Official Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Effects of SOtagLiflozin on Clinical Outcomes in HemodynamIcally STable Patients with Type 2 Diabetes POST Worsening Heart Failure

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AMENDED CLINICAL TRIAL PROTOCOL 01

COMPOUND: sotagliflozin/SAR439954

A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Effects of SOtagLiflozin on Clinical Outcomes in Hemodynamically STable Patients with Type 2 Diabetes POST Worsening Heart Failure

STUDY NUMBER: EFC15156

STUDY NAME: SOLOIST-WHF Trial

Regulatory agency identifying number(s):		EudraCT IND Number WHO universal trial number:	2017-003510-16 [redacted] U1111-1190-7891
Approval Date:	17-Dec-2018	Total number of pages:	142

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		

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 01	All	17-Dec-2018; version 1 (electronic 1.0)
Original Protocol		05-Jan-2018; version 1 (electronic 1.0)

Amended protocol 01 (17-Dec-2018)

This amended protocol (amendment 01) is considered to be substantial based on the criteria set forth in Article 10 (a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The procedures related to the endpoint of detection of premature ventricular complexes in the subgroup of patients with an implantable cardioverter defibrillator or cardiac resynchronization therapy device are not operationally feasible. Therefore, the protocol has been amended to remove this endpoint. The mechanistic sub study will not be conducted for this study as the procedures for the assessments are not operationally feasible; the protocol has been amended accordingly.

Following advice from the external steering committee which provides scientific and clinical leadership for the study, a new objective and endpoint have been added to compare sotagliflozin versus placebo on the time of first occurrence of cardiovascular death and hospitalization for heart failure, in subgroups of patients who started first IMP dose before and after hospital discharge.

The protocol has been revised to clarify the use of the clinical laboratory and 12-lead ECG assessments obtained by the time of hospitalization due to heart failure to formally screen the patients, thereby reducing the redundancy of procedures in recently hospitalized patients. This facilitates the Screening and Randomization on the same day.

The order of secondary endpoints has been revised and the multiplicity testing procedure has been updated from fixed sequence approach to graphical approach in response to U.S. Food and Drug Administration (FDA) recommendation.

