjustment or discontinuation of antihyperglycemic therapy could occur (see Section 8.8).

After Visit 3, patients will attend on-site visits at Weeks 8 (Visit 4) and 26 (Visit 5). After Visit 5, patients will attend on-site visits every 6 months. In between each on-site visit, starting with Visit 5, patients will be contacted by phone twice at 9 week intervals (ie, 9 weeks after the on-site visit and again 18 weeks after the on-site visit) to collect drug accountability information, concomitant medications, endpoint events, and AEs.

All randomized patients, will be followed from Randomization until their Follow-up Visit (or Study Closeout Visit, for patients who prematurely permanently discontinued from IMP) or death, whichever comes first.

The study is event driven, therefore, it will continue until approximately 844 primary CV events of CV death or HHF and approximately 1189 3-point MACEs are positively adjudicated. All randomized patients will be asked to return to the study site for a Study Closeout Visit once the date the required number of events are projected to be positively adjudicated has been determined. The timing and window of this visit will be communicated to sites.

If a patient permanently discontinues treatment with IMP prematurely, the patient will undergo a premature End-of-Treatment (pEOT) Visit as soon as possible. Every effort will then be made to have the patients return to the site at the times corresponding to their scheduled visits, until the Study Closeout Visit. For patients who prematurely permanently discontinue IMP, the Study Closeout Visit will be the final study visit and no further visits are planned. Study Closeout Visit procedures will differ for patients who do not prematurely permanently discontinue IMP and those who do prematurely permanently discontinue IMP (see Section 10.1.4.1 and Section 10.1.4.2, respectively).

See Section 10.3.2 for details on patients who refuse to continue in the study after premature IMP discontinuation.

All patients will continue to be followed after a CV or renal endpoint occurs. Patients with a suspected renal event (reduction of eGFR) should be brought in for an unscheduled visit and have a repeat assessment of renal function 30 to 45 days following the onset of the event to confirm it is sustained. If acute renal failure is suspected, further clinical evaluation should be performed as per local standard of care, including confirmation of renal laboratory parameters, and consideration should be given to a nephrology referral. Patients will continue with IMP treatment after a CV or renal endpoint occurs unless they have prematurely permanently discontinued treatment or the criteria for permanent treatment discontinuation have otherwise been met (see Section 10.3.3).

6.1.3 Post-treatment period

Patients still taking the IMP at the time of the Study Closeout Visit (ie, who have not prematurely permanently discontinued IMP) will have their final study visit (Follow-up Visit) 14 days (±4 days) after their Study Closeout Visit.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

All patients participate in a Screening period of 1 to 4 weeks. The study is event driven, therefore the duration of the study for each patient will be determined by when approximately 844 primary events of CV death or HHF and approximately 1189 3-point MACEs have been positively-adjudicated.

The estimated study treatment duration for a given patient will be approximately 27 to 51 months, assuming approximately 24 months of recruitment, and approximately 27 months of follow-up, after the last patient is randomized.

6.2.2 Determination of end of clinical trial (all patients)

All randomized patients will be asked to return to the study site for a Study Closeout Visit when approximately 844 primary CV events of CV death or HHF and approximately 1189 3-point MACE are positively adjudicated. The timing and window of this visit will be communicated to sites. For patients who previously prematurely permanently discontinued IMP, the Study Closeout Visit will be the final study visit and no further visits are planned. Patients still taking the IMP at the time of the Study Closeout Visit (ie, who have not prematurely permanently discontinued IMP) will have their final study visit (Follow-up Visit) 14 days (±4 days) after their Study Closeout Visit.

6.3 INTERIM ANALYSIS

Refer to Section 11.5 for details of a potential interim analysis.

6.4 STUDY COMMITTEES

6.4.1 Executive Committee

The Executive Committee (EC) will oversee all the sotagliflozin outcomes trials. The EC is responsible for supporting the Sponsor in designing a scientifically sound study. The EC is also responsible for ensuring accurate reporting of the study results.

6.4.2 Steering Committee

The Steering Committee (SC) is responsible for supporting the Sponsor and EC, in designing a scientifically sound study. In this capacity, the SC shall address and resolve scientific issues encountered during the study. The Chair and Co-Chair of the SC will be members of the EC.

6.4.3 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will meet on a regular basis to review accumulating unblinded clinical study data. Following each meeting, the DMC will make a recommendation to the Sponsor regarding the study.

6.4.4 Adjudication Committee

An independent Clinical Endpoint Committee (CEC) will review and adjudicate all events of death, MACE (CV death, non-fatal MI or non-fatal stroke), selected CV and renal events, diabetic ketoacidosis (DKA) and bone fractures in a treatment-blinded manner.

6.4.5 Independent Expert Committee to Evaluate Liver Injury

An expert committee will review all potential cases of drug-induced liver injuries (DILIs) in a treatment blinded manner to evaluate causality.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

Mandatory Inclusion Criteria (all 4 criteria are necessary)

I 01. Signed written informed consent

I 02. Type 2 diabetes with HbA1c ≥7% (53 mmol/mol) at Screening (central laboratory)

I 03. Estimated glomerular filtration rate ≥25 and ≤60 mL/min/1.73 m^2 by the 4 variable Modification of Diet in Renal Disease (MDRD) equation (at Screening, based on central laboratory)

I 04. Patients either:

- Age ≥18 years with at least 1 (one) of the major CV risk factors listed below **OR**
- In the absence of a major CV risk factor, age ≥55 years with at least 2 (two) of the minor CV risk factors listed below

In order to be considered eligible to participate in the study, patients must meet all 4 (four) of the mandatory criteria. Patients can be eligible if they have both major and minor CV risk factors, as long as 1 of the 2 conditions in Inclusion Criterion Number 4 is met. Major and minor CV risk factors are listed below.

Major CV risk factors (at least 1 criterion to fulfill Inclusion Criterion Number 4)

A) Hospitalization for HF during previous 2 years

B) Ejection Fraction (EF) ≤40%

Documented within the past year by previous imaging modality (such as echocardiogram, MUltiple Gated Acquisition (MUGA) scan, Magnetic Resonance Imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), left ventricular (LV) angiography)
Note: *An echocardiogram to assess EF at the time of Screening* ***MUST*** *be performed in all patients* ***if an assessment of EF has not been documented within 1 year prior to Screening***

C) Diagnosis of left ventricular hypertrophy

By either electrocardiogram (ECG) or echocardiogram

D) Coronary artery calcium (CAC) score ≥300 Agatston Units

Documented by coronary artery CT scan
Note: *a coronary artery CT scan* ***MAY*** *be performed to measure the CAC score if required for eligibility* ***if not previously documented***

E) N-terminal pro-B-type natriuretic peptide ≥400 pg/mL (47 pmol/L)

At Screening, based on central laboratory

F) High-sensitivity troponin T >15.0 pg/mL (0.015 µg/L) for men and >10.0 pg/mL (0.010 µg/L) for women

At Screening, based on central laboratory

G) High-sensitivity C-reactive protein >3 mg/L (28.6 nmol/L)

At Screening, based on central laboratory, if the Investigator does not consider the elevation to be due to an acute inflammatory condition (eg, acute infection)

H) Urinary albumin-to-creatinine ratio ≥300 mg/g (34 mg/mmol)

At Screening, based on central laboratory

Minor CV risk factors (if no major CV risk factors, at least 2 criteria to fulfill Inclusion Criterion Number 4)

I) Body mass index (BMI) ≥35 kg/m^2 at Screening

J) Dyslipidemia despite maximally-tolerated statin therapy:

- Low-density lipoprotein cholesterol >130 mg/dL (>3.36 mmol/L)

Or

- High-density lipoprotein cholesterol <40 mg/dL (<1.03 mmol/L) for men or <50 mg/dL (<1.29 mmol/L) for women

Based on the last measured and documented laboratory measurement in the previous 6 months

K) Currently smoking tobacco

Consumes an average of at least 1 cigarette, pipe, or cigar per day, at Screening

L) Coronary artery calcium score >100 and <300 Agatston Units

Documented by coronary artery CT scan
Note:** a coronary artery CT scan **MAY** be performed to measure the CAC score if required for eligibility **if not previously documented

M) Urinary albumin-to-creatinine ratio ≥30 mg/g and <300 mg/g (3 and 34 mg/mmol)

During Screening period, based on central laboratory

N) Systolic Blood Pressure >140 mmHg and DBP >90 mmHg despite antihypertensive therapy at the Screening Visit

O) Family history of premature coronary heart disease (defined as MI or coronary revascularization procedure) in a first degree relative

In a male relative <55 years or in a female relative <65 years

To participate in the DXA sub-study, patients also need to provide signed written informed consent for the sub-study (see Appendix B).

7.2 EXCLUSION CRITERIA

E 01. History of DKA or nonketotic hyperosmolar coma within 3 months prior to the Screening Visit or between Screening and Randomization

E 02. Antihyperglycemic treatment (if applicable) has not been stable in the 12 weeks prior to Screening or between Screening and Randomization, in the opinion of the Investigator

E 03. Patients who are planning to start a SGLT2 inhibitor (other than study drug) during the study. This includes patients who, **in the opinion of the Investigator**, based on their comorbid profile, are likely to receive an SGLT2 inhibitor (other than study drug) during the study

E 04. Any SGLT2 inhibitor <1 month prior to the Screening Visit, or between Screening and Randomization

E 05. Lower extremity complications (such as skin ulcers, infection, osteomyelitis, and gangrene) identified during the Screening period, and still requiring treatment at Randomization

E 06. Any allergic reaction to any SGLT2 inhibitor or sotagliflozin

E 07. Blood pressure ≥180 mmHg (systolic) or ≥110 mmHg (diastolic) at both the Screening and Randomization Visits

E 08. Hospitalization for hypertensive emergency within 3 months prior to Randomization

E 09. End-stage HF: requiring LV assist device, intra-aortic balloon pump (IABP), or any type of mechanical support at the time of Screening

E 10. Planned coronary revascularization procedures, electrophysiologic device implantation, cardiac mechanical support implantation, or other cardiac surgery after Randomization

E 11. History of dialysis within 1 year prior to Randomization

E 12. History of solid organ transplant

E 13. Serum creatinine altering drugs ≤30 days before Screening, or between Screening and Randomization (trimethoprim, cimetidine, cephalosporins, probenecid, aminoglycosides, ketoconazole). *Please note that diuretics are allowed within 30 days of Screening*

E 14. Clofibrate, fenofibrate, dronedarone, or ranolazine treatment that has not been at a stable dose in the 30 days prior to Screening or between Screening and Randomization or a dose adjustment is expected during the study based on the judgement of the Investigator

E 15. Use of systemic glucocorticoids (excluding topical application or inhaled forms) for more than 10 consecutive days within 3 months prior to Screening Visit or for more than 10 consecutive days between Screening and randomization

E 16. Digoxin plasma level >1.2 ng/mL (in a patient treated with digoxin, at Screening based on local laboratory*)

E 17. Use of any investigational drug(s) within 5 half-lives prior to the Screening Visit or between Screening and Randomization

E 18. Severe disease or short life expectancy making implementation of the protocol or interpretation of the study results difficult (CV disease [including congestive HF New York Heart Association IV], respiratory, hepatic, neurological [including stroke in 3 months prior to Screening], psychiatric, or active malignant tumor [except for non-melanoma skin cancers, which are not exclusionary] or other major systemic disease [including any diseases with evidence of malabsorption or severe anemia])

E 19. Presence of any other conditions (eg, geographic, social) actual or anticipated, that the Investigator feels would restrict or limit the patient's participation for the duration of the study

E 20. Patient is the Investigator or any Sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol

E 21. Any country-related specific regulation that would prevent the patient from entering the study (eg, individuals committed to an institution by virtue of an order issued either by the judicial or the administrative authorities)

E 22. Pregnant (demonstrated by serum pregnancy test at Screening) or breastfeeding women

E 23. Women of childbearing potential (WOCBP) not willing to use a highly-effective method(s) of birth control during the study treatment period and the follow-up period or who are unwilling or unable to be tested for pregnancy (see contraceptive guidance in Appendix A), during the study

E 24. Laboratory findings at the Screening Visit:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of the normal laboratory range (ULN)(1 repeat is allowed)*
- Total bilirubin >1.5 times the ULN (except in case of Gilbert's syndrome)
- Specific to India: HbA1c >10% (86 mmol/mol) (central laboratory); see Appendix F

One time rescreening is allowed at the Investigator's medical judgment for any manageable reasons that caused the Screening failure and if the patient is likely to be eligible before the enrollment completion.

*If a patient meets exclusion criteria E 16 or E 24, a one-time repeat testing is allowed for digoxin level, ALT, or AST without the need to rescreen the patient. Refer to Section 10.1.1 for details on rescreening. Further eligibility criteria for inclusion in the DXA sub-study are detailed in Appendix B.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCTS

The IMPs are sotagliflozin and matching placebo. Sotagliflozin will be supplied in 200-mg tablets. Patients will be provided with 70-tablet bottles of sotagliflozin 200-mg tablets or matching placebo. Each patient will be supplied with the appropriate number of bottles according to the dispensing scheme indicated in the study flow chart. Table 1 provides a summary of each IMP.

Table 1 - Investigational medicinal products

IMP:	Sotagliflozin	Placebo
Name of the IMPs	Sotagliflozin (SAR439954)	Placebo
Pharmaceutical form	Sotagliflozin (SAR439954) will be supplied as 200-mg tablets	Placebo will be supplied as tablets (identical to sotagliflozin in appearance)
Dose, timing and route of administration	1 or 2 200-mg tablets (depending on visit number and dose titration status[a]), taken orally once daily, before first meal of the day	1 or 2 tablets (depending on visit number and dose titration status[a]), taken orally once daily, before first meal of the day
Duration of treatment	The estimated study treatment duration will be approximately 27 to 51 months	The estimated study treatment duration will be approximately 27 to 51 months
Storage conditions at clinical site:	Store between +15°C and +30°C (59°F and 86°F)	Store between +15°C and +30°C (59°F and 86°F)
Storage conditions by patient:	Store between +15°C and +30°C (59°F and 86°F)	Store between +15°C and +30°C (59°F and 86°F)
Storage conditions (when not in use):	Store between +15°C and +30°C (59°F and 86°F)	Store between +15°C and +30°C (59°F and 86°F)

a Details of up-titration of IMP can be found in Section 8.1.1.1

IMP: investigational medicinal product

8.1.1 Dose up-titration and adjustments

8.1.1.1 Dose up-titration

Patients receive 200 mg sotagliflozin or matched placebo from Visit 2 (Day 1; Randomization) onwards. Unless there are safety concerns, the dose should be up-titrated to 400 mg sotagliflozin or matched placebo at Visit 3 (Week 4), or if not, then Visit 4 (Week 8) or Visit 5 (Week 26). Please see below for details.

If, at Visit 3 (Week 4), in the opinion of the Investigator the patient's clinical condition is satisfactory and the patient has tolerated the IMP well without evidence of dehydration, symptomatic hypotension (eg, dizziness, lightheadedness), or other AEs intolerable to the patient such as severe polyuria or nocturia, the dose will be increased to 400 mg of sotagliflozin or

matching placebo. If the Investigator chooses not to increase the dose of IMP for safety reasons (eg, hypotension), the Investigator may continue IMP at the 200 mg dose, with adjustment of the patient's concomitant medications, as needed. If the Investigator feels that it is not in the patient's best interest to continue IMP, the Investigator may discontinue IMP. Please note that IMP should be discontinued temporarily unless the criteria for permanent treatment discontinue have been met (see Section 10.3). If the dose is not up-titrated for safety reasons, all attempts will be made to up-titrate the dose at 1 of the next 2 subsequent visits: Visit 4 (Week 8) or, if not Visit 4, then Visit 5 (Week 26), if at all possible.

The 400 mg dose (or 200 mg in those who cannot tolerate up-titration by Visit 5) will be maintained for the duration of the remaining double-blind study treatment period.

8.1.1.2 Dose adjustments

If, at any time during the study, a patient does not tolerate 2 tablets of IMP qd (corresponding to sotagliflozin 400 mg or matching placebo), consideration should be given to reducing the dose to 1 tablet qd (corresponding to sotagliflozin 200 mg or matching placebo) prior to any decision to temporarily discontinue treatment if it is felt to be safe to do so according to the Investigator's judgment. In this case, the 200 mg dose will be maintained for the duration of the remaining double-blind study treatment period.

All IMP discontinuation should initially be considered as temporary unless permanent discontinuation is mandated by the protocol (see Section 10.3.3).

Guidelines for reinitiation of IMP after temporary discontinuation are described in Section 10.3.1.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCTS

There are no noninvestigational medicinal products in this study.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

To maintain blinding, sotagliflozin and placebo tablets and packaging will be blinded and indistinguishable.

During the double-blind Treatment period each treatment package will be labeled with a number, which is generated by a computer program from Sanofi. Investigators will not have access to the Randomization (treatment) code except under circumstances described in Section 8.3.2.

The Randomization and the treatment allocation will be performed centrally by an IRT. The study biostatistician provides the Randomization scheme to the IRT. Then, the IRT generates the patient Randomization list from which it allocates treatment to the patients.

The CEC will review and adjudicate events in a blinded manner.

Regular DMC safety analyses will be performed by an external independent statistical group and will be reviewed under the supervision of the DMC. The DMC will receive blinded by treatment group or unblinded confidential reports for review.

8.3.2 Randomization code breaking during the study

In case of an AE, the code must only be broken in circumstances when knowledge of the IMP is required for treating the patient.

Code breaking can be performed at any time by using the proper module of the IRT and/or by calling any other phone number provided by the Sponsor for that purpose. Code breaking can be performed by a local study Investigator, sponsor physician, or healthcare professional with direct responsibility for patient care. If the blind is broken, the Investigator must document the date, time of day, and reason for code breaking. The identity of the unblinded personnel, how the code was broken, and the treatment kit number should also be recorded. The Sponsor should also be informed when unblinding occurs, however note that when documenting the reason for unblinding, the Investigator must not provide any detail regarding the nature of the IMP. The Investigator should not divulge IMP detail to the Sponsor's representative or to any staff members until database (DB) closure. Furthermore, when completing forms (eg, AE, SAE, adjudication information), the study treatment should not be disclosed on the forms. If the code is broken by the Investigator (or other medical doctor in an emergency situation), the patient must be permanently withdrawn from IMP administration but shall continue to be followed in the study.

Refer to Section 10.5 for suspected unexpected serious adverse drug reaction unblinding by the Sponsor.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The randomized treatment kit number list will be generated centrally by Sanofi. The IMPs are packaged in accordance with this list.

Patients will be randomized to receive either sotagliflozin or placebo qd during the randomized Double-blind Treatment period. Randomization (ratio 1:1) will be stratified by region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) and by HF-related criteria (Yes/No; HF-related criteria is categorized as 'Yes' when a patient meets at least 1 of: EF ≤40% documented within the past year; hospitalization for HF during previous 2 years).

The randomization and the treatment package allocation are performed centrally by an IRT. At the Screening Visit the Investigator or designee has to contact the IRT to receive the patient number. [redacted] At Visit 2, once Screening results have been reviewed and all Baseline assessments are completed, if the patient is eligible for the study, the IRT is contacted for randomization and allocation of the treatment package.

For each randomized patient, the IRT will allocate a treatment package number corresponding to the treatment group assigned. After Visit 2, the IRT is contacted again each time new treatment package(s) allocation is required by the protocol. Treatment packages are allocated by the IRT using their treatment kit number.

A patient may not be enrolled in this study more than once (ie, being randomized twice). A patient can be rescreened once in case of manageable exclusion as deemed by the Investigator (see Section 10.1.1).

8.5 INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING

Packaging will be undertaken in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

The appropriate number of packages will be dispensed to ensure that the patient has enough IMP for daily administration up to the next dispensing visit (please refer to Section 1.2). Storage conditions and use-by-end date are part of the label text.

Treatment labels will indicate the treatment number (used for treatment allocation and reported in the electronic case report form [e-CRF]).

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of IMP storage conditions, especially control of temperature and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

The expiry date and storage conditions are written on the IMP labels. The IMP should be stored between +15°C and +30°C (59°F and 86°F).

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc.) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 10.4.8).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for direct-to-patient shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

Accountability and compliance for IMPs will be performed at Visit 3 and all subsequent on-site visits up to the Study Closeout Visit (or pEOT if patient prematurely permanently discontinues study treatment). Compliance will also be assessed during telephone visits.

Measures taken to ensure and document IMP compliance and accountability are described below:

- The Investigator or designee will obtain the treatment kit number(s) via IRT and he/she will dispense the treatment kit(s) to the patient
- The in-use, used, and unused bottle(s) should be brought back at all on-site visits for accounting purposes
- The Investigator or designee will complete the corresponding treatment log form
- The Investigator/study coordinator will enter data in the appropriate e-CRF pages, according to data recorded in the treatment log form
- The monitor will check data consistency according to the monitoring plan

If compliance is inadequate as determined by the Principal Investigator (PI), patients will be trained again and mentored.

8.7.2 Return and/or destruction of treatments

Patients are to return all IMP (in-use, used, and unused bottle[s]) at each on-site visit. At Visits 3 and 4 (Weeks 4 and 8), because no IMP resupply is planned during these visits, patients will be sent home after these visits with the in-use bottle(s) dispensed at Randomization.

Patients are to return all the used, in-use, and unused IMP at their Study Closeout Visit or pEOT Visit, as applicable.

A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy the in-use and unused IMP unless the Sponsor provides written authorization.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s).

All concomitant medications should be documented in the e-CRF. Additionally, all medications taken in the month prior to Visit 1 should be reported.

8.8.1 Antihyperglycemic concomitant medication

Antihyperglycemic therapy shall be unchanged for the first 12 weeks after Randomization. However, in cases of medical necessity, addition of antihyperglycemic therapy, dose adjustment or discontinuation of antihyperglycemic therapy can occur.

For patients with a Screening HbA1c <7.5% (58.5 mmol/mol) and treated with either insulin, glinide, or sulfonylurea, the doses of the glucose-lowering medications may be decreased at Randomization in order to prevent possible hypoglycemia.

After the first 12 weeks post Randomization and during the remaining Double-blind Treatment period, the management of glycemia will be left to the Investigator's and/or treating provider's judgment, informed by clinical guidelines and local/regional standards of care. The Investigator and/or treating provider will therefore be allowed to undertake appropriate action, ie,

- Adjust the dose of the background antihyperglycemic treatment
- Prescribe an additional antihyperglycemic medication according to its labeling (no SGLT2 inhibitor should be used)
- Remove an antihyperglycemic treatment

Specific to India: Rescue criteria for patients with uncontrolled hyperglycemia (see Appendix F).

Antihyperglycemic therapy is to be reported in the e-CRF.

8.8.2 Other concomitant medications

Concomitant medications such as antihypertensive medications, statins, and anti-platelet therapy should be used to manage risk factors per standard of care. Renin-angiotensin-aldosterone system inhibitors should be at optimal or maximally tolerated doses in accordance with the Investigator's and/or treating provider's judgment.

The dose of any concomitant RAAS inhibitors and beta-blockers should be collected at Baseline and at all study visits. For patients receiving RAAS inhibitors and/or beta blockers, the Investigator will need to confirm that patient is receiving the optimal or maximally tolerated dose, or otherwise record the reason for taking a lower dose.

During the double-blind study treatment period, the management of hypertension will be left to the Investigator's and/or treating provider's judgment, informed by clinical guidelines. For patients with a SBP <110 mmHg, at Randomization, the doses of the diuretic or other antihypertensive medication may be decreased in order to prevent possible hypotension. However,

all attempts should be made not to modify or discontinue the angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, which should be at optimum or maximally tolerated doses.

If clinically significant volume depletion occurs during co-administration of IMP with loop diuretics, or in vulnerable populations, consideration should be given to temporarily withhold IMP administration.

8.8.3 Forbidden concomitant medication

8.8.3.1 Prohibited Medications

During the study treatment period, the following medications are prohibited:

- Any SGLT2 inhibitor (other than IMP)
- Non-approved drug(s) (ie, investigational drugs) other than sotagliflozin

8.8.3.2 Other Medications

For patients who are taking digoxin, the Investigator has to consider if an adjustment of the dose level of coadministered digoxin is necessary because sotagliflozin acts as a weak P-glycoprotein (P-gp) inhibitor and increases systemic exposure to digoxin. Thus, sotagliflozin increases systemic exposure of digoxin. For the total study population in study LX4211.114, the geometric LS mean C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}\infty}$ for digoxin administered in the presence of steady-state sotagliflozin compared to digoxin administered alone were 51.9%, 31.1%, and 26.9% higher, respectively.

Patients taking sotagliflozin with concomitant digoxin should have digoxin concentrations monitored and doses reduced as needed. If digoxin treatment is being managed by another physician (ie, not the Investigator or Sub-investigator), he/she should be informed about this potential interaction. In patients treated with digoxin, digoxin levels should be measured at Screening and at Visit 3 (Week 4). Digoxin levels should be reassessed 2 to 4 weeks after an up-titration has been implemented (at an unscheduled visit, if indicated). If no up-titration is implemented, there is no requirement for digoxin level assessment beyond Visit 3. Throughout the study, additional digoxin plasma level assessments to be performed as per Investigators' judgment.

In addition, sotagliflozin could also increase the exposure of other P-gp substrates and the labels of P-gp substrate drugs should be consulted with regards to monitoring and dose adjustments.

Other medications which are unlikely to interfere with the pharmacokinetics or pharmacodynamics of the IMP or confound interpretation of the study endpoints are allowed as needed. However, doses of chronically administered medicines should be kept fixed during the trial if at all possible.

8.9 POST-STUDY TREATMENT

Because sotagliflozin may reduce BP, adjustment of antihypertensive medication may be needed during the study in patients with hypertension. Conversely, monitoring for an increase in BP should be performed after discontinuation of study treatment. If BP is elevated after withdrawal of study treatment, the Investigator should consider adding or adjusting antihypertensive medication.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 EFFICACY ENDPOINTS

9.1.1 Primary efficacy endpoints

- Time to the first occurrence of any of the following clinical events:
  - Cardiovascular death
  - Non-fatal MI
  - Non-fatal stroke
- Time to the first occurrence of any of the following clinical events:
  - Cardiovascular death
  - Hospitalization for heart failure

Selected CV and renal events assessed as endpoints will be adjudicated by the CEC (see Section 6.4.4).

Of note, suspected events according to the Investigator but not confirmed by the CEC will not be part of the primary efficacy outcome; their description will be provided separately.

9.1.1.1 Definitions of cardiovascular and renal components of efficacy endpoints (primary, secondary, and other)

Detailed outcome definitions are provided in a specific CEC Manual of Operations. Definitions of the CV endpoints will be consistently defined across the sotagliflozin project and therefore will be finalized before the DB lock of the first Phase 3 T2D study. Renal and other trial specific endpoints may be amended and updated during the course of the trial and will be finalized prior to the DB lock of the study.

9.1.2 Secondary efficacy endpoints

- Time to the first occurrence of any of the following clinical events in patients with Baseline eGFR ≥30 mL/min/1.73 m^2:
  - Sustained ≥50% decrease in eGFR from Baseline (for ≥30 days)
  - Chronic dialysis
  - Renal transplant
  - Sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days)
- Time to the first occurrence of any of the following clinical events in patients with Baseline eGFR ≥30 mL/min/1.73 m^2 and Baseline UACR ≥300 mg/g (34 mg/mmol):
  - Sustained ≥50% decrease in eGFR from Baseline (for ≥30 days)

- Chronic dialysis
- Renal transplant
- Sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days)

- Total number (ie, including recurrent events) of the following clinical events:
  - Cardiovascular death
  - Hospitalization for heart failure
  - Urgent HF visit (defined in Appendix E)
- Time to CV death
- Time to all-cause mortality

9.1.2.1 Estimated glomerular filtration rate and dialysis

Serum creatinine will be assessed as part of serum clinical chemistry at all on-site visits by central laboratory. Estimated glomerular filtration rate will be calculated by the central laboratory using the MDRD equation. The Baseline eGFR value for each patient will be the average of all values assessed by the central laboratory from Screening up to and including Randomization.

Patients 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. If acute renal failure is suspected, further clinical evaluation should be performed as per local standard of care, including confirmation of renal laboratory parameters, and consideration should be given to a nephrology referral.

9.1.3 Other efficacy endpoints

- Time to the first occurrence of any of the following clinical events in patients with Baseline eGFR ≥30 mL/min/1.73 m^2:
  - Sustained ≥50% decrease in eGFR from Baseline (for ≥30 days)
  - Chronic dialysis
  - Renal transplant
  - Sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days)
  - Cardiovascular death
  - Renal death
- Time to first occurrence of any CV death, non-fatal MI, non-fatal stroke, or unstable angina requiring hospitalization
- Time to worsening nephropathy in patients with Baseline eGFR ≥30 mL/min/1.73 m^2, defined as: new onset or progression to macro albuminuria (≥300 mg/g [34 mg/mmol]) accompanied by a UACR value increase of ≥30% from Baseline, or sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), or need for renal transplant, chronic dialysis, eGFR <15 mL/min/1.73 m^2 (for ≥30 days), or renal death

- Changes from Baseline to 6 months, 12 months, and 24 months in:
  - Hemoglobin A1c
  - Body weight
  - Blood pressure
  - Urinary albumin-to-creatinine ratio
  - Estimated glomerular filtration rate
  - Hematocrit
  - Hemoglobin
  - Albumin
  - Total protein
- Changes from Baseline to 6 months and 12 months in:
  - N-terminal pro-B-type natriuretic peptide
  - High sensitivity troponin T
  - High sensitivity C-reactive protein
- Proportion of patients who start insulin (who are not taking insulin at baseline)

9.1.3.1 Hemoglobin A1c

For the eligibility and efficacy assessments of the study, HbA1c is measured by a certified level I "National Glycohemoglobin Standardization Program" central laboratory to allow estimation of the change from Baseline in HbA1c.

9.1.3.2 Body weight

Body weight is measured at all on-site Visits. Height will be measured only at Screening.

Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder.

It is recommended that the same scale should be used throughout the study when possible.

9.1.3.3 Blood pressure

Sitting BP will be assessed at all on-site visits.

9.1.3.4 Urinary albumin-to-creatinine ratio

Urinary albumin-to-creatinine ratio will be collected at Screening and at all on-site visits. Further details are provided in Section 9.2.2.1.

9.1.3.5 Hematocrit, hemoglobin, albumin, and total protein

Hematocrit, hemoglobin, albumin, and total protein are collected as described in Section 9.2.2.

9.1.3.6 Antihyperglycemics

All antihyperglycemics are collected as described in Section 8.8.1. Details of the analysis will be included in the Statistical Analysis Plan (SAP).

9.2 SAFETY ENDPOINTS

- All AEs including adverse events of special interest (AESIs), events of special interest (EOSIs), and SAEs
- Severe hypoglycemia (also an EOSI)
- Clinical laboratory results and vital signs (including heart rate, BP)
- For patients in the DXA sub study, change from Baseline in:
  - Bone mineral density (BMD)
  - The following markers of bone and calcium metabolism: serum and urinary calcium; serum 25-hydroxyvitamin D; serum 1,25 dihydroxyvitamin D; serum and urinary phosphorus, serum parathyroid hormone (PTH); serum N telopeptide of type 1 collagen (NTX); serum β-C-terminal telopeptide of type 1 collagen (β-CTX 1); serum N-terminal propeptide of type 1 procollagen (P1NP); serum magnesium

Safety observation periods are as defined in Section 11.4.3.1.

9.2.1 Adverse events, adverse events of special interest, and events of special interest

Adverse events including SAEs, AESIs, and EOSIs will be assessed. Refer to Section 10.4 to Section 10.7 for details.

All AEs will be collected starting from signing informed consent. The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until stabilization, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.

9.2.1.1 Adverse events of special interest

Adverse events of special interest are listed in Section 10.4.1.3, reporting requirements for AESIs are presented in Section 10.4.5.

9.2.1.2 Events of special interest

Events of special interest are separate from AESIs. For a list of events defined as EOSIs and their reporting requirements see Section 10.4.1.4 and Section 10.4.6, respectively.

9.2.2 Laboratory safety variables

The clinical laboratory data consist of blood analyses (including hematology, clinical chemistry, and lipids) and urinalysis (including dipstick and reflexive microscopy and culture, as applicable). Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables. Table 2 lists the hematology, clinical chemistry, and other blood safety parameters to be assessed by the central laboratory. The schedule for assessment of clinical laboratory data is shown in Section 1.2.

Pregnancy tests will be performed for WOCBP at all on-site visits (except the Follow-up Visit). Serum pregnancy testing is only performed at Screening; urine pregnancy testing subsequently. Any positive urine test results must be confirmed based on serum pregnancy test. The Investigator may perform additional tests at their discretion or as required by local regulations.

Table 2 - Chemistry parameters

Serum clinical chemistry	Serum hematology	Serum lipid profile	Plasma digoxin
Sodium	Complete blood count (CBC)	Total cholesterol (TC)	Plasma digoxin (if applicable)[a]
Potassium	White blood cell count with differential	High-density lipoprotein cholesterol (HDL-C)	
Chloride	Platelet count	Low-density lipoprotein cholesterol (LDL-C) will be calculated by Friedwald equation	
Carbon dioxide (bicarbonate)	Hemoglobin	Non-HDL-C (calculated as the difference between TC and HDL-C)	
Blood urea nitrogen (BUN)	Hematocrit	Triglycerides (TG)	
Creatinine (eGFR will be calculated)[b]			
Glucose (serum)			
Alanine aminotransferase (ALT)			
Aspartate aminotransferase (AST)			
Total bilirubin (TB)			
Alkaline phosphatase (ALP)			
Uric acid			
Calcium			

Serum clinical chemistry	Serum hematology	Serum lipid profile	Plasma digoxin
Phosphorus			
Total protein			
Albumin			
Magnesium			
Creatine phosphokinase (CPK)			
Lactic acid dehydrogenase (LDH)			

All assessment measured in serum except, if applicable, plasma digoxin assessment.

a In patients treated with digoxin, digoxin levels should be measured at Screening and at Visit 3 (Week 4). Digoxin levels should be reassessed 2 to 4 weeks after an up-titration has been implemented (at an unscheduled visit, if indicated). If no up-titration is implemented, there is no requirement for digoxin level assessment beyond Visit 3. Throughout the study, additional digoxin plasma level assessments to be performed as per Investigators' judgment. If applicable, plasma digoxin assessment should be performed via a local laboratory.

b Estimated glomerular filtration rate (eGFR) will be calculated by the Modification of Diet in Renal Disease (MDRD) equation.