In addition, minor editorial corrections, and document formatting revisions have been made throughout the document.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial summary: Study Objective: Secondary objectives, Endpoints: Secondary endpoints, Statistical considerations Section 5.2: Secondary objectives Section: 9.1.2 Secondary efficacy endpoints	Re-ordered secondary objectives and secondary endpoints.	Re-ordered as per FDA recommendation.
Clinical Trial Summary: Other Objective, Other endpoint Section 5.3: Other Objectives Section 9.1.3: Other endpoint	Objective and endpoint added to compare sotagliflozin versus placebo on the time of first occurrence of cardiovascular death and hospitalization for heart failure in subgroups of patients who started first IMP dose prior vs after hospital discharge (or urgent care facility where appropriate).	New endpoint is added following advice from the external steering committee which provides scientific and clinical leadership for the study.
Clinical Trial Summary: Other Objective, Other endpoint, Section 1.2: Study Flow Chart Section 5.3: Other objectives Section 9.1.3: Other efficacy endpoints Section 10.1.2.3: On-site Visit 5 (Week 4) Section 10.1.2.4: On-site Visit 6 (Month 4)	Deleted other objective to compare sotagliflozin versus placebo on the occurrence of premature ventricular complexes in the subgroup of patients with an implantable cardioverter defibrillator or cardiac resynchronization therapy device at Baseline. All corresponding measurements and endpoint are removed.	The objective, corresponding measurements, and endpoint are removed as the procedures for these assessments were not operationally feasible.
Clinical Trial Summary: Study Objective; Study design; Main selection criteria: inclusion criteria and exclusion criteria; Endpoints; Section 5.4: Mechanistic substudy Section 6.1 Description of the study Section 7.1.3 Mechanistic substudy Section 7.2.3 Mechanistic substudy	Deleted information regarding mechanistic substudy.	Mechanistic substudy will not be performed for this study as the procedures for the assessments are not operationally feasible for the sites.
Clinical Trial Summary: Statistical consideration: Multiplicity adjustment Section 11.4.2.4: Multiplicity considerations	The fixed sequence approach changed to an alpha passing concept (eg, Bretz et al.) to allow for testing important secondary endpoint(s) without requiring previous tested endpoints to be statistically significant.	Changed based on FDA recommendation.
Clinical Trial Summary: Main selection criteria-Exclusion criteria Section 7.2.1 Exclusion criteria related to study methodology: E 12	Deleted hypertrophic obstructive cardiomyopathy from E 12.	This information is repeated in E 13.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary: Study committees	Deleted Independent Expert Committee	Removed as the mention of independent expert committees is not part of the clinical trial summary protocol template. These additional committees are described further in the text of the protocol.
Section 1.2 Study flow Chart; Footnote k Section :9.2.2.1: Urinalysis Section 10.1.2.1: On-site Visit 2 (Day 1) Randomization Section 10.1.2.4: On-site Visit 6 (Month 4) Section 10.1.2.5: On-site Visits 7 to 12 (Months 8,12,16,20,24,28) Section 10.1.3.1: Premature End-of-Treatment Visit Section 10.1.4.1: Study closeout Visit for patients who do not prematurely permanently discontinue investigational medicinal product Section 10.1.4.2: Study closeout Visit for patients who prematurely permanently discontinue investigational medicinal product	Removed urine glucose testing throughout the protocol.	Suggested by the Steering committee to remove reporting of urine glucose results as it may potentially unblind the Investigators and the Sponsor.
Section 8.7.1: Treatment accountability and compliance	Deleted sentence regarding telephone visit.	Although the protocol specifies that the patient may be contacted by telephone to inquire about safety status (including outcomes), there are no mandatory telephone visits in this study.
Section 9.1.3.2: Kansas City Cardiomyopathy Questionnaire-12	Deleted sentence on open-ended questions within KCCQ-12 questionnaire.	Removed as the KCCQ-12 questionnaire does not include open-ended questions.
Section 10.4.2: Serious adverse events waived from expedited regulatory reporting to regulatory authorities	Deleted renal adverse events from AEs waived from expedited reporting.	Renal events will not be waived from regulatory reporting to health authorities.
Section 11.4.3.1: Analysis of adverse events; Death and serious adverse events	Deleted details of the analysis of death.	Changes are being implemented to be consistent with Sponsor protocol template. The details will be further specified in the SAP.
Section 17: Appendix F: Diabetic ketoacidosis	Deleted the text to complete the “Possible DKA” in eCRF.	This information is not relevant for instructions targeted to the patient audience. These instructions were more relevant to the investigator and provided separately.
Section 10.4.2: Serious adverse events waived from expedited regulatory reporting to regulatory authorities	Added unstable angina to the list of CV events waived from expedited reporting.	To be consistent with feedback from Health Authorities.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary: Main selection criteria-Exclusion criteria: E 18 Section 7.2.1 Exclusion criteria related to study methodology: E 18	Modified E 18 to include hypersensitivity to any of the excipients included in placebo.	Exclusion criterion modified as per request from a health authority.
Clinical trial summary: Exclusion criteria E29 Section 1.2: Study Flow Chart: footnote m Section 7.2.2: Exclusion criteria: Exclusion criteria related to the current knowledge of sotagliflozin, E 29 Section 9.2.2: Laboratory safety variables	Revised to include additional tests on pregnancy to be performed as per Investigator's discretion or at frequency specified by local regulations.	Revised as per the request from health authority and ethics committee of certain countries, to perform pregnancy tests every 3 months.
Section 1.2 Study flow chart; footnote k Section 10.1.2.5: On-site Visits 7 to 12 (Months 8,12,16,20,24,28)	Added the measurement of HbA1c to be performed at month 16 (Visit 9)	The HbA1c should be performed every 4 months to be consistent with glycemic monitoring throughout the study.
Section 1.2 Study flow chart; footnote l Section 10.1.5.1: Follow-Up Visit	Added the measurement of eGFR to the assessments to be conducted at the follow-up visit performed 10 days ± 4 days after discontinuation of study treatment.	Sotagliflozin may cause hemodynamic changes in renal function. Per, FDA recommendation, eGFR to be measured after discontinuation of study treatment.
Section 4.3: Benefit/Risk Profile	Added potential benefits of sotagliflozin outweigh potential risks for patients with T1D and T2D.	Updated to be consistent with IB and program level information.
Section 8.8.2: Management of blood pressure and renal function Section 10.1.2.1 On-site Visit 2 (Day 1) Randomization	Corrected to 'all attempts should be made not to modify or discontinue the ACE-i/ARB, which should be at optimum **or** maximally tolerated doses'.	Corrected to provide guidance to Investigators to ensure patients will receive standard of care with approved therapies consistent with clinical guidelines.
Section 8.8.3 Management of heart failure Section 9.1.3.3: Concomitant medication by class Section 10.1.2.1: On-site Visit 2 (day 1) randomization	Defined direct renin inhibitors as RAAS inhibitors.	Clarified as direct renin inhibitors are part of the Renin-Angiotensin-Aldosterone System.
Section 14.5: Data protection	General Data Protection Regulation reference added.	Included as per ethics committee request.
Section 17: Appendix C: KCCQ-12 questionnaire	A watermarked KCCQ-12 questionnaire added to Appendix C.	The PRO questionnaires should be indicated with a footnote with the version number and with a watermark "for review only".
Section 8.8.5: Other medications	P glycoprotein substrates and labels of P glycoprotein substrates added as other prohibited medications.	To clarify the questions from local countries and provide further clinically relevant information to investigators. This information also supplements guidance from the IB.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary: Other objective, other endpoint Section 5.3: Other objectives Section 9.1.3: Other efficacy endpoints	Clarified objective and endpoint related to the clinical events in patients with LVEF >50% to LVEF ≥50% and re-arranged in Section 5.3.	Clarified so that the patients with LVEF =50% will not be missed from analysis.
Clinical Trial Summary: Main selection criteria, Inclusion criteria Section 7.1.1: Inclusion criteria: At the Screening Visit	Clarified that the sites that plan to enroll patients who are not hospitalized (ie, admitted for at least 24 hours) should be qualified by Sponsor at the pre-site visit or a site visit to ensure the existence of appropriate facilities.	Sponsor must ensure appropriate facilities are present in sites enrolling patients who are not hospitalized.
Clinical Trial Summary: Main selection criteria-Inclusion criteria I 02 and I 08 Section 7.1.1: Inclusion criteria: At the Screening Visit I 02 Section 7.1.2: Inclusion criteria: At the Randomization Visit I 08	Clarified the inclusion of patients receiving treatment with IV **loop** diuretics and transitioning from IV to administration of oral **loop** diuretics.	Change is being implemented to further clarify for Investigators that patients must specifically be receiving loop diuretics at a minimum. The use of thiazide or other types of diuretics alone does not qualify the patient for the study.
Clinical Trial Summary: Main selection criteria-Exclusion criteria :E 06 Section 1.2: Study Flow Chart: footnote h Section 7.2.1: Exclusion criteria related to study methodology: E 06	Clarified exclusion of patients whose LVEF measurement is not available within 12 months prior to Screening instead of Randomization.	To be consistent across the document.
Clinical Trial Summary: Exclusion criteria E 06 Section 7.2.2: Exclusion criteria E06	Modified to include all diagnostic imaging to document historical LVEF at Screening.	Included all imaging modalities to document historical LVEF at Screening.
Clinical Trial Summary: Main selection criteria-Exclusion criteria :E 07 Section 7.2.1: Exclusion criteria related to study methodology: E 07	Clarified that patients with end-stage HF requiring LVAD, IABP or any mechanical support at the time of randomization will be excluded, but patients will not be excluded if IABP was used during index event.	Clarified that temporary use of IABP during index event does not exclude the patient from the study.
Clinical Trial Summary: Main selection criteria-Exclusion criteria: E 25 Section 7.2.1 Exclusion criteria related to the current knowledge of sotagliflozin: E 25	Clarified that patients with severe kidney disease will be excluded based on the eGFR value at Screening visit and not based on laboratory results during Randomization.	Eligibility for patients with severe kidney disease is assessed based on Screening eGFR value.
Clinical Trial Summary: Inclusion criteria I 09 Section 1.2: Study Flow Chart: footnote i Section 7.1.2: Inclusion criteria I 09 Section 10.1.1.1: On site Visit 1 (Week-2) Screening Visit	Clarified that if sites are unable to perform laboratory assessments at Screening locally, the tests can be done by central laboratory.	Since a number of sites are unable to perform the laboratory assessment locally, the tests may be done at the central laboratory.