9.2.2.1 Urinalysis

A urine dipstick will be performed by the central laboratory and will include assessment of specific gravity, pH, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase.

If the urine dipstick is positive for nitrite and leukocyte esterase, the central laboratory will perform reflexive testing to include microscopy and urine culture (microscopy includes detection of formed cellular elements, casts, bacteria, yeast, parasites, and crystals in centrifuged urine sediment). If additional testing is needed it will be performed according to the judgment of the Investigator. Referral to urology/urologic evaluation is recommended for recurrent urinary tract infections despite appropriate use of antibiotics.

If the urine dipstick is positive for blood, the central laboratory will perform reflexive testing to include microscopy. Additional testing will be performed according to the judgment of the Investigator. Referral to urology/urologic evaluation is recommended for new or unexplained cases of confirmed hematuria (urology/urologic evaluation is not required where hematuria is considered to be related to diabetic nephropathy).

Screening UACR will be measured by spot urine and will be assessed throughout the study. The Baseline UACR value for each patient will be the average of all values assessed by the central laboratory from Screening up to and including randomization.

If the Screening UACR is <300 mg/g (34 mg/mmol), but >100 mg/g (11 mg/mmol), then a 24-hour urine collection for measurement of UACR will be performed.

24-hour urine collection will also be performed for patients in the DXA sub-study.
See Appendix B for further details.

9.2.2.2 Markers of bone and calcium metabolism

Samples for markers of bone and calcium metabolism will be collected as part of the DXA sub-study. See Appendix B for details.

9.2.3 Vital signs and physical exam

Vital signs (sitting BP and heart rate) measurements will be made at every on-site visit.

General physical examinations will be performed according to the schedule in Section 1.2. Examination of the lower extremities to evaluate for any evidence of foot ulcers or infection should be performed as part of the general physical examination. Lower extremity complications (such as skin ulcers, infection, osteomyelitis, and gangrene) requiring treatment should lead to temporary discontinuation of IMP.

9.2.4 Electrocardiogram variables

A 12-lead ECG record is performed locally at Randomization (Visit 2), the pEOT Visit (if patient prematurely discontinues study treatment), and the Study Closeout Visit. The 12-lead ECG should be performed after at least 10 minutes in the supine position and be obtained at Randomization prior to first dose of double-blind IMP.

The ECGs will be interpreted locally by the Investigator. Any clinically significant abnormality should be documented as medical history, an AE/SAE or endpoint as applicable (see Section 10.4). All ECG traces will be kept as source data.

9.2.5 Severe hypoglycemia

Severe hypoglycemia will be collected from signature of the informed consent and continue until the Follow-up Visit (or Study Closeout Visit, for patients who prematurely permanently discontinued from IMP). See Section 10.6.1 for the definition of severe hypoglycemia.

Patients will be asked whether they have experienced any signs/symptoms consistent with an episode of severe hypoglycemia during all on-site and telephone visits. Patients will be asked to report any episodes of severe hypoglycemia to the site immediately, and not wait for the next scheduled visit.

Episodes of non-severe hypoglycemia should be reported as standard AEs, if the episode of hypoglycemia meets the criteria for AE reporting.

9.2.6 Change in bone mineral density

Patients in the DXA sub-study will have the change from Baseline in BMD assessed. See Appendix B for details.

9.3 OTHER ENDPOINTS

9.3.1 Health economic variables

An analysis of health care utilization, including HHF and urgent HF visit, will be described and reported in a separate document(s).

[redacted]

[redacted]

9.5 APPROPRIATENESS OF MEASUREMENTS

As explained in Section 4, the first primary endpoint of 3-point MACE is in concordance with appropriate FDA guidance (*2008 FDA Guidance for Industry: Diabetes Mellitus- Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*; 35). The second primary endpoint is of interest to prospectively evaluate the potential benefit of sotagliflozin on HF and CV death, 2 important clinical events in patients with T2D that have been shown previously to be influenced by SGLT2 inhibition (20). If NI of sotagliflozin is met on 3-point MACE, superiority will also be assessed.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The visit schedule and procedures/assessments are listed in the "Study Flow Chart" (Section 1.2). The aim of this section is to provide details on how some of the procedures/assessments should be performed.

This is an outpatient study that consists of 5 on-site visits in the first 6 months. Subsequently, on-site visits are every 6 months until the Study Closeout Visit. Additionally, in between each on-site visit, starting with Visit 5, patients will be contacted by phone twice at 9-week intervals (ie, 9 weeks after the on-site visit and again 18 weeks after the on-site visit) to collect endpoint events, IMP administration information, and safety data. If occurrence of a renal event is suspected at a telephone visit, arrangements should be made for the patient to attend an unscheduled on-site visit to confirm.

The visit windows for Visit 3 and Visit 4 are ±3 days and ±7 days, respectively. The window for all subsequent visits is ±10 days. Patients still taking the IMP at the time of the Study Closeout Visit (ie, who have not prematurely permanently discontinued IMP) will have their final study visit (Follow-up Visit) 14 days (±4 days) after their Study Closeout Visit.

If 1 visit date is changed, the next visit should occur according to the original schedule, ie, calculated from the date of the Randomization Visit (Visit 2, Day 1).

All data obtained during the trial visits are reviewed by the Investigator and/or Sub-investigators who are qualified in the treatment of T2D and are trained on the study.

10.1.1 Screening period

The Screening period will be 1 to 4 weeks in duration, and includes Visit 1 (up to Week -4). It must be long enough to collect the data required to establish whether the patient satisfies the inclusion/exclusion criteria.

Patients will undergo Screening assessments at Visit 1 following signing of the ICF. Patients who meet the inclusion criteria as noted in Section 7.1 and have no exclusion criteria as noted in Section 7.2, will be randomized at Visit 2 (Day 1).

In cases where a patient fails Screening due to reasons expected to change upon rescreening based on the Investigator's clinical judgment, the patient can be rescreened once. In these cases, the patient should be registered as a screen failure in IRT. The patient will then need to sign a new ICF, be registered as a rescreen in IRT and assigned a new patient number, and again complete Screening Visit procedures/assessments.

10.1.1.1 On-site Visit 1 (Week -4) Screening Visit

The following procedures/assessments will be performed at Visit 1 (up to Week -4):

- Obtaining the informed consent (for main study and those for [redacted] and [at sites participating in sub-study] DXA sub-study):
  - The patient will receive verbal information concerning the aims and methods of the study, its constraints and risks, and the study duration. Written information will be provided to the patient. Written informed consent must be signed by the patient and Investigator or delegate prior to any investigations
  - Written informed consent must be obtained prior to any additional corresponding sample collections/assessments for [redacted], the DXA sub-study, [redacted]
- Assessment of all inclusion/exclusion criteria
- Collection of demographic data (age, gender, race, and ethnicity; as allowed per local regulations)
- Collection of contact information (address, email, home, and cell phone number) for patient, patient's family and patient's general practitioner (GP)/cardiologist/diabetologist/nephrologist (as applicable, to be recorded in source documents)
- Assessment of the patient's complete medical and surgical history: to include history of T2D, CV disease/risk factors, an assessment of the patient's family history of premature coronary heart disease, and history of smoking/tobacco and alcohol use; postmenopausal history (for women)
- For WOCBP, contraceptive measures will be reviewed
- Measurement of body height and weight
- Vital signs (sitting BP, heart rate) and a general physical examination
- IRT to be contacted (for allocation of patient ID, registration of Screening)
- Prior and concomitant medications, including for 1 month prior to Screening
- The following laboratory testing:
  - HbA1c
  - Hematology
  - Chemistry (including eGFR)
  - Serum pregnancy testing for WOCBP
  - Urinalysis (dipstick) and UACR
  - NT-proBNP, hsTnT, and hsCRP (**ALL** patients **MUST** have these biomarkers assessed)
  - 24-hour urine albumin if needed for eligibility purposes, see Section 9.2.2.1

- The following laboratory testing (by local laboratory):
  - Plasma digoxin (if applicable, see Section 9.2.2)
- The following tests may be performed if needed:
  - 24-hour urine collection for all patients with UACR at screening >100 and <300 mg/g (11 and 34 mg/mmol; see Section 7.1)
  - Echocardiogram in all patients if an EF has not been documented in previous year
  - Cardiac CT for CAC if needed to meet eligibility criteria but not previously documented (see Section 7.1)

    Note: If a patient has a diagnosis of T2D, age ≥18 years, a HbA1c ≥7% (53 mmol/mol), and an eGFR ≥25 and ≤60 mL/min/1.73 m^2, and does not have either 1 major or 2 minor risk factors based upon available information, additional testing (echocardiogram and/or coronary artery CT scan) **MAY** be ordered. If both tests are needed to meet I 04, they can be ordered at the same time.
    Specific to India: HbA1c ≥7% (53 mmol/mol) to ≤10% (86 mmol/mol) (central laboratory); see Appendix F.
- For patients participating in the DXA sub-study:
  - A sample will be taken for 25-hydroxyvitamin D
  - 24-hour urine collection will need to be scheduled during Screening/prior to the Randomization Visit (Visit 2) (see Appendix B)
  - A DXA scan will need to be scheduled during Screening/prior to the Randomization Visit (Visit 2) for eligibility assessment (see Appendix B)
  - Specific for Canada and USA: To remind patients to fast prior to Visit 2 (see Appendix F)

    Note: If a patient has had a BMD value documented within the last year and the T-score is not <-2.0 at any site the patient may proceed to Randomization prior to receiving the results of the BMD value performed during Screening.
- An appointment will be made for Visit 2

10.1.2 Randomized Double-blind Treatment period

The randomized Double-blind Treatment period starts at Visit 2 (Day 1, Randomization) and continues until the Study Closeout Visit. Patients will continue with IMP treatment after a CV or renal endpoint occurs unless they have prematurely permanently discontinued treatment or the criteria for permanent treatment discontinuation have otherwise been met. Whether taking IMP or not, patients will continue to be followed after a CV or renal endpoint occurs.

Guidance for dose increases (Visits 3 to 5) and other dose adjustments can be found in Section 8.1.1.1, Section 8.1.1.2, and Section 10.3.1.

Study Closeout Visit procedures will differ for patients who do not prematurely permanently discontinue IMP and those who do prematurely permanently discontinue IMP (see Section 10.1.4.1 and Section 10.1.4.2, respectively).

Endpoint events, severe hypoglycemic episodes, and other AEs should be captured at each patient contact, including questioning the patient about any lower extremity abnormalities (such as, sores/ulcers or infections). Lower extremity complications (such as skin ulcers, infection, osteomyelitis, and gangrene) requiring treatment should lead to temporary discontinuation of IMP. Patients 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. If acute renal failure is suspected, further clinical evaluation should be performed as per local standard of care, including confirmation of renal laboratory parameters, and consideration should be given to a nephrology referral.

10.1.2.1 On-site Visit 2 (Day 1) Randomization

The following procedures/assessments will be performed at Visit 2 (Day 1):

- Review of inclusion/exclusion criteria
- Measurement of body weight
- Vital signs (sitting BP, heart rate)

AEs, including SAEs/AESIs/EOSIs (including severe hypoglycemia) and endpoint events (if any) are collected (if a renal endpoint relating to a reduction in eGFR is suspected, see Section 9.1.2.1)

- Concomitant medications are assessed
  - It is **critical** that background medications at time of Randomization are accurately and fully captured
  - The dose of any concomitant RAAS inhibitors and beta-blockers should be collected **at Baseline and at all study visits**. Where patients are receiving RAAS inhibitors and/or beta-blockers at lower than the optimal or maximally tolerated dose, the reason for this should also be recorded.
- Contact information is reviewed and updated if needed (address, email, home, and cell phone number) for patient, patient's family and patient's GP/cardiologist/diabetologist/nephrologist (as applicable, to be recorded in source documents)
- 12-lead ECG, prior to IMP administration
- The following laboratory testing; prior to IMP administration:
  - Chemistry (including eGFR)
  - Lipids
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
  - Urinalysis (dipstick) and UACR

- [redacted]
- [redacted]

- IRT to be contacted and Randomization will occur if the patient is eligible for the study
- IMP is dispensed
- For patients at sites participating in the DXA sub-study who have consented to, and are eligible for, DXA sub-study:
  - Markers of bone and calcium metabolism (see Appendix B for details). Specific to Canada and USA: Fasting markers (see Appendix F)
- An appointment for Visit 3 will be made; for accountability and compliance purposes, patients are instructed to return to the site with their unused, in-use and empty bottle(s) at Visit 3

10.1.2.2 On-site Visit 3 (Week 4)

The following procedures/assessments will be performed at Visit 3 (Week 4):

- Measurement of body weight
- Vital signs (sitting BP, heart rate)
- IMP accounting and compliance
- AEs, including SAEs/AESIs/EOSIs (including severe hypoglycemia) and endpoint events (if any) are collected (if a renal endpoint relating to a reduction in eGFR is suspected, see Section 9.1.2.1)
- Concomitant medications are assessed
- Contact information is reviewed and updated if needed (address, email, home, and cell phone number) for patient, patient's family and patient's GP/cardiologist/diabetologist/nephrologist (as applicable, to be recorded in source documents)
- The following laboratory testing:
  - Chemistry (including eGFR)
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
  - Urinalysis (dipstick) and UACR
- The following laboratory testing (by local laboratory):
  - Plasma digoxin (if applicable, see Section 9.2.2)
- Where possible, the dose may be increased to 2 tablets qd (sotagliflozin 400 mg or matching placebo). See Section 8.1.1.1
- An appointment for Visit 4 will be made; for accountability and compliance purposes, patients are instructed to return to the site with their unused, in-use and empty bottle(s) at Visit 4

10.1.2.3 On-site Visit 4 (Week 8)

The following procedures/assessments will be performed at Visit 4 (Week 8):

- Measurement of body weight
- Vital signs (sitting BP, heart rate)
- IMP accounting and compliance
- AEs, including SAEs/AESIs/EOSIs (including severe hypoglycemia) and endpoint events (if any) are collected (if a renal endpoint relating to a reduction in eGFR is suspected, see Section 9.1.2.1)
- Concomitant medications are assessed
- Contact information is reviewed and updated if needed (address, email, home, and cell phone number) for patient, patient's family and patient's GP/cardiologist/diabetologist/nephrologist (as applicable, to be recorded in source documents)
- The following laboratory testing:
  - Chemistry (including eGFR)
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
  - Urinalysis (dipstick) and UACR
- The following laboratory testing (by local laboratory):
  - Plasma digoxin (if applicable, see Section 9.2.2)
- If the dose was not increased to 2 tablets qd (sotagliflozin 400 mg or matching placebo) at Visit 3 a dose increase should be performed if the Investigator feels that it is safe to do so; see Section 8.1.1.1
- An appointment for Visit 5 will be made; for accountability and compliance purposes, patients are instructed to return to the site with their unused, in-use and empty bottle(s) at Visit 5

10.1.2.4 On-site Visit 5 (Week 26), and all subsequent on-treatment, on-site visits

The following procedures/assessments will be performed (except when noted) at on-site Visits 5 (Week 26), 8 (Week 52), 11 (Week 78), 14 (Week 104), 17 (Week 130), 20 (Week 156), 23 (Week 182), and 26 (Week 208) up until the end of study:

- Measurement of body weight
- Vital signs (sitting BP, heart rate)
- General physical exam (Visits 8 [Week 52], 14 [Week 104], 20 [Week 156], 26 [Week 208], and every other on-site, on-treatment visit thereafter)
- IRT contact for IMP resupply

- IMP is dispensed
- IMP accounting and compliance
- AEs, including SAEs/AESIs/EOSIs (including severe hypoglycemia) and endpoint events (if any) are collected (if a renal endpoint relating to a reduction eGFR is suspected, see Section 9.1.2.1)
- Concomitant medications are assessed
- Contact information is reviewed and updated if needed (address, email, home, and cell phone number) for patient, patient's family and patient's GP/cardiologist/diabetologist/nephrologist (as applicable, to be recorded in source documents)
- The following laboratory testing:
  - HbA1c
  - Hematology
  - Chemistry (including eGFR)
  - Lipids (Visits 8 [Week 52], 14 [Week 104], 20 [Week 156], and 26 [Week 208], and every other on-site, on-treatment visit thereafter)
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
  - Urinalysis (dipstick) and UACR
  - NT-proBNP, hsTnT, and hsCRP (Visits 5 [Week 26] and 8 [Week 52] only)
  - [redacted]
- The following laboratory testing (by local laboratory):
  - Plasma digoxin after Visit 5 (Week 26), if applicable (see Section 9.2.2)
- **Study treatment dose <u>at Visit 5 only</u>**: if the dose was not increased to 2 tablets qd (sotagliflozin 400 mg or matching placebo) at Visit 3 or 4, a dose increase should be performed if the Investigator feels that it is safe to do so, see Section 8.1.1.1
- An appointment for the next on-site visit will be made; for accountability and compliance purposes, patients are instructed to return to the site with their unused, in-use and empty bottle(s) at the next on-site visit

10.1.2.5 Telephone visits

Visits 6 (Week 35) and 7 (Week 44) are telephone visits held 9 and 18 weeks after Visit 5 (Week 26), respectively. Subsequently, 2 telephone visits (with visit windows of ±10 days) will be held in each 26-week period between on-site visits, 9 and 18 weeks after each on-site visit until the Study Closeout Visit.

If a potential CV or renal event is identified during a telephone visit, arrangements should be made for the patient to attend an unscheduled on-site visit to further evaluate/confirm, when possible.

The following procedures/assessments will be performed at telephone visits:

- AEs, including SAEs/AESIs/EOSIs (including severe hypoglycemia) and endpoint events (if any) are collected (if a renal endpoint relating to a reduction in eGFR is suspected, see Section 9.1.2.1)
- Concomitant medications are assessed
- IMP compliance
- Contact information is reviewed and updated if needed (address, email, home, and cell phone number) for patient, patient's family and patient's GP/cardiologist/diabetologist/nephrologist (as applicable, to be recorded in source documents)
- For accountability and compliance purposes, patients are instructed to return to the site with their unused, in-use and empty bottle(s) at their next on-site visit

10.1.3 Premature End-of-Treatment

Patients who prematurely permanently discontinue IMP will attend a pEOT Visit as soon as possible. These patients will be asked to continue in the study, attending scheduled visits, if at all possible until the end of the study, and will continue to be followed after a CV or renal endpoint occurs.

If the patient does not agree to on-site visits, he/she will be contacted by telephone to inquire about safety status (including hospitalizations and outcomes). Every effort should be made to collect endpoint information and vital status at least once a year and at the time of Study Closeout.

If a patient refuses to continue in the study after premature IMP discontinuation, and the pEOT Visit is <10 days after the last IMP administration, see Section 10.3.2 for guidance.

10.1.3.1 Premature End-of-Treatment Visit

The following procedures/assessments will be performed at the pEOT Visit for patients who prematurely permanently discontinue study treatment:

- Measurement of body weight
- Vital signs (sitting BP, heart rate) and physical examination
- IRT contacted for end of treatment
- IMP accounting and compliance
- AEs, including SAEs/AESIs/EOSIs (including severe hypoglycemia) and endpoint events (if any) are collected (if a renal endpoint relating to a reduction in eGFR is suspected, see Section 9.1.2.1)

- Contact information is reviewed and updated if needed (address, email, home, and cell phone number) for patient, patient's family and patient's GP/cardiologist/diabetologist/nephrologist (as applicable, to be recorded in source documents)
- Concomitant medications are assessed
- 12-lead ECG
- The following laboratory testing:
  - HbA1c
  - Hematology
  - Chemistry (including eGFR)
  - Lipids
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
  - Urinalysis (dipstick) and UACR
  - NT-proBNP, hsTnT, and hsCRP (**only** if pEOT occurs before Visit 8 [Week 52])
  - [redacted]
- For patients at participating sites who are participating in the DXA sub-study:
  - DXA scan
  - Markers of bone and calcium metabolism (including 24-hour urine collection; see Appendix B for full list). Specific for Canada and USA: Fasting markers (see Appendix F)
- An appointment for the next on-site visit will be made (patients should, if possible, continue with scheduled visits until end of study)

10.1.4 Study Closeout

All randomized patients will be asked to return to the study site for a Study Closeout Visit when approximately 844 primary CV events of CV death or HHF and approximately 1189 3-point MACE are positively adjudicated. The timing and window of this visit will be communicated to sites once the date the required number of events are projected to be positively adjudicated has been determined. For patients who previously prematurely permanently discontinued IMP, the Study Closeout Visit will be the final study visit and no further visits are planned (see Section 10.1.4.1 and Section 10.1.4.2, respectively).

10.1.4.1 Study Closeout Visit for patients who do not prematurely permanently discontinue investigational medicinal product

The following procedures/assessments will be performed at the Study Closeout Visit for patients who do not prematurely permanently discontinue IMP:

- Measurement of body weight
- Vital signs (sitting BP, heart rate) and physical examination
- IRT contacted for end of treatment
- IMP accounting and compliance
- AEs, including SAEs/AESIs/EOSIs (including severe hypoglycemia) and endpoint events (if any) are collected (if a renal endpoint relating to a reduction in eGFR is suspected, see Section 9.1.2.1)
- Contact information is reviewed and updated if needed (address, email, home, and cell phone number) for patient, patient's family and patient's GP/cardiologist/diabetologist/nephrologist (as applicable, to be recorded in source documents)
- Concomitant medications are assessed
- 12-lead ECG
- The following laboratory testing:
  - HbA1c
  - Hematology
  - Chemistry (including eGFR)
  - Lipids
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
  - Urinalysis (dipstick) and UACR
- For patients at participating sites who are participating in the DXA sub-study:
  - DXA scan
  - Markers of bone and calcium metabolism (see Appendix B for full list). Specific for Canada and USA: Fasting markers (see Appendix F)
- An appointment for the Follow-up Visit will be made

10.1.4.2 Study Closeout Visit for patients who prematurely permanently discontinue investigational medicinal product

The following procedures/assessments will be performed at the Study Closeout Visit for patients who prematurely permanently discontinue IMP:

- Measurement of body weight
- Vital signs (sitting BP, heart rate) and physical examination
- IRT contacted for end of study
- AEs, including SAEs/AESIs/EOSIs (including severe hypoglycemia) and endpoint events (if any) are collected (if a renal endpoint relating to a reduction in eGFR is suspected, see Section 9.1.2.1)
- Concomitant medications are assessed
- 12-lead ECG
- The following laboratory testing:
  - HbA1c
  - Hematology
  - Chemistry (including eGFR)
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
  - Urinalysis (dipstick) and UACR

10.1.5 Follow-up

Patients still taking the IMP at the time of the Study Closeout Visit (ie, who have not prematurely permanently discontinued IMP) will have their final study visit (Follow-up Visit) 14 days (±4 days) after their Study Closeout Visit.

10.1.5.1 Follow-up Visit

Patients who have attended a pEOT Visit do **not** need to attend this Visit. The following procedures/assessments will be performed at this Visit:

- Measurement of body weight
- Vital signs (sitting BP, heart rate)
- AEs, including SAEs/AESIs/EOSIs (including severe hypoglycemia) and endpoint events (if any) are collected (if a renal endpoint relating to a reduction in eGFR is suspected, see Section 9.1.2.1)
- The following laboratory testing:
  - Estimated glomerular filtration rate

  - Hemoglobin/hematocrit
  - Albumin
  - Total protein
- IRT contacted for end of study

10.2 DEFINITION OF SOURCE DATA

Evaluations recorded in the e-CRF must be supported by appropriately signed source documentation related but not limited to the following:

- Agreement and signature of ICF with the study identification
- Study identification (name)
- Patient number, confirmation of randomization, treatment batch number, dates and doses of study treatment administration
- Medical, surgical, diabetes history, including information on:
  - Demography, inclusion and exclusion criteria
  - Last participation in a clinical trial
  - Contraception method for WOCBP
  - Previous and concomitant medication
- Dates and times of visits and assessments including examination results
- Vital signs, height, body weight, laboratory reports, investigation results (eg, ECG traces, imaging reports)
- Adverse events and follow-up:
  - In case of AESI/SAE, the site should file in the source documents at least copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the SAE
- In case of endpoint events, the site should file in the source documents at least copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the event
- Date of premature treatment discontinuation (if any) and reason
- Date of premature study discontinuation (if any) and reason
- Nursing notes
- Dietician’s notes
- Physician’s notes

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the e-CRF. In any case, the patient should remain in the study and followed for the remainder of the study duration to collect vital safety status and endpoint data. Where the patient is taking 2 tablets of IMP qd (corresponding to sotagliflozin 400 mg or matching placebo), consideration should be given to reducing the dose to 1 tablet of IMP qd (corresponding to sotagliflozin 200 mg) prior to temporary treatment discontinuation (see Section 8.1.1.2). In this case, the 200 mg dose will be maintained for the duration of the remaining double-blind study treatment period.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

All IMP discontinuation should initially be considered as temporary unless permanent discontinuation is mandated by the protocol (see Section 10.3.3), and the Investigator should make best effort to resume IMP treatment as early as practically possible. There is no defined limit to the duration of temporary discontinuation.

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Lower extremity complications (such as skin ulcers, infection, osteomyelitis, and gangrene) requiring treatment should lead to temporary discontinuation of IMP.

Reinitiation of treatment with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator is satisfied that, according to his/her best medical judgment, the IMP was unlikely to be responsible for the event concerned.

Temporary discontinuation of IMP due to intolerance should be followed by reinitiation of 1 tablet of IMP qd (sotagliflozin 200 mg/matching placebo). Temporary discontinuation for any other reason should be followed by reinitiation of IMP at the last dose tolerated prior to discontinuation where possible.

For all confirmed temporary treatment discontinuations, the start date and end date of the period with no IMP treatment should be recorded by the Investigator in the appropriate pages of the e-CRF. Additionally, temporary discontinuation should be recorded in the IRT.

Patients who temporarily discontinue IMP should be reassessed at every visit to determine whether it is possible to safely resume IMP. If a decision has been made that the discontinuation is permanent, then the patient should be considered as permanently discontinued and the corresponding e-CRF page should be completed. Please note that permanent discontinuation should be a last resort.

Temporary treatment discontinuation corresponds to more than 1 dose not administered to the patient as decided by the Investigator.

10.3.2 Permanent treatment discontinuation with investigational medicinal product

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator not to re-expose the patient to the IMP at any time during the study, or from the patient not to be re-exposed to the IMP whatever the reason.

If a patient refuses to continue in the study after premature IMP discontinuation, and the pEOT Visit is <10 days after the last IMP administration, then every effort should be made to secure a follow-up contact is performed at least 14 days (±4 days) after the last IMP intake with procedures normally performed at the Follow-up Visit (see Section 10.1.5.1). If the patient does not agree to on-site visits, he/she will be contacted by telephone to inquire about safety status (including hospitalizations and endpoints). Every effort should be made to collect endpoint information and vital status at least once a year and at the time of Study Closeout.

If after permanent treatment discontinuation, a patient who has withdrawn consent for treatment has reconsidered the decision to permanently discontinue treatment and wishes to later resume IMP, and if the Investigator has determined there is no safety reason prohibiting the patient from resuming IMP and the selection criteria for the study are still met, the patient may resume IMP with Sponsor approval.

10.3.3 List of criteria for permanent treatment discontinuation

Patients may withdraw from treatment with the IMP at any time for any reason or this may be the Investigator's decision. Patients should discuss stopping study medication with the site before doing so in order that questions can be addressed, concomitant therapy can be adjusted if needed, and a follow-up assessment arranged. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

Patients who report a CV or renal endpoint as described in Section 10.4.2 should remain on IMP until the end of the study, unless there is a safety concern.

The following reasons shall lead to permanent IMP discontinuation:

- At the patient's own request (ie, withdrawal of consent for treatment) (note that this is regardless of whether or not the patient continues in the study)
- If, in the Investigator's opinion, continuation with the administration of the study treatment would be detrimental to the patient's well-being
- Pregnancy (in female patients)
- Any code breaking requested by the Investigator
- Specific request of the Sponsor
- Patient requires dialysis or renal transplantation
- Estimated glomerular filtration <15 mL/min/1.73 m^2

Note: the central laboratory will alert the Investigator for eGFR values <15 mL/min/1.73 m^2. A repeat determination should be performed within 2 weeks, and study treatment discontinued if the repeat eGFR is <15 mL/min/1.73 m^2 (unless a reversible cause is identified [eg, short-term illness or transient volume depletion], in which case an additional repeat determination can be performed after resolution of the short-term illness).

Any abnormal laboratory value will be immediately rechecked for confirmation before making a decision to permanently discontinue IMP for the concerned patient.

10.3.4 Handling of patients after permanent treatment discontinuation

Every effort should be made to maintain patients in the study. All patients will be followed until the last visit according to the study procedures specified in this protocol, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last. The scientific value of the complete collection of data will be explained to patients, and site personnel will receive training regarding strategies for patient retention, and access to tools to assist with this during the study.

For patients who prematurely permanently discontinue the IMP, a pEOT Visit (see Section 10.1.3) will be scheduled as soon as possible after time of discontinuation (the latest at the next on-site visit). The reason for the IMP discontinuation shall be clearly specified.

For patients who discontinue IMP but remain in the study, the remaining visits should occur as scheduled where possible. All efforts should be made to continue to follow the patients for primary and secondary endpoints, after the discontinuation of treatment.

All cases of permanent treatment discontinuation must be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

Patients participating in the DXA sub-study shall continue participation in the sub-study if they permanently discontinue IMP; their final DXA scan should be performed at the pEOT Visit.

10.3.5 Procedure and consequence for patient withdrawal from study

Patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason without any effect on their care. However, if patients no longer wish to take the IMP, they will be encouraged to remain in the study and attend the remaining visits.

The Investigators should discuss with them key visits to attend. The value of critical study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Patients who withdraw from the study treatment should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals must be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a patient may withdraw his/her consent to stop participating in the study. Withdrawal of consent for treatment (ie, treatment discontinuation at patient request) should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

For patients who fail to return to the site or otherwise withdraw from the study, unless the patient withdraws consent for follow-up, the Investigator must make the best effort to re-contact the patient (eg, contact patient's family or private physician, review available registries, or health care DBs) to determine the patient's health status, including at least his/her vital status (including time of death). Attempts to contact such patients (3 phone call attempts followed by a certified letter) must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter). If a patient withdraws consent for follow-up, the Investigator should still make best efforts to determine the patient's health status, including at least his/her vital status (including time of death), where permitted by local regulations. The patient's final vital status will be confirmed at the time of the study close-out visit.

Patients who have withdrawn from the study cannot be rerandomized in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. Cardiovascular and renal efficacy endpoints, and their components, specified in this study (as per Section 10.4.2) will not generally be considered as AEs, and will be waived from expedited reporting to Health Authorities, Investigators, institutional review boards (IRBs)/independent ethics committees (IECs), etc. For further details please refer to Section 10.4.2.

10.4.1.2 Serious adverse event

A **serious adverse event** (SAE) is any untoward medical occurrence (with the exception of those events waived as efficacy endpoints, see Section 10.4.2) that at any dose:

- Results in death, or
- Is life-threatening, or

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect, or
- Is a medically important event
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent 1 of the other outcomes listed in the definition above.

  Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered a medically important event. The list is not intended to be exhaustive:
- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc)
- Development of drug dependence or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or worsened during the study, including but not limited to breast, bladder, renal cell, Leydig cell, pancreatic, prostate, and thyroid follicular cell carcinoma
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study
- Venous thrombotic events to include deep venous thrombosis and thromboembolism (to include pulmonary embolism)
- Pancreatitis
- Bone fractures
- Events leading to amputation(s)
- Diabetic ketoacidosis

10.4.1.3 Adverse events of special interest

An **adverse event of special interest** (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified, or removed during a study by protocol amendment.

The AESI for this study are:

- Pregnancy of a female patient entered in a study as well as pregnancy occurring in a female partner of a male patient entered in a study with IMP:
  - It will qualify as an SAE only if it fulfills 1 of the seriousness criteria (see Section 10.4.1.2).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or non-serious) with IMP:
  - A symptomatic overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and resulting in clinical symptoms and/or signs accompanied by administration of more than twice the intended daily dose of IMP within a 24-hour period. It will be recorded in the e-CRF as "Symptomatic OVERDOSE (accidental)" or "Symptomatic OVERDOSE (intentional)", as applicable. It will be qualified as an SAE only if it fulfills the SAE criteria.

    (Please note that an asymptomatic overdose with the IMP, accidental or intentional, is an event defined as administration of more than twice the intended daily dose within a 24-hour period, without clinical symptoms and/or signs, either suspected by the Investigator or spontaneously notified by the patient, not based on accountability assessment. It will be recorded as an AE "Asymptomatic OVERDOSE, accidental" or "Asymptomatic overdose, intentional"; it will not be recorded as an AESI)
- ALT increase >3 x ULN (refer to related flow chart, Appendix C)

10.4.1.4 Events of special interest

An **event of special interest** (EOSI) is a serious or non-serious AE of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring may be appropriate. Such events may require further investigation in order to characterize and understand them. These events should be reported in e-CRF (where applicable) and will only qualify for expedited reporting when serious (fulfilling SAE criteria). Please refer to the study e-CRF completion guidelines for additional details on e-CRF completion.

A dedicated safety analysis will be performed as described in Section 11.4.3.4 and in the SAP to evaluate whether there is an imbalance in any of the below events with sotagliflozin relative to placebo.

The EOSI for this study are:

- Venous thrombotic events to include deep venous thrombosis and thromboembolism (to include pulmonary embolism)
- Pancreatitis
- Bone fractures
- Events leading to amputation(s)
- Diabetic ketoacidosis
- Malignancies of special interest (breast, bladder, renal cell, Leydig cell, pancreatic, prostate, and thyroid follicular cell carcinoma)
- Genital mycotic infections (to include vulvovaginal candidiasis in females and candidal balanitis in males)
- Urinary tract infections
- Diarrhea
- Clinically relevant volume depletion and events related/possibly related to volume depletion
- Severe hypoglycemia (see Section 10.6.1)

10.4.2 Serious adverse events waived from expedited regulatory reporting to regulatory authorities

Unlike most studies where the primary efficacy variable is the resolution or improvement of an existing condition, in this study efficacy endpoints include the occurrence of life-threatening events. Indeed, participants to this study are recruited precisely because they are at high risk for these life-threatening events. They are therefore expected to have at least 1 primary and secondary CV or renal efficacy endpoint during the course of the study.

Cardiovascular and renal efficacy endpoints will be reported (within 1 working day) in the e-CRF. Detailed process for the exchanges with the CEC will be described in a specific Manual of Operations.