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary: Other endpoint Section 9.1.3: Other efficacy endpoints	Time point specified for changes from baseline in loop diuretics.	Clarified time points for statistical analysis.
Section 1.2: Study Flow Chart: footnote n Section 9.2.2.1: Urinalysis	Modified to clarify urinalysis will be performed at the local laboratory at Visit 1 and subsequently at the central laboratory. If the urinalysis is positive for nitrite and leukocyte esterase or blood, reflexive testing will be performed at the local laboratory at Visit 1, and at the central laboratory for subsequent visits.	Availability of urinalysis results for nitrite and leukocyte esterase performed at the local laboratory may facilitate a diagnosis of urinary tract infection during screening.
Section 1.2: Study Flow Chart: footnote o Section 6.1.1: Study Design, Screening period Section 6.1.2: Study Design: Randomized double-blind treatment period Section 10.1.1: Study procedures: Screening period Section 10.1.2: Study procedures: Randomization double-blind treatment period	Clarified that blood samples for BNP or NT-proBNP collected at Screening to assess the patient's eligibility will be analyzed by the local laboratory. In addition, a blood sample for NT-proBNP will be collected at Randomization before taking IMP, and at any subsequent visits (when NT-proBNP is scheduled to be collected) will be analyzed by the central laboratory.	Clarified which BNP and NT-proBNP samples (at the Screening visit versus the Randomization visit and subsequent study visits) will be analyzed by the local laboratory and which ones will be analyzed by the central laboratory.
Clinical trial Summary: Exclusion criteria, E 30 Section 1.2: Study Flow Chart: footnote o Section 7.2.1: Exclusion criteria related to study methodology, E 30 Section 8.8.5: Other medications Section 9.2.2: Laboratory Safety variable: Table 2 footnotes Section 10.1.2.2 On-site Visits 3 (Week 1) and 4 (Week 2)	Clarified that digoxin assessment is performed using either serum or plasma, and that if sites are unable to perform the test locally the assessment will be done by central laboratory.	Since several sites are unable to perform the digoxin assessment locally, the tests may be done at the central laboratory.
Section 6.1.2 Randomized double-blind treatment period Section 8.1: Table 1 footnotes	Clarified the timing of the first IMP dosage for patients who come to the Randomization visit after having food. In such scenario, only those patients who are not fasting will be allowed to start treatment the following day before the first meal.	The IMP dose should be taken when fasting, before first meal of the day.