In light of the above, suspected CV and renal efficacy endpoints as specified in this protocol will not be considered as AEs, will not be reported to pharmacovigilance, and are waived from regulatory reporting to Health Authorities except if the Investigator, according to his/her best medical judgment, considers these events as related to the IMP taking into consideration the patient's underlying disease. In that case, the Investigator will report it within 24 hours to the Sponsor.

Expedited reporting for the following CV and renal endpoints will be waived:

- Cardiovascular death
- Any MI
- Any stroke
- Unstable angina requiring hospitalization

- Heart failure leading to hospitalization
- Urgent HF visit (as defined in Appendix E)
- Sustained ≥50% decrease in eGFR from Baseline (for ≥30 days)
- Events leading to chronic dialysis
- Sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days)
- Events leading to renal transplant

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the drug and the event (suspected unexpected serious adverse reaction [SUSAR]), the event must be reported, even if it is a component of the study endpoint.

10.4.3 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP, spanning from the signature of the ICF until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the e-CRF.
- For this study, an endpoint assessment/adjudication committee is in place. This committee reviews important endpoints reported by the Investigators to determine whether the endpoints meet protocol-specified criteria. This is a periodic process, occurring after internal processing of the reported event (endpoint). The event as categorized by the Investigator will remain as such, even if judged differently by the adjudication committee later.
- Whenever possible, a diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until stabilization, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs if they are medically relevant based on the Investigator's medical judgement eg,:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI or EOSI

10.4.4 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the Sponsor after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the Sponsor. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc.) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.5 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.4, even if not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF.

10.4.6 Guidelines for reporting events of special interest

If an EOSI fulfills the criteria of an SAE, reporting should be performed according to the instructions for reporting of SAEs (see Section 10.4.4). Otherwise, reporting should follow the instructions for an AE (see Section 10.4.3).

10.4.7 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix C. The study population will be enrolled with preexisting impairment of renal function; rapid change in renal function of greater than **30% as compared** with the **mean of the prior two study visits** should be followed up as described in Appendix D.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices:

- Neutropenia
- Thrombocytopenia
- Increase in ALT
- Increase in creatine phosphokinase suspected to be of non-cardiac origin and not related to intensive physical activity
- Acute worsening of renal function (see Appendix D)

In the event that the 'general guidance for the follow-up of laboratory abnormalities by Sanofi' Appendix C requires discontinuation of IMP, temporary discontinuation should be considered unless otherwise specified (please see Section 10.3.1).

10.4.8 Guidelines for reporting product complaints (investigational medicinal product)

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team (ie, site monitor) that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.
- The following AESIs to those regulatory authorities who require such reporting:
  - Pregnancy
  - Symptomatic overdose with IMP
  - ALT increase >3 x ULN

Adverse events that are considered expected will be specified by the reference safety information provided in the current IB.

If required, unblinding of SUSARs will be the responsibility of the Sponsor.

The Sponsor will report all safety observations made during the conduct of the trial in the CSR.

10.6 SAFETY INSTRUCTIONS

10.6.1 Severe hypoglycemia

Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrate, glucagon, intravenous glucose, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure, unconsciousness, or coma. Plasma glucose values may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place participants at risk for injury to themselves or others.

Note: "requiring assistance of another person" means that the patient could not help himself or herself. Assisting a patient out of kindness, when assistance is not required, should not be considered a "requires assistance" incident.

Severe hypoglycemia will be reported as an AE. Additional information will be recorded including symptoms and/or signs, associated glucose value (if available), whether assistance was required and the treatment.

Severe hypoglycemia will be qualified as an SAE only if it fulfills SAE criteria. For example, events of seizure, unconsciousness or coma must be reported as SAEs.

The definition of severe hypoglycemia is based on the American Diabetes Association workgroup on hypoglycemia classification (36, 37).

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final CSR.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The study is powered based on the endpoints of time to CV death or first HHF and time to 3-point MACE. In order to achieve the targeted number of events of 844 CV death/HHF and 1189 3-point MACE, it is estimated that approximately 10,500 patients will be randomized over an estimated 24 months of enrollment period with approximately 27 months of follow-up after the last randomized patients.

This is based on the following trial design assumptions:

- A recruitment period of approximately 24 months with approximately 3.6%, 20.0%, 36.5%, and 39.9% of patients recruited during each of the 4 (four) 6-month periods
- Approximately 27 months of follow-up after the last patient is randomized, with treatment duration ranging from 27 to 51 months
- A 2% annual censoring rate
- A 3.5% annual event rate of CV death/HHF and 4.5% annual event rate of 3-point MACE in the placebo group

This will provide:

- 99% power to demonstrate NI on 3-point MACE
- 90% power to demonstrate the superiority in CV death/HHF
- 80% power to demonstrate the superiority in 3-point MACE

The actual end date of the study is event driven. Therefore, the study will continue until approximately 844 events of CV death or HHF and approximately 1189 3-point MACE are positively adjudicated.

Calculations were made using nQuery Advisor 7.0 simulation for the log-rank test with user defined survival rates, accrual, and drop-outs.

11.2 DISPOSITION OF PATIENTS

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

Randomized patients consist of all patients, with signed informed consent, with a treatment kit number allocated and recorded in the IRT DB, regardless of whether the treatment kit was used or not. These patients form the randomized population.

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population.

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.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

Efficacy analyses will be based on the treatment group allocated by the IRT according to the randomization schedule at the Randomization Visit (as randomized), irrespective of the treatment group actually received.

11.3.1.1 Intent–to-treat population

Intent-to-treat (ITT) population: all randomized population analyzed according to the treatment group allocated by randomization.

11.3.2 Safety population

Safety analyses will be based on the safety population, defined as all randomized patients who receive at least 1 dose of double-blind IMP (regardless of the amount of treatment administered).

Patients will be analyzed for safety analyses according to the treatment actually received.

In addition:

- Nonrandomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- When a patient is exposed to both sotagliflozin and placebo, the patient will be analyzed according to the treatment to which the patient was treated the longest duration.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

11.4.1.1 Extent of investigational medicinal product exposure

Duration of IMP exposure is defined as: last dose date – first dose date + 1 day, regardless of unplanned intermittent discontinuations.

The number (%) of patients randomized and exposed to double-blind IMP will be presented by specific time periods for each treatment group. The time periods of interest will be defined in the SAP.

Descriptive statistics of duration of treatment exposure (number, mean, SD, minimum, median, and maximum) and cumulative exposure in patient year will also be presented by treatment group in the safety population.

The number (%) of patients with an up-titration as well as number (%) of patients with an up-titration followed by a down-titration will be summarized.

11.4.1.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Treatment compliance will be summarized descriptively (N, mean, SD, median, min, and max). The percentage of patients with compliance <80% will be summarized.

11.4.2 Analyses of efficacy endpoints

All efficacy analyses will be performed on the ITT population. All events occurring from Randomization to the patient's Follow-up Visit (or Study Closeout Visit, if patient prematurely permanently discontinues), inclusive, will be included, unless otherwise specified.

11.4.2.1 Analysis of primary efficacy endpoints

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 (sotagliflozin, placebo), region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world), and HF-related criteria (yes, no) as the factors. The hazard ratio between sotagliflozin and placebo will be estimated along with the associated 2-sided 95% CI. Non-inferiority will be claimed if the UB of the 2-sided 95% CI is less than 1.3.

The time to the first occurrence of the composite CV death or HHF will be analyzed using the same Cox proportional hazards model described above with treatment (sotagliflozin, placebo), region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) and HF-related criteria (yes, no) as the factors. The stratified log-rank test will be used to compare the 2 treatment groups. Superiority will be claimed if the p-value is less than 0.05 (and NI on 3-point MACE is met).

Kaplan-Meier curves of the cumulative incidence rate will be provided by treatment groups for both primary endpoints. Patients who do not experience a primary outcome event will be considered censored at their final study visit (for patients who completed the study), or date of non-CV death, or date of last contact when information on efficacy endpoints has been retrieved (for patients who discontinued the study). Underlying assumptions of the Cox proportional hazards model will be checked using graphical methods. If proportionality is not observed, the Mantel-Haenszel test will be performed.

In addition, the primary analysis will be supported by a sensitivity analysis including events from patient's Randomization up to 30 days after the last administration of IMP (or study completion), but not beyond the patient's Follow-up Visit (or Study Closeout Visit, if patient prematurely permanently discontinued), using the same Cox model described above.

Subgroup analysis

Subgroup analyses will be conducted for the primary endpoints with respect to region, HF-related criteria, age group, gender, race, Baseline BMI group, Baseline UACR group, and Baseline eGFR group. Additional subgroups and analysis details will be provided in the SAP.

11.4.2.2 Analyses of secondary efficacy endpoints

Secondary time to event endpoints will be analyzed using the same Cox proportional hazards model described above with treatment, region, and HF criteria as factors. The hazard ratios between sotagliflozin and placebo will be estimated along with the associated 2-sided 95% CIs. The stratified log-rank tests will be used to compare the time-to-first-event curves. Secondary endpoints will be tested and claimed as described in the multiplicity considerations section (Section 11.4.2.3). Kaplan-Meier curves of the cumulative incidence rates will be provided by treatment groups.

The total number of events of CV death, HHF, or urgent HF visit will be analyzed using the Andersen-Gill approach (38), a generalization of the Cox proportional hazards model for recurrent events with treatment, region, and HF-related criteria as factors. For standard errors in the Andersen-Gill model, a robust variance estimator that allows for heterogeneity in HF rates between patients will be used (39).

Other endpoints

Other time to event endpoints will be analyzed using the same Cox proportional hazards model described for the primary endpoints with treatment, region, and HF criteria as factors. Nominal p-values from the stratified log-rank test may be provided.

Summary statistics of results and changes from Baseline in HbA1C, body weight, BP, UACR, and eGFR at scheduled visits using observed cases with no formal testing will be provided. Graphical presentations will also be used to illustrate trends over time. Baseline for eGFR and UACR is defined as the average of all values assessed by the central laboratory from Screening up to and including Randomization. For the remaining parameters, baseline is defined as the last available value before the first dose of double-blind IMP or the last available value on or before the day of randomization for patients who were randomized but never exposed to IMP.

11.4.2.3 Multiplicity considerations

To control the family-wise type I error at alpha=0.05 level (1-sided alpha=0.025), a fixed-sequence testing procedure will be applied to the primary endpoints. The hierarchy will be:

1. Non-inferiority of sotagliflozin versus placebo on 3-point MACE
2. Superiority of sotagliflozin versus placebo on time to first event of CV death or HHF

If the hypotheses above are met, the family-wise Type-1 error rate at 0.05 (1-sided alpha=0.025) will be controlled by the Hochberg procedure for the first 2 secondary endpoints listed below:

- Superiority of sotagliflozin versus placebo on 3-point MACE
- Superiority of sotagliflozin versus placebo in patients with Baseline eGFR ≥30 mL/min/1.73 m^2 on a composite renal endpoint of sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days)

If the hypotheses above are statistically significant, a fixed-sequence testing procedure will be applied to the other secondary endpoints listed below. The hierarchy will be:

1. Superiority of sotagliflozin versus placebo in patients with Baseline eGFR ≥30 mL/min/1.73 m^2 on a composite renal endpoint and Baseline UACR ≥300 mg/g (34 mg/mmol) of sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days)
2. Superiority of sotagliflozin versus placebo on the composite endpoint of CV death, HHF, or urgent HF visit (defined in Appendix E)
3. Superiority of sotagliflozin versus placebo on CV death
4. Superiority of sotagliflozin versus placebo on all-cause mortality

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 will be provided for descriptive purpose only.

11.4.3 Analyses of safety data

Safety endpoints are presented in Section 9.2. The summary of safety results will be presented by treatment group. All safety analyses will be performed on the Safety population as defined in Section 11.3.2 using the following common rules:

The Baseline value is generally defined as the last available value before the first dose of double-blind IMP.

The following definitions will be applied to laboratory parameters and vital signs:

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor's Global Pharmacovigilance and Epidemiology department and in effect at the time of the final SAP approval. PCSA criteria for parameters not cited in the protocol as safety parameters will not be analyzed.

- 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 "observation periods" defined below are applicable for classification of AEs, determination of on-treatment PCSA values and the last on-treatment value for the laboratory, and vital sign parameters. The observation period of safety data will be divided into 3 segments:

- The pre-treatment period is defined as the time between the date of the informed consent and the first dose of double-blind IMP.
- The on-treatment period (treatment-emergent AE [TEAE] period) is defined as the time from the first dose of double-blind IMP up to 10 days (1 day for hypoglycemia) after the last dose of double-blind IMP. The 10-day interval is chosen based on the half-life of the IMP in patients with moderate renal dysfunction.
- The post-treatment period is defined as the time starting 11 days after the last dose of double-blind IMP (after the on-treatment period).

11.4.3.1 Analysis of adverse events

Pre-treatment AEs are AEs that developed or worsened or became serious during the pre-treatment period.

Treatment-emergent AEs are AEs that developed or worsened (according to the Investigator's opinion) or became serious during the on-treatment period.

Post-treatment AEs are AEs that developed or worsened or became serious during the post-treatment period.

The primary focus of AE reporting in the CSR will be on TEAEs. Pre- and post-treatment AEs will be described separately. Efficacy events that are waived from reporting as AEs are described in Section 10.4.2.

All adverse events

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment period. The denominator for computation of percentages is the safety population within each treatment group.

Summaries of all TEAEs in each treatment group will include:

- The overview of AEs, summarizing number (%) of patients with any:
  - Treatment-emergent AE
  - Serious TEAE

  - Treatment-emergent AE leading to death
  - Treatment emergent AE leading to permanent treatment discontinuation
- The number (n) and percentage (%) of patients with at least 1 TEAE by primary SOC, HLGT, HLT and PT
- Summary of TEAEs by maximal severity (severe, moderate, mild), presented by primary SOC and PT
- Summary of TEAEs possibly related to IMP, presented by primary SOC, HLGT, HLT and PT

A detailed listing of TEAE summaries will be provided in the SAP.

Death and serious adverse events

Death and treatment-emergent SAEs will be summarized and presented as number and percent of patients in each treatment group.

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (on-study, on-treatment, post-study) and adjudicated reasons, summarized on the safety population by treatment received
- Death in nonrandomized patients or randomized and not treated patients
- All AEs leading to death (death as an outcome on the AE e-CRF page as reported by the Investigator), by primary SOC, HLGT, HLT, and PT, showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT
- TEAE leading to death (death as an outcome on the AE e-CRF page as reported by the Investigator) by primary SOC, HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT

Adverse events leading to permanent treatment discontinuation

TEAEs leading to permanent treatment discontinuation will be summarized and presented as number and percent of patients in each treatment group.

11.4.3.2 Analysis of severe hypoglycemia

The number (%) of patients and rate in patient years (2 types: the number of patients with events and the total number of events per 100 patient-year) of severe hypoglycemia will be summarized by treatment group respectively. Their pattern of occurrence over time will also be assessed, as appropriate.

11.4.3.3 Analysis of adverse events of special interest

Pregnancy and symptomatic overdose with IMP will be included in overall AE summaries if any are reported. An ALT increase >3 x ULN is included in laboratory PCSA summary if any.

11.4.3.4 Analysis of events of special interest

The number (%) of patients with each EOSI event will be summarized by treatment group. All events reported by the Investigators on the AE forms for special interest will be listed along with the adjudication outcome (if applicable).

The incidence of each EOSI will be summarized by treatment group. The selection of PTs will be based on standardized MedDRA query (SMQ) for each corresponding item wherever possible and will be further detailed in the SAP.

The incidence of liver-related AEs will be summarized by treatment group. The selection of PTs will be based on SMQ Hepatic disorder. Time to liver-related treatment discontinuation and time to liver death may also be provided based on hepatic disorder SMQ.

11.4.3.5 Analysis of laboratory variables

The number and percentage of patients with PCSA or by the predefined categories (if no PCSA criterion is defined) at any evaluation during the on-treatment period will be summarized for each clinical laboratory test within each treatment group. The summaries will include patients in the safety population who have at least 1 laboratory test performed during the on-treatment period and, when required by the definition of the abnormality, with an available Baseline value and available laboratory normal ranges.

Descriptive statistics will be used to summarize the laboratory results and the changes from Baseline by visit and for the last on-treatment value within each treatment group. Shift tables and other tabular and graphical methods may be used to present the results for laboratory tests of interest. Listings will be provided with flags indicating the out of laboratory range values as well as the PCSA values.

<u>Liver tests</u>

The liver function tests, namely ALT, AST, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any Postbaseline visit by Baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any Postbaseline visit will also be displayed by duration of exposure for each treatment group.

Time to onset of the initial ALT and AST elevation (>3 x ULN) and total bilirubin elevation (>2 x ULN) will be analyzed for each parameter using Kaplan-Meier estimates, using the midpoint of the time interval between the first assessment showing the elevation and the previous assessment, presented by treatment group. Consideration should be given to the impact of the spacing of scheduled tests. A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

The normalization (to ≤1 x ULN or return to Baseline if Baseline > ULN) of elevated liver function tests will be summarized by categories of elevation (3 x ULN, 5 x ULN, 10 x ULN, 20 x ULN for ALT and AST; 1.5 x ULN for alkaline phosphatase; and 1.5 x ULN and 2 x ULN for total bilirubin), with the following categories of normalization: never normalized, normalized after permanent discontinuation of study drug. Note that a patient will be counted only under the maximum elevation category.

11.4.3.6 Analysis of vital sign variables

The number and percentage of patients with PCSA at any evaluation during the on-treatment period will be summarized for each vital sign parameter within each treatment group. The summaries will include patients in the safety population who have at least 1 parameter to be analyzed during the on-treatment period. Descriptive statistics will be used to summarize the results and the changes from Baseline by visit and for the last on-treatment value within each treatment group. Tabular and graphical methods may be used to present the results for parameters of interest. Listings will be provided with flags indicating the PCSA values.

11.5 INTERIM ANALYSIS

If a CV meta-analysis of other T2D sotagliflozin Phase 3 studies does not meet the pre-marketing requirement, in accordance with the *2008 FDA Guidance for Industry: Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (35), an interim analysis will be conducted in this trial and included in the initial New Drug Application submission.

The alpha-spending to control the overall type I error at the 1-sided α=0.025 for assessing the 1.8 criterion is as follows: spend 1-sided α=0.02 for the meta-analysis (ie, assessment using UB of 96% CI) and 1-sided α=0.005 for the interim analysis in this CVOT (ie, assessment using UB of 99% CI). The 1.8 boundary will be assessed using the time to first occurrence of any positively-adjudicated MI, stroke, CV death, or hospitalization for unstable angina (4-point MACE). This interim analysis will be conducted when the expected number of events will provide sufficient power.

To maintain the blind, either the DMC and independent statistical group or a Sanofi fire-walled group, independent of the study, will perform the interim analysis. Additional details will be described in separate documents (eg, DMC charter, DMC SAP, and a dedicated CV safety SAP).

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Sub-investigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the written ICF should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written ICF will be provided to the patient.

Informed consent will also be sought for [redacted], DXA sub-study (at participating sites), and [redacted].

The ICF, including [redacted] and DXA sub-study participation (where applicable) used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, ICF, Investigator's Brochure with any addenda or labeling documents [summary of product characteristics, package insert], Investigator's curriculum vitae [CV], etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure or labeling information, will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator(s) and delegated Investigator staff undertake(s) to perform the clinical trial in accordance with this clinical trial protocol, ICH guidelines for GCP and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the e-CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Sub-investigators shall be appointed and listed in a timely manner. The Sub-investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the e-CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use, and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the e-CRF entries against the source documents, except for the pre-identified source data directly recorded in the e-CRF. The ICF will include a statement by which the patient allows the Sponsor's duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the e-CRFs (eg, patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate e-CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All e-CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor trial master file.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification, and training of each Investigator and Sub-investigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure, and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-investigators of the confidential nature of the clinical trial.

The Investigator and the Sub-investigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents, and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Sub-investigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents, and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Sub-investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor DB shall be treated in compliance with all applicable laws and regulations
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's DBs, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations

Patient race and ethnicity (race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, not reported, unknown; ethnicity: Hispanic, Not Hispanic) will be collected in this study because these data are required by several regulatory authorities (eg, on Afro American population for FDA, on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan, or on Chinese population for the China Food and Drug Administration in China).

[redacted]

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/risk ratio, efficacy, and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio
- Patient enrollment is unsatisfactory
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon

- Noncompliance of the Investigator or Sub-investigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP
- The total number of patients are included earlier than expected

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon 30 (thirty) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a CSR and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor’s written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the ICF. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised ICF prior to implementation of the change and patient signature should be re-collected if necessary.

16 BIBLIOGRAPHIC REFERENCES

1. Emerging Risk factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215-22.

2. Emerging Risk factors Collaboration, Di Angelantonio E, Kaptoge S, Wormser D, Willeit P, Butterworth AS, et al. Association of cardiometabolic multimorbidity with mortality. JAMA. 2015;314(1):52-60.

3. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(214):2545-59.

4. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560-72.

5. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-53.

6. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577-89.

7. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry: Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. December 2008.

8. European Medicines Agency, 2015 Committee for Medicinal Products for Human Use (CHMP). Reflection paper on assessment of cardiovascular safety profile of medicinal products. 25 February 2016. EMA/CHMP/50549.

9. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87(1):4-14.

10. Thrainsdottir IS, Aspelund T, Thorgeirsson G, Gudnason V, Hardarson T, Malmberg K, et al. The association between glucose abnormalities and heart failure in the population-based Reykjavik study. Diabetes Care. 2005;28(3):612-6.

11. Juhaeri J, Gao S, Dai WS. Incidence of heart failure, stroke and acute myocardial infarction among Type 2 diabetic patients using insulin glargine and other insulin. Pharmacoepidemiol Drug Saf. 2009;18(6):497-503.

12. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC Jr. Heart failure prevalence, incidence and mortality in the elderly with diabetes. Diabetes Care. 2004;27(3):699-703.

13. Vaur L, Gueret P, Lievre M, Chabaud S, Passa P, DIABHYCAR Study Group (type 2 DIABetes, Hypertension, CARdiovascular Events and Ramipril) study. Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: observations from the DIABHYCAR study. Diabetes care. 2003;26(3):855-60.

14. Carr AA, Kowey PR, Devereux RB, Brenner BM, Dahlöf B, Ibsen H, et al. Hospitalization for new heart failure among subjects with diabetes mellitus in the RENAAL and LIFE studies. Am J Cardiol. 2005;96(11):1530-6.

15. Cubbon RM, Adams B, Rajwani A, Mercer BN, Patel PA, Gherardi G, et al. Diabetes mellitus is associated with adverse prognosis in chronic heart failure of ischemic and non-ischemic aetiology. Diab Vasc Dis Res. 2013;10(4):330-6.

16. Murphy D, McCulloch CE, Lin F, Banerjee T, Bragg-Gresham JL, Eberhardt MS, et al. Trends in prevalence of chronic kidney disease in the United States. Ann Intern Med. 2016;165(7):473-81.

17. Sattar N, McLaren J, Kristensen SL, Preiss D, McMurray JJ. SGLT2 Inhibition and cardiovascular events: why did EMPA-REG Outcomes surprise and what were the likely mechanisms? Diabetologia. 2016;59(7):1333-9.

18. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117-28.

19. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 doi: 10.1056/NEJMoa1611925. [Epub ahead of print]

20. U.S. Food and Drug Adminstration. FDA approves Jardiance to reduce cardiovascular death in adults with type 2 diabetes. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm531517.htm. Accessed Dec. 5, 2016.

21. Abdul-Ghani M, Del Prato S, Chilton R, DeFronzo RA. SGLT2 Inhibitors and cardiovascular risk: Lessons Learned from the EMPA-REG OUTCOME study. Diabetes Care. 2016;39(5):717-25.

22. McMurray J. EMPA-REG – The “diuretic hypothesis”. J Diabetes Complications. 2016;30(1):3-4.

23. Raz I, Cahn A. SGLT2 inhibitors and heart failure – clinical implications. Nat Rev Cardiol. 2016;13(4):185-6.

24. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME trial. Eur Heart J. 2016;37(19):1526-34.

25. Ferannini E, Mark M, Mayoux E. Cardiovascular Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis. Diabetes Care. 2016;39(7):1108-14.

26. Skrtic M, Cherney DZ. Sodium-glucose cotransporter-2 inhibition and the potential for renal protection in diabetic nephropathy. Curr Opin Nephrol Hypertens. 2015;24(1):96-103.

27. Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375(4):323-34.

28. Sands AT, Zambrowicz BP, Rosenstock J, Lapuerta P, Bode BW, Garg SK, et al. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as an adjunct therapy to insulin in type 1 diabetes. Diabetes Care. 2015;38(7):1181-8.

29. Wright EM. Glucose galactose malabsorption. Am J Physiol. 1998;275(5Pt1):G879-82.

30. Zinman B, McGuire DK, Wanner C, Lachin JM, Inzucchi SE, Herman WH. Update from EMPA-REG OUTCOME Trial. 3-CT-SY29 at the American Diabetes Association Annual Scientific Meeting New Orleans, June 2016.

31. Greene SJ, Gheorghiade M, Vaduganathan M, Ambrosy AP, Mentz RJ, Subacius H, et al. EVEREST Trial investigators. Haemoconcentration, renal function, and post-discharge outcomes among patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial. Eur J Heart Fail. 2013;15(12):1401-11.

32. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation. 2010;122(3):265-72.

33. van der Meer P, Postmus D, Ponikowski P, Cleland JG, O'Connor CM, Cotter G, et al. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. J Am Coll Cardiol. 2013;61(19):1973-81.

34. Oh J, Kang SM, Hong N, Youn JC, Han S, Jeon ES, et al. Hemoconcentration is a good prognostic predictor for clinical outcomes in acute heart failure: data from the Korean Heart Failure (KorHF) Registry. Int J Cardiol. 2013;168(5):4739-43.

35. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. 2008.

36. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care. 2005;28(5):1245-9.

37. FDA Guidance for Industry: Diabetes Mellitus - Developing Drugs and Therapeutic Biologics for Treatment and Prevention. Lines 1144 – 1215. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071624.pdf. Accessed July 12, 2016

38. Andersen PK, Borgan O, Gill RD, Keiding, N. Statistical Models Based on Counting Processes. 1992 New York: Springer-Verlag.

39. Lin DY, Wei LJ. The robust inference for the Cox proportional-hazards model. J Am Stat Assoc. 1989;84:1074-8.

40. Janssen Pharmaceuticals Inc. Endocrinologic and Metabolic Drugs Advisory Committee: Canagliflozin as an Adjunctive Treatment to Diet and Exercise Alone or Co-administered with Other Antihyperglycemic Agents to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus. Available from: http: //www.fda.gov/downloads/AdvisoryCommittees/.../UCM334551.pdf.

41. Bristol-Myers Squibb Company, Astra Zeneca AB. FDA Advisory Committeee Background Document: Dapagliflozin. Available from https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM262996.pdf

42. FDA, Center for Drug Evaluation and Research. Chong WH. Cross discipline team leader review. Jardiance (empagliflozin) - NDA 204629. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204629Orig1s000MedR.pdf

43. FDA, Center for Drug Evaluation and Research. Pucino F. Clinical review. Farxiga (dapagliflozin) – NDA 202293. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/202293Orig1s000MedR.pdf

44. Bilezikian JP, Watts NB, Usiskin K, Polidori D, Fung A, Sullivan D, et al. Evaluation of Bone Mineral Density and Bone Biomarkers in Patients With Type 2 Diabetes Treated With Canagliflozin. J Clin Endocrinol Metab. 2016;101:44-51.

45. Watts NB, Bilezikian JP, Usiskin K, Edwards R, Desai M, Law G, and Meininger G. Effects of Canagliflozin on Fracture Risk in Patients With Type 2 Diabetes Mellitus J Clin Endocrinol Metab. 2016;101:157-66.

46. Kohan DE, Fioretto P, Tang W, List JF. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. Kidney Intl. 2014;85:962-71.

47. Scheen AJ & Paquot N. Metabolic effects of SGLT2 inhibitors beyond increased glucosuria: A review of the clinical evidence. Diabetes & Metabolism. 2014;40:S4-11.

48. Cariou B & Charbonnel B. Sotagliflozin as a potential treatment for type 2 diabetes mellitus. Expert Opinion on Investigational Drugs. 2015;24(12):1647-56.

49. Soltani S, Hunter GR, Kazemi A, Shab-Bidar S.The effects of weight loss approaches on bone mineral density in adults: a systematic review and meta-analysis of randomized controlled trials. Osteoporosis International. 2016;27(9):2655-71.

50. Tiirosh A, de Souza RJ, Sex Differences in the Effects of Weight Loss Diets on Bone Mineral Density and Body Composition: POUNDS LOST Trial. J Clin Endocrinol Metab. 2015;100:2463-71.

51. Hicks KA, Hung HMJ, Mahaffey KW, Mehran R, Nissen SE, Stockbridge NL, et al. Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials. Draft Definitions for CDISC July 3, 2014.

17 APPENDICES

Appendix A Contraceptive guidance and collection of pregnancy information

DEFINITIONS

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTION GUIDANCE

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 1.

Table 1: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] - oral - intravaginal - transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation - oral - injectable
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation - Intrauterine device (IUD) - Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

COLLECTION OF PREGNANCY INFORMATION

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 1 year following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 1 year beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

  Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 10.4.1.2. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- The Investigator must immediately discontinue study treatment for any female participant who becomes pregnant while participating in the study.

Appendix B Dual-energy x-ray absorptiometry sub-study

INTRODUCTION

A key safety objective of this study is to evaluate the effects of sotagliflozin on bone mass measured by the change in BMD throughout the treatment duration. Evaluation of bone safety is relevant due to findings of hyperostosis and decreases in bone turnover observed in animal studies with other compounds in the class (40, 41). These effects have been hypothesized to be associated with off-target SGLT1 inhibition leading to an increased intestinal calcium absorption and changes in calcium homeostasis and vitamin D metabolism (40, 41). Small and inconsistent changes in bone biomarkers and no imbalance in fracture rate were reported in clinical trials with dapagliflozin and empagliflozin (42, 43). Changes in bone markers (increase in β-CTX-1) after 1 year and a small decrease in BMD after 2 years were reported with canagliflozin treatment (44), although the clinical significance is unknown. These clinical findings were inconsistent with the preclinical data and could be explained at least in part by the weight loss occurred with canagliflozin treatment (44). An increased risk of fractures was observed in older patients participating in the canagliflozin CV outcomes trial (CANVAS; 45) and in a 2-year study with dapagliflozin in patients with renal impairment (46), but in both cases, the findings were not seen in the pooled data from Phase 3 studies. It is possible that these subgroups present higher susceptibility to hemodynamic events or falls, which could be associated with fractures (46).

Preclinical studies with sotagliflozin in rats showed increases in trabecular bone and small reversible decreases in calciotropic hormone and bone markers (P1NP, osteocalcin, 1,25-dihydroxyvitamin D), which were not considered biologically significant. No clinically significant changes in calcium and bone biomarkers have been observed in clinical studies with sotagliflozin. However, as changes in bone markers and BMD were reported in clinical studies with canagliflozin (40), this study will also further assess the effects of sotagliflozin on bone mass, markers of calcium metabolism and bone turnover in this group of patients at higher risk for osteoporosis and fractures. In order to assess the risk of fractures with sotagliflozin treatment, the number of fractures will be evaluated and independently adjudicated in this study and in the totality of sotagliflozin Phase 3 studies, including in patients with various degrees of renal impairment.

Clinically meaningful weight loss is observed with SGLT2 inhibitors (47) and a significant weight reduction is expected and as a result of the dual SGLT1-2 inhibition with sotagliflozin (48). Reduction of BMD is reported following weight loss interventions (49, 50) and decline in estradiol levels was observed in association with weight loss in women treated with canagliflozin in a 2- year study (44). Decrease in estradiol levels affects bone turnover and can represent an additional negative effect to bone mass. Selected markers of bone formation and resorption and other biochemical parameters of relevance to bone metabolism will also be evaluated in this trial.

PRIMARY OBJECTIVE

To compare sotagliflozin versus placebo with respect to changes in BMD in patients with T2D, CV risk factors, and moderately impaired renal function.

SECONDARY OBJECTIVES

To compare sotagliflozin versus placebo in patients with T2D, CV risk factors, and moderately impaired renal function with respect to:

- Changes in markers of bone and calcium metabolism

STUDY DESIGN

A total of approximately 190 patients (approximately 95 female and 95 male) will participate in the DXA sub-study. Patients participating in the sub-study will complete a dedicated informed consent.

Patients who agree to participate in the sub-study will have a DXA scan performed at Baseline along with the collection of laboratory markers of bone and calcium metabolism. Investigations will be repeated at the pEOT Visit (if discontinuing treatment early) or at the Study Closeout Visit (patients who completed treatment [ie, without prematurely permanently discontinuing IMP]). If a patient prematurely withdraws from the sub-study, they will be encouraged to continue in the main trial.

ENDPOINTS

Primary endpoint:

- Change from Baseline in BMD (lumbar spine, total hip, and femoral neck) measured by DXA

Secondary endpoints:

- Change from Baseline in:
  - The following markers of bone and calcium metabolism: serum and urinary calcium, serum 25-hydroxyvitamin D, serum 1,25-dihydroxyvitamin D, serum and urinary phosphorus, serum PTH, serum NTX, serum β-CTX-1, serum P1NP, serum magnesium

SUB-STUDY PROCEDURES

Select sites from this trial will be asked to participate in the DXA sub-study. Sites selected to participate in the sub-study will have IRB/EC approval for the main study and for the sub-study, and an additional informed consent. Patients who have signed informed consent for the main study of this trial at these select sites and are deemed eligible for the study at Screening will be asked to participate in the sub-study. Once the additional written informed consent is obtained for the sub-study, the patients will undergo the following assessments. Written informed consent must be obtained prior to any study investigations.