Section # and Name	Description of Change	Brief Rationale
Section 1.2: Study Flow Chart: footnotes c and i; Section 9.2.4: Electrocardiogram variables Section 10.1.1.1: On site Visit 1 (Week-2) Screening Visit	Modified to allow collection of historical data for laboratory and ECG assessments performed as standard of care after the Index event to formally screen the patients. Additionally, the Screening labs required to determine eligibility is clarified. Serum pregnancy test must be collected at Screening. Added collection of historical data for height if the patient is on bed rest at Screening.	Laboratory and ECG assessment are completed as standard of care for the patient population in this study since they are hospitalized. In order to reduce the redundancy of procedures, historical data following the Index Event obtained in the routine clinical management of the patient while hospitalized, can be used for Screening.
Clinical Trial Summary: Footnotes r	Clarified that Investigators should ensure to follow up all AEs until clinical recovery, or until death.	In order to ensure safety of the patients AEs should be followed up until clinical recovery which may continue beyond last planned visit.
Section 6.4.5 Safety events requiring ongoing monitoring Section 8.3.1: Methods of blinding Section 10.4.1.4: Events of special interest	Modified the title of subsection 6.4.5 to remove reference to adjudication. Also removed 'adjudication' from Section 8.3.1. Clarified that the safety committees will review the adverse events leading to amputation(s).	The events referred to in this section do not require adjudication, but require ongoing monitoring. Safety committee will review the adverse events leading to amputation(s).
Section 10.1.2: Study procedures: Randomization double-blind treatment period	Clarified that fasting is not necessary before blood draw.	Laboratory assessments performed at these time points need not be taken after fasting.
Section 10.3.1: Temporary treatment discontinuation with investigational medicinal products	Clarified that there is no defined limit for temporary discontinuation as the patient is expected to participate in the study for several years.	Not limiting the duration for temporary treatment discontinuation is standard for cardiovascular outcomes studies and an intention to treat analysis.
Section 10.4.1.3: Adverse event of special interest	Clarified the definition of overdose.	Defined to provide more clarity.
Section 10.4.1.2: Serious Adverse Event Section 10.4.1.3: Adverse event of special interest Section 10.5: Obligation of the sponsor Section 11.4.3.3: Analysis of adverse events of special interest	Clarified that the AESI criteria for ALT increase is defined as ALT ≥3 ULN (if baseline ALT < ULN) or ALT ≥2 times the baseline value (if baseline ALT ≥ ULN). Further clarified potential difference of AESI ALT elevation vs. SAE ALT elevation which may include assessment of bilirubin or degree of ALT elevation in asymptomatic patients.	Clarified to maintain consistency throughout the document and across the Sotagliflozin program.
Clinical Trial Summary: Inclusion criteria I 06 Section 7.1.1: At the Screening Visit, I 06	Clarified that a legally acceptable representative too can sign the informed consent.	Added to address comments and questions from Ethic committee and Health Authorities.