Specific to Canada and USA: Instructions for patients for fasting visits (see Appendix F)

VISIT SCHEDULE

Screening period (at the Week -4 Screening Visit [Visit 1] and before Day 1 [Randomization, Visit 2])

- Assessment of eligibility criteria
- For patients who at the time of the screening Visit meet the inclusion criteria for the DXA sub-study and do not meet any known exclusion criterion:
- DXA scan for BMD

  Note: It is recommended that the same DXA instrument is used for both study assessments.
- Sample for central laboratory assessment:
  - Serum: 25-hydroxyvitamin D (at Visit 1)
  - 24-hour urine collection (calcium, phosphorus, creatinine). Urine samples should be returned prior to or at Visit 2 (Randomization)

Visit 2 (Day 1)

- Assessment of eligibility criteria
- Samples for central laboratory assessment of markers of bone and calcium for patients who meet all entry criteria as follows:
  - Serum: calcium, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, phosphorus, PTH, NTX, β-CTX-1, and P1NP. Specific for Canada and USA: Fasting morning samples (see Appendix F)

Premature End-of-Treatment/Study Closeout Visit

- DXA scan for BMD

  Note: It is recommended that the same DXA instrument is used for both study assessments.
- Samples for central laboratory assessment of markers of bone and calcium as follows:
  - 24-hour urine collection: calcium, phosphorus, creatinine
  - Serum: Calcium, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, phosphorus, PTH, NTX, β-CTX-1, and P1NP. Specific for Canada and USA: Fasting morning serum samples (see Appendix F)

SELECTION OF PATIENTS

Approximately 190 patients (95 female and 95 male) will participate in the sub-study. In order to be eligible for this sub-study, all patients must meet eligibility criteria for the main EFC14875 study and the additional eligibility criteria outlined for this sub-study.

Additional Inclusion Criteria:

- Signed written informed consent for DXA sub-study of EFC14875 protocol

Additional Exclusion Criteria:

- Patient who withdraws consent for DXA sub-study of EFC14875 protocol during the Screening period (patient who is not willing to continue)
- Patient unable to complete the DXA testing during the Screening period, or any contraindications to DXA testing, or conditions making interpretation of the DXA results difficult (eg, imaging procedure requiring contrast within 10 days prior to Screening, recent administration of radionuclides [within 10 half-lives of the injected tracer])
- Women who have been postmenopausal (or undergone bilateral oophorectomy) for less than 5 years
- Bone mineral density T-score <-2.0 at any site (ie, lumbar spine, total hip, or femoral neck) measured by DXA obtained during the screening period.

  Note: If a patient has had a BMD documented within the last 1 year and the T-score is not <-2.0 at any site the patient may proceed to Randomization prior to receiving the results of the BMD performed during screening.
- Hypercalcemia based on total serum calcium level >10.5 mg/dL (2.63 mmol/L) at Screening by central laboratory
- Diagnosis of vitamin D deficiency within 12 months prior to the Screening Visit or serum 25-hydroxyvitamin D levels ≤20 ng/mL at Screening by central laboratory
- History of fracture within 12 months of screening (except for fractures of the fingers, hands, toes, feet, face, and skull)
- Treatment with medications known to affect bone mass or increase risk of fractures within 36 months prior to the Screening Visit (eg, bisphosphonates, selective estrogen receptor modulators, calcitonin, teriparatide, denosumab, aromatase inhibitors, androgen deprivation therapy), or anticonvulsants (eg, carbamazepin, phenytoin, and phenobarbital) within 36 months prior to the Screening Visit. Use of hormonal replacement that includes systemic or transdermal estrogen and testosterone is excluded unless is stable for at least 24 months prior to screening
- Use of a thiazolidinedione or a SGLT2 inhibitor within 24 months of the Screening Visit

Patients who are not eligible for the sub-study based on the additional eligibility criteria may still take part in the main study.

Patients who wish to withdraw their participation in this sub-study may do so at any time. If they do so, they will be encouraged to continue participation in the main study.

Patients who discontinue the main study, must also discontinue participation in the sub-study.

Patients who prematurely permanently discontinue study treatment (regardless of the reason) should perform the sub-study procedures at their pEOT Visit and continue with all study visits as otherwise planned until their Study Closeout Visit.

STATISTICAL CONSIDERATIONS

The statistical analysis of the DXA sub-study will be fully developed in the SAP.

This sub-study will involve approximately 190 randomized patients (95 female and 95 male) who are randomized in the main study, give informed consent to participate in this sub-study, and are enrolled in the sub-study through the IRT. The analysis will be conducted on the safety population.

The primary and safety endpoints will be descriptive (results and change from Baseline); no statistical tests will be performed. Summaries will include number of observations available, mean, SD, minimum, median, and maximum.

Additional summaries by gender and postmenopausal females may also be produced.

SAFETY REPORTING

Adverse events and SAEs will be captured and reported in accordance with the main EFC14875 study (see Section 10.4 to Section 10.7).

ADMINISTRATION

Informed Consent

A separate informed consent will be obtained from patients who voluntarily agree to participate in the sub-study. The ICF reflecting this sub-study will be submitted for review and approval to the IRB/EC charged with this responsibility.

Confidentiality

Data collection and handling by the Sponsor for this sub-study will be will be in accordance with that described in the main EFC14875 protocol and in accordance with local guidelines (see Section 14.3 and Section 14.5), and every effort will be made to protect patient confidentiality. When the results are published, they will be done so anonymously.

Institutional Review Board/Ethics Committee

This sub-study, the ICF for this sub-study, and any advertisement for patient recruitment will be submitted for review and approval to the IRB/EC charged with this responsibility.

Records Retention

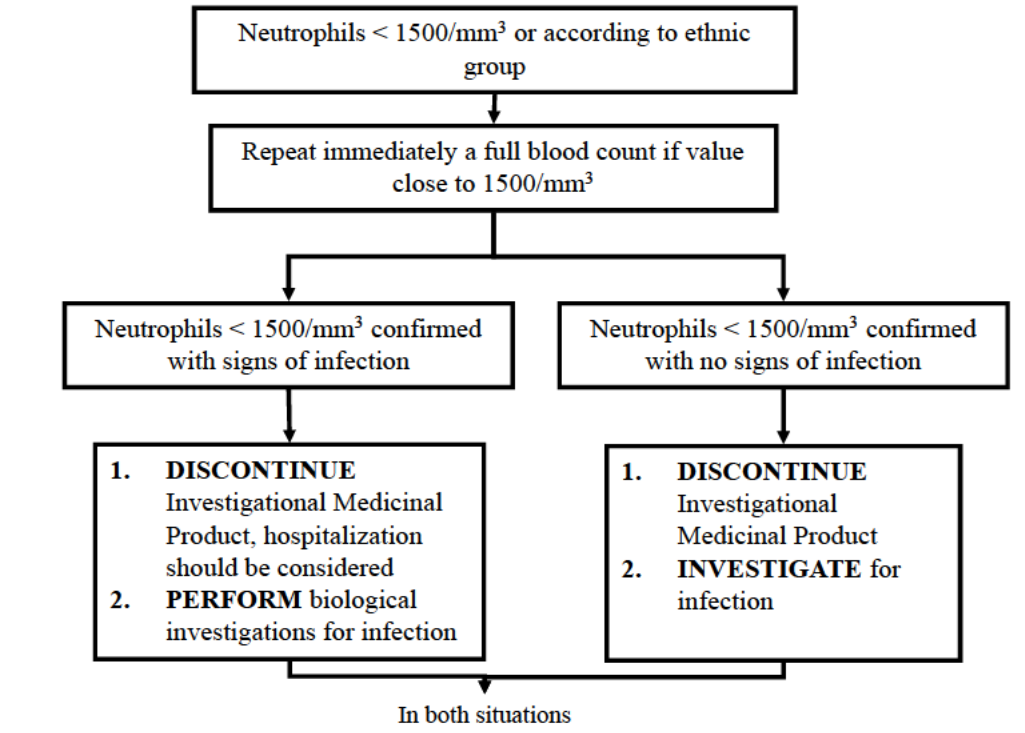
Investigators must retain records pertaining to this sub-study as described in the main EFC14875 study protocol (see Section 14.2).

Miscellaneous

Section 10.4.1 to Section 17 will also apply to the sub-study.

Appendix C General guidance for the follow-up of laboratory abnormalities by sanofi

NEUTROPENIA

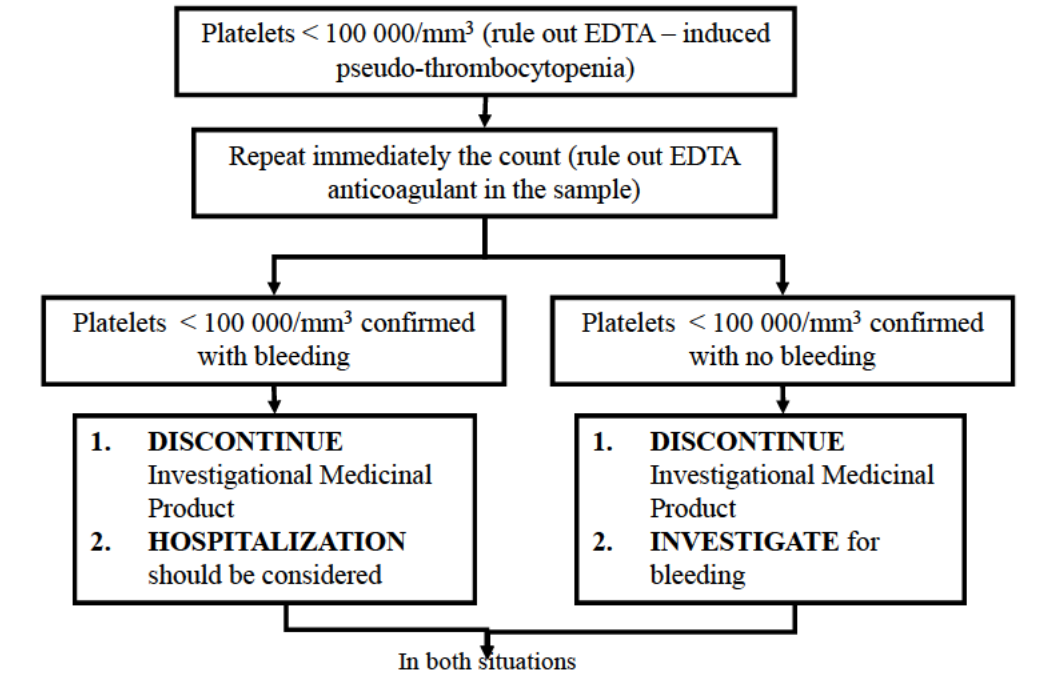


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

Note:
•The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
•For individuals of African descent, the relevant value of concern is <1000/mm3

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.3 is met.

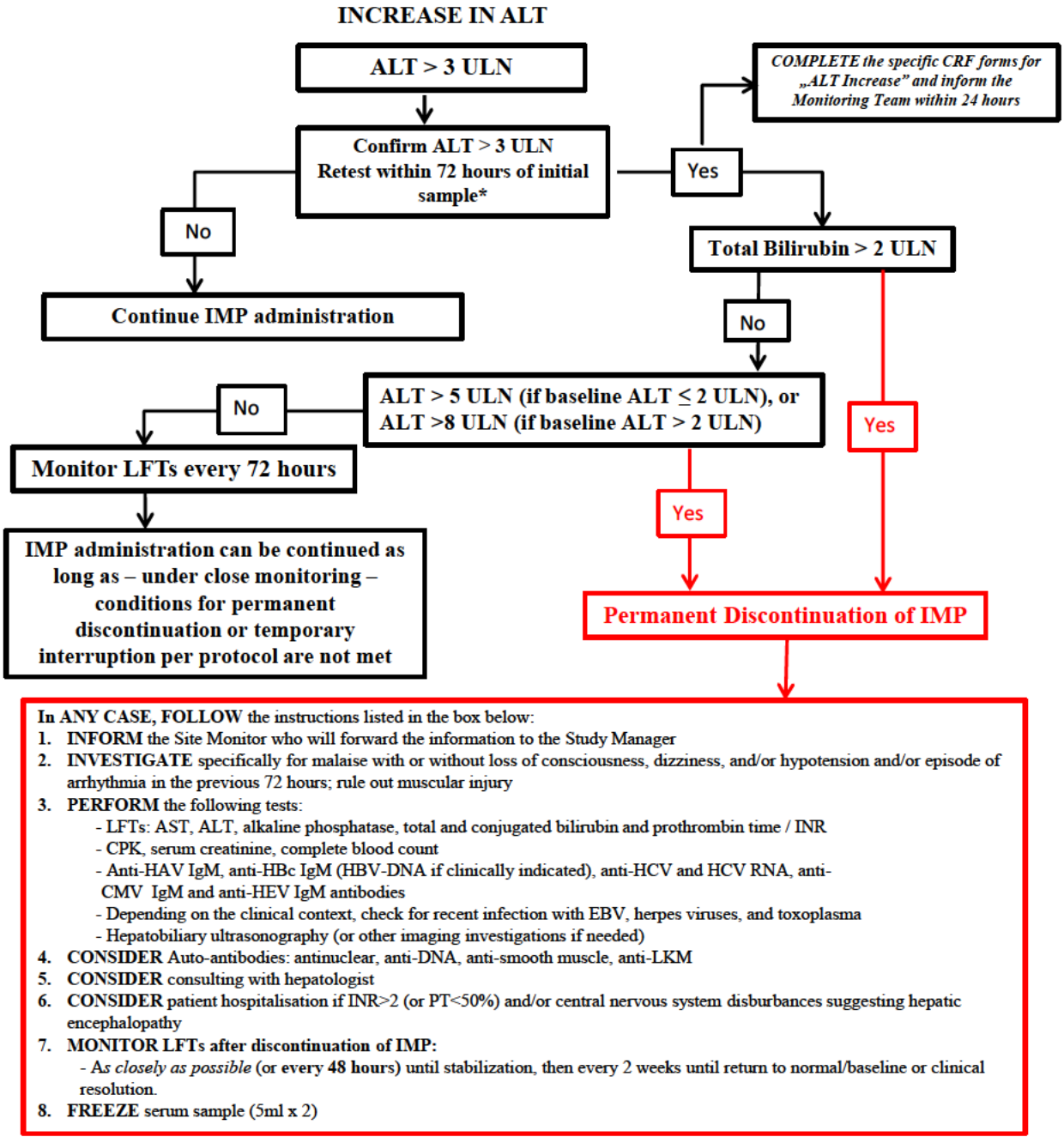
THROMBOCYTOPENIA



3. **INFORM** the local Monitor
4. **QUESTION** about last intake of quinine (drinks), alcoholism, heparin administration
5. **PERFORM** or collect the following investigations:
   - Complete blood count, schizocytes, creatinine
   - Bleeding time and coagulation test (fibrinogen, INR or PT, aPTT), Fibrin Degradation Product
   - Viral serology: EBV, HIV, mumps, measles, rubella
6. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
7. **DECISION** for bone marrow aspiration: to be taken in specialized unit
   - On Day 1 in the case of associated anemia and/or leukopenia
   - On Day 8 if platelets remain < 50 000/mm³
8. **MONITOR** the platelet count every day for at least one week and then regularly until it returns to normal

Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

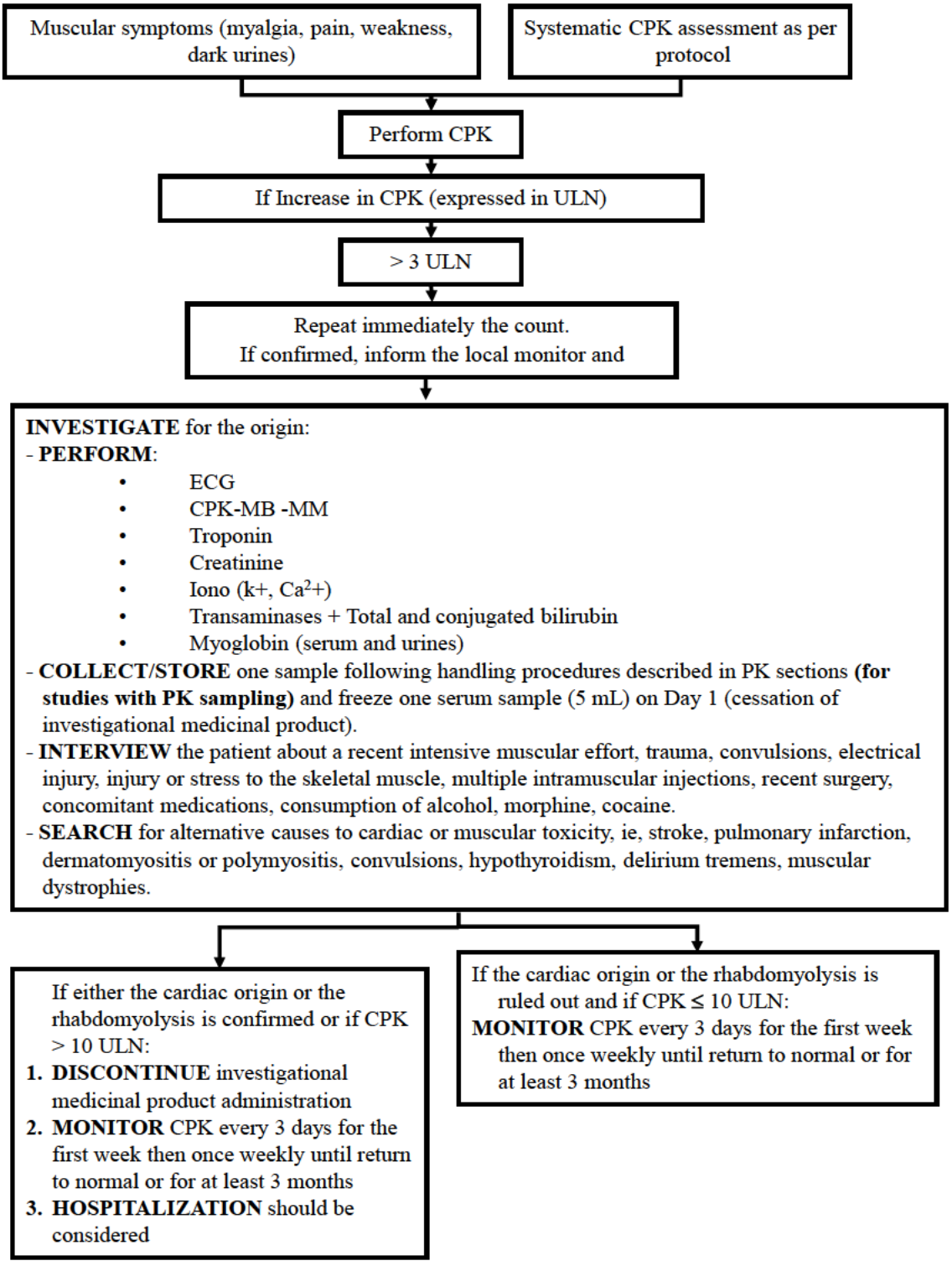
Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.3 is met.