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Study flow Chart Section 8.7.1: Treatment accountability and compliance Section 10.1.2.1: On-site Visits 2 (Day 1) Randomization Section 10.1.2.2: On-site Visits 3 (Week 1) and 4 (Week 2) Section 10.1.2.3: On-site Visits 5 (Week 4)	Separated IMP accounting and compliance in the study flow chart and deleted the accountability of IMP at Visit 3, 4, and 5.	IMP accountability cannot be checked during the visits where IMP is not dispensed.
Section 1.2: Study Flow Chart: footnote g Section 8.7.1: Treatment accountability and compliance Section 8.7.2: Return and/or destruction of treatments Section 10.1.2.3: On-site Visit 5 (Week 4)	Clarified that in-use, used, and unused bottles should be brought back at Visit 6.	Pharmacies unable to comply with planned IMP accountability checks at each visit as it is not operationally feasible.
Clinical Trial Summary: Study Design Flowchart footnote f Section 6.1.2: Study Design, Randomized double-blind treatment period Section 10.1.2: Study procedures, Randomized double-blind treatment period	Clarified that Screening and Randomization visits can be conducted on the same day.	There is maximum 14 days between Screening and Randomization, and Randomization should occur prior to discharge or within 3 days after discharge, hence both visits can be on the same day.
Section 1.1: Graphical study design: footnote b Section 7.1.1: Inclusion criteria: At the Screening Visit: I 02	Patient admitted to the hospital or had ~~unplanned~~**urgent** HF visit to ED, Heart Failure Unit, or infusion center for WHF associated with intravascular volume overload (the Index Event), as determined by Investigator (based on appropriate supportive documentation).	Typographical error
Throughout the document	Minor editorial, typographical error corrections, and document formatting revisions have been made throughout the document.	Minor changes, therefore have not been summarized

Abbreviations: ACE-I = angiotensin-converting enzyme inhibitor; AE = adverse event; AESI = adverse event of special interest; ALT = alanine transaminase; ARB = angiotensin receptor blocker; BNP = b type natriuretic peptide; CV = cardiovascular; DKA = diabetic ketoacidosis; ECG = electrocardiogram; eCRF = electronic case report form; ED = emergency department; eGFR = glomerular filtration rate; FDA = Food and Drug Administration; HbA1c = glycated hemoglobin; HF = heart failure; IABP = intra-aortic balloon pump; IB = investigator's brochure; IMP = investigational medicinal product; IV = intravenous; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVAD = left ventricular assist device; LVEF = left ventricle ejection fraction; NT-proBNP = N-terminal B-type natriuretic peptide; PRO = patient reported outcome; RAAS = renin-angiotensin-aldosterone system; SAP = statistical analysis plan; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus; ULN = upper limit of normal; WHF = worsening heart failure.