*If unable to retest in 72 hours, use original laboratory results to decide on further reporting/monitoring/discontinuation.
Note:

- "Baseline" refers to ALT sampled at Baseline visit; or if Baseline value unavailable, to the latest ALT sampled before the Baseline visit. The algorithm does not apply to the instances of increase in ALT during Screening.
- See Section 10.4 for guidance on safety reporting.
- Normalization is defined as ≤ ULN or Baseline value, if Baseline value is >ULN.

INCREASE IN CPK SUSPECTED TO BE OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



Increase in creatine phosphokinase (CPK) is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting AEs in Section 10.4.3 is met.

Appendix D Guidance for the follow-up of acute worsening of renal function

Rapid change in renal function of greater than **30% as compared** with the **mean of the prior two study visits**

- Evaluate if the patient is taking medications which alter serum creatinine such as: trimethoprim, fenofibrate, non-steroidal anti-inflammatory agents, cimetidine, cephalosporins, probenecid, aminoglycosides, amphotericin, ketoconazole, clofibrate, contrast agents
- Evaluate if any of the following conditions are present that may alter serum creatinine:
  - Significant increase or decrease in blood pressure due to changes in antihypertensive therapy or diuretic treatment
  - Plasma volume depletion or expansion
  - Flu-like symptoms
  - Infected urine
  - Obstructive uropathy
  - New onset or exacerbation of heart failure
- If any of the above conditions are met, the Investigator should take corrective measures to resolve and schedule an interim visit to evaluate the serum creatinine/GFR and the patient's clinical status 1 week from the institution of corrective measures. Patients 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. If acute renal failure is suspected, further clinical evaluation should be performed as per local standard of care, including confirmation of renal laboratory parameters, and consideration should be given to a nephrology referral.
- Permanent discontinuation of IMP should be a last resort, and if IMP needs to be withheld, it should be done so temporarily when possible. Permanent discontinuation of IMP is required if eGFR <15 mL/min/1.73m^2 that has been confirmed on repeated testing and in the absence of a reversible cause (see protocol Section 10.3.3).

Appendix E Definition of urgent heart failure visit

An urgent HF visit is defined as an event that meets all of the following (adapted from 51):

- The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization
- All signs and symptoms for HF hospitalization must be met, including:
  - Symptoms as noted in **Section I** below
  - Physical examination findings/laboratory evidence of new or worsening HF, as indicated in **Section II** below
- The patient receives initiation or intensification of treatment specifically for HF, as detailed in **section III** (below) (note that oral diuretic therapy will not be sufficient)

Section I Symptoms:

The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following:

A) Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)

B) Decreased exercise tolerance

C) Fatigue

D) Other symptoms of worsened end-organ perfusion or volume overload (as detailed in the CEC charter)

Section II Physical examination findings/laboratory evidence

The patient has objective evidence of new or worsening HF, consisting of at least **TWO** physical examination findings **OR ONE** physical examination finding and at least **ONE** laboratory criterion, including:

A) Physical examination findings considered to be due to HF, including new or worsened:

1. Peripheral edema
2. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
3. Pulmonary rales/crackles/crepitations
4. Increased jugular venous pressure and/or hepatojugular reflux
5. S3 gallop
6. Clinically significant or rapid weight gain thought to be related to fluid retention

B) Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:

1. Increased B-type natriuretic peptide (BNP)/NT-proBNP concentrations consistent with decompensation of HF (such as BNP >500 pg/mL or NT-proBNP >2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline
2. Radiological evidence of pulmonary congestion
3. Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' >15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract minute stroke distance (time velocity integral)
   OR
4. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mmHg, central venous pressure ≥12 mmHg, or a cardiac index <2.2 L/min/m^2

Section III Initiation or intensification of treatment specifically for HF

At least **ONE** of the following:

A) Intravenous diuretic or vasoactive agent (eg, inotrope, vasopressor, or vasodilator)

B) Mechanical or surgical intervention, including:

1. Mechanical circulatory support (eg, intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)
2. Mechanical fluid removal (eg, ultrafiltration, hemofiltration, dialysis)

Appendix F Country-specific requirements

Amendment for India

Clinical Trial Summary and Section 7.2 Exclusion criteria (Section 7.2)

The following text has been added to E 24. Laboratory findings at the Screening Visit:

Specific to India: HbA1c >10% (86 mmol/mol) (central laboratory); see Appendix F

Section 10.1.1.1 On-site Visit 1 (Week -4) Screening Visit (Section 10.1.1.1)

The following text has been added:

Specific to India: HbA1c ≥7% (53 mmol/mol) to ≤10% (86 mmol/mol) (central laboratory); see Appendix F.

Section 8.8.1 Antihyperglycemic concomitant medication (Section 8.8.1)

The following text:

After the first 12 weeks post Randomization and during the remaining Double-blind Treatment period, the management of glycemia will be left to the Investigator's and/or treating provider's judgment, informed by clinical guidelines and local/regional standards of care. The Investigator and/or treating provider will therefore be allowed to undertake appropriate action, ie,

- Adjust the dose of the background antihyperglycemic treatment
- Prescribe an additional antihyperglycemic medication according to its labeling (no SGLT2 inhibitor should be used)
- Remove an antihyperglycemic treatment

Antihyperglycemic therapy is to be reported in the e-CRF.

Is replaced with:

After the first 12 weeks post Randomization and during the remaining Double-blind Treatment period, the management of glycemia will be left to the Investigator's and/or treating provider's judgment, informed by clinical guidelines and local/regional standards of care. The Investigator and/or treating provider will therefore be allowed to undertake appropriate action, ie,

- Adjust the dose of the background antihyperglycemic treatment
- Prescribe an additional antihyperglycemic medication according to its labeling (no SGLT2 inhibitor should be used)
- Remove an antihyperglycemic treatment

Specific to India: Rescue criteria for patients with uncontrolled hyperglycemia (see Appendix F).

Antihyperglycemic therapy is to be reported in the e-CRF.

Related to this amendment for India:

It has to be noted that at any time during the study after 12 weeks, if, in the opinion of the Investigator/treating healthcare provider, glucose control is not adequate over a sustained period of time, despite up-titration of background antihyperglycemic therapy, rescue medication should be considered, if medically indicated. The choice of rescue medication should be based on the Investigator's/treating healthcare provider's medical judgment, taking into consideration the patient's clinical status, co-morbidities and background therapy, in accordance with clinical guidelines such as the Research Society for the Study of Diabetes in India (RSSDI) clinical practice recommendations for the management of Type 2 diabetes mellitus, American Diabetes Association (ADA), Standards of Medical Care in Diabetes or European Association for the Study of Diabetes (EASD) management of hyperglycaemia in Type 2 diabetes. All medication must be administered in accordance with the local prescribing information, taking into account potential contraindications for the individual patient. Other SGLT2 inhibitors must not be used.

Amendment for Canada and United States of America

Section 1.2 Study Flow Chart (Section 1.2)

The following text in Footnote 'o':

Approximately 190 patients (95 females and 95 males) will be enrolled into the DXA sub-study. 25-hydroxyvitamin D will be drawn at the Screening Visit to allow assessment of eligibility for the sub-study. The DXA scan and 24-hour urine collection (for calcium, creatinine, and phosphorus) will be performed during the Screening period prior to Randomization for patients who sign the dedicated informed consent form and otherwise meet the eligibility criteria for the sub-study at the time of the Screening Visit; urine samples specific to the sub-study (see Appendix B) should be returned prior to or at Visit 2 (Randomization).

Serum markers of bone and calcium metabolism will otherwise be performed at Day 1 (Visit 2). At the end of treatment (pEOT Visit for patients who prematurely permanently discontinue and the Study Closeout Visit for patients who completed treatment), a DXA scan, 24-hour urine collection and serum markers of bone and calcium metabolism will be performed.

Is replaced with:

Approximately 190 patients (95 females and 95 males) will be enrolled into the DXA sub-study. 25-hydroxyvitamin D will be drawn at the Screening Visit to allow assessment of eligibility for the sub-study. The DXA scan and 24-hour urine collection (for calcium, creatinine, and phosphorus) will be performed during the Screening period prior to Randomization for patients who sign the dedicated informed consent form and otherwise meet the eligibility criteria for the sub-study at the time of the Screening Visit; urine samples specific to the sub-study (see Appendix B) should be returned prior to or at Visit 2 (Randomization).

Fasting serum ~~Serum~~ markers of bone and calcium metabolism will otherwise be performed at Day 1 (Visit 2). At the end of treatment (pEOT Visit for patients who prematurely permanently discontinue and the Study Closeout Visit for patients who completed treatment), a DXA scan, 24-hour urine collection and fasting serum markers of bone and calcium metabolism will be performed.

Section 10.1.1.1 On-site Visit 1 (Week -4) Screening Visit (Section 10.1.1.1)

The following text:

- For patients participating in the DXA sub-study:
  - A sample will be taken for 25-hydroxyvitamin D
  - 24-hour urine collection will need to be scheduled during Screening/prior to the Randomization Visit (Visit 2) (see Appendix B)
  - A DXA scan will need to be scheduled during Screening/prior to the Randomization Visit (Visit 2) for eligibility assessment (see Appendix B)

    Note: If a patient has had a BMD value documented within the last year and the T score is not <-2.0 at any site the patient may proceed to Randomization prior to receiving the results of the BMD value performed during Screening.

Is replaced with:

- For patients participating in the DXA sub-study:
  - A sample will be taken for 25-hydroxyvitamin D
  - 24-hour urine collection will need to be scheduled during Screening/prior to the Randomization Visit (Visit 2) (see Appendix B)
  - A DXA scan will need to be scheduled during Screening/prior to the Randomization Visit (Visit 2) for eligibility assessment (see Appendix B)
  - Please remind patients to fast prior to Visit 2 (see Appendix B)

    Note: If a patient has had a BMD value documented within the last year and the T score is not <-2.0 at any site the patient may proceed to Randomization prior to receiving the results of the BMD value performed during Screening.

Section 10.1.2.1 On-site Visit 2 (Day 1) Randomization (Section 10.1.2.1)

The following text:

- For patients at sites participating in the DXA sub-study who have consented to, and are eligible for, DXA sub-study:
  - Markers of bone and calcium metabolism (see Appendix B for details)

Is replaced with:

- For patients at sites participating in the DXA sub-study who have consented to, and are eligible for, DXA sub-study:
  - Fasting markers ~~Markers~~ of bone and calcium metabolism (see Appendix B for details)

Section 10.1.3.1 Premature End-of-Treatment Visit (Section 10.1.3.1)

The following text:

- For patients at participating sites who are participating in the DXA sub-study:
  - DXA scan
  - Markers of bone and calcium metabolism (including 24-hour urine collection; see Appendix B for full list)

Is replaced with:

- For patients at participating sites who are participating in the DXA sub-study:
  - DXA scan
  - Fasting markers ~~Markers~~ of bone and calcium metabolism (including 24-hour urine collection; see Appendix B for further details ~~full list~~)

Section 10.1.4.1 Study Closeout Visit for patients who do not prematurely discontinue investigational medicinal product (Section 10.1.4.1)

The following text:

- For patients at participating sites who are participating in the DXA sub-study:
  - DXA scan
  - Markers of bone and calcium metabolism (see Appendix B for full list)

Is replaced with:

- For patients at participating sites who are participating in the DXA sub-study:
  - DXA scan
  - Fasting markers ~~Markers~~ of bone and calcium metabolism (see Appendix B for further details ~~full list~~)

Section 11.4.2.2 Analyses of secondary efficacy endpoints (Section 11.4.2.2)

The following text:

Other endpoints

Other time to event endpoints will be analyzed using the same Cox proportional hazards model described for the primary endpoints with treatment, region, and HF criteria as factors. Nominal p-values from the stratified log-rank test may be provided.

Summary statistics of results and changes from Baseline in HbA1C, body weight, BP, UACR, and eGFR at scheduled visits using observes cases with no formal testing will be provided. Graphical presentations will also be used to illustrate trends over time. Baseline for eGFR and UACR is defined as the average of all values assessed by the central laboratory from Screening up to and

including Randomization. For the remaining parameters, baseline is defined as the last available value before the first dose of double-blind IMP or the last available value on or before the day of randomization for patients who were randomized but never exposed to IMP.

Is replaced with:

Other endpoints

Other time to event endpoints will be analyzed using the same Cox proportional hazards model described for the primary endpoints with treatment, region, and HF criteria as factors. Nominal p-values from the stratified log-rank test may be provided.

Summary statistics of results and changes from Baseline in HbA1C, body weight, BP, UACR, and eGFR at scheduled visits using ~~observes~~ observed cases with no formal testing will be provided. Graphical presentations will also be used to illustrate trends over time. Baseline for eGFR and UACR is defined as the average of all values assessed by the central laboratory from Screening up to and including Randomization. For the remaining parameters, baseline is defined as the last available value before the first dose of double-blind IMP or the last available value on or before the day of randomization for patients who were randomized but never exposed to IMP.

Appendix B Dual-energy X-ray absorptiometry sub-study (Appendix B)

SUB-STUDY PROCEDURES

The following text:

Select sites from this trial will be asked to participate in the DXA sub-study. Sites selected to participate in the sub-study will have IRB/EC approval for the main study and for the sub-study, and an additional informed consent. Patients who have signed informed consent for the main study of this trial at these select sites and are deemed eligible for the study at Screening will be asked to participate in the sub-study. Once the additional written informed consent is obtained for the sub-study, the patients will undergo the following assessments. Written informed consent must be obtained prior to any study investigations.

Is replaced with:

Select sites from this trial will be asked to participate in the DXA sub-study. Sites selected to participate in the sub-study will have IRB/EC approval for the main study and for the sub-study, and an additional informed consent. Patients who have signed informed consent for the main study of this trial at these select sites and are deemed eligible for the study at Screening will be asked to participate in the sub-study. Once the additional written informed consent is obtained for the sub-study, the patients will undergo the following assessments. Written informed consent must be obtained prior to any study investigations.

Note: Patients should be instructed to come to Visit 2 (Day 1) and other fasting visits (either premature end-of-treatment or study closeout visit) in the morning after at least an 8 hour fast. This includes no food or drink other than water, and no medications, multivitamins or dietary supplements for the duration of the fast. Attempts should be made to perform blood sampling at the premature-end-of-treatment/study closeout visit at approximately the same time of day as the samples performed on the day of randomization.

Visit 2 (Day 1)

The following text:

- Samples for central laboratory assessment of markers of bone and calcium for patients who meet all entry criteria as follows:
  - Serum: calcium, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, phosphorus, PTH, NTX, β-CTX-1, and P1NP

Is replaced with:

- Fasting morning samples ~~Samples~~ for central laboratory assessment of markers of bone and calcium metabolism for patients who meet all entry criteria as follows:
  - Serum: calcium, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, phosphorus, PTH, NTX, β-CTX-1, and P1NP

Premature End-of-Treatment/Study Closeout Visit

The following text:

- Samples for central laboratory assessment of markers of bone and calcium as follows:
  - 24-hour urine collection: calcium, phosphorus, creatinine
  - Serum: Calcium, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, phosphorus, PTH, NTX, β-CTX-1, and P1NP

Is replaced with:

- ~~Samples for central~~ Central laboratory assessment of markers of bone and calcium metabolism, including fasting morning serum samples, as follows:
  - 24-hour urine collection: calcium, phosphorus, creatinine
  - Serum: Calcium, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, phosphorus, PTH, NTX, β-CTX-1, and P1NP.

Appendix G Protocol amendment history

Protocol Amendment 01: 12-Jan-2018 Canada and United States of America only

- Change to the conditions under which laboratory assessments for the bone sub-study at the randomization and end of treatment visits are being conducted

In section(s): Study Flow Chart, sections 10.1 & Appendix B of the protocol

Rationale: In order to secure the reliability of the markers of bone turnover, the study protocol is being amended to secure that this testing is performed under controlled conditions, including after an overnight fast and in the early morning hours in order to limit the impact of circadian rhythms and meal intake on the markers of bone turnover in order to reduce these controllable sources of variability.

In addition, other minor changes are listed in the description of changes.

Please note that this protocol amendment is applicable to the following regions only: Canada and the United States of America.

EFC14875 16.1.1 Amended Protocol 01

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Regulatory Approval	31-Aug-2018 13:42 GMT+0200
[redacted]	Clinical Approval	03-Sep-2018 08:56 GMT+0200
[redacted]	Clinical Approval	03-Sep-2018 10:55 GMT+0200