CLINICAL TRIAL SUMMARY

COMPOUND: sotagliflozin/SAR439954	**STUDY No.: EFC15156** **STUDY NAME: SOLOIST-WHF Trial**
TITLE	A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Effects of SOtagLiflozin on Clinical Outcomes in HemodynamIcally STable Patients with Type 2 Diabetes POST Worsening Heart Failure
INVESTIGATOR/TRIAL LOCATION	Multinational
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVES	**Primary objectives:** • To demonstrate that sotagliflozin reduces cardiovascular (CV) mortality and morbidity (composite of CV death or hospitalization for heart failure [HHF]) compared to placebo in hemodynamically stable patients with type 2 diabetes (T2D) and heart failure (HF) with a left ventricular ejection fraction (LVEF) <50%, after admission for worsening heart failure (WHF). • To demonstrate that sotagliflozin reduces CV mortality and morbidity (composite of CV death or HHF) compared to placebo in hemodynamically stable patients with T2D and heart failure, irrespective of LVEF, after admission for WHF (total patient population). **Secondary objectives:** • To demonstrate that, when compared to placebo, in the total patient population, sotagliflozin reduces the total number (ie, including recurrent events) of the following clinical events: - Cardiovascular death, HHF, or urgent HF visit (see Appendix B) • To demonstrate that, when compared to placebo, sotagliflozin reduces: - Cardiovascular death in patients with LVEF <50% - All-cause mortality in patients with LVEF <50% - The composite of positively adjudicated sustained ≥50% decrease in estimated glomerular filtration rate (eGFR) from Baseline (for ≥30 days), chronic dialysis, renal transplant or positively adjudicated sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days) in the total patient population - Cardiovascular death in the total patient population - All-cause mortality in the total patient population • To demonstrate the safety and tolerability of sotagliflozin in the total patient population

	Other: • To compare sotagliflozin versus placebo on the occurrence of the following events in the total patient population: - Hospitalization for heart failure or urgent HF visit (see Appendix B) within 30 days of Randomization - At least 50% decrease in eGFR from Baseline (for ≥30 days) - Myocardial infarction (MI; fatal and nonfatal) - Stroke (fatal and nonfatal) • To compare sotagliflozin versus placebo with respect to the proportion of patients with ≥1 new onset of atrial fibrillation, atrial flutter, or ventricular arrhythmia from Randomization in the total patient population • To demonstrate that sotagliflozin reduces CV mortality and morbidity (composite of CV death or HHF) compared to placebo in hemodynamically stable patients with T2D and HF with LVEF <40%, after admission for WHF • To demonstrate that sotagliflozin reduces CV mortality and morbidity (composite of CV death or HHF) compared to placebo in hemodynamically stable patients with T2D and HF with LVEF ≥40% to <50%, after admission for WHF • To demonstrate that sotagliflozin reduces CV mortality and morbidity (composite of CV death or HHF) compared to placebo in hemodynamically stable patients with T2D and HF with LVEF ≥50% after admission for WHF • To demonstrate that, when compared to placebo, sotagliflozin reduces all-cause mortality in patients with LVEF <40% • To compare sotagliflozin versus placebo in the total patient population with respect to changes from Baseline in the following endpoints: - Hemoglobin A1c - Body weight • To compare sotagliflozin versus placebo with respect to changes in Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) scores from Baseline in the total patient population • To compare sotagliflozin versus placebo with respect to changes in N-terminal B-type natriuretic peptide (NT-proBNP) from Baseline in the total patient population • To compare sotagliflozin versus placebo with respect to changes in loop diuretics from Baseline in the total patient population • To compare sotagliflozin versus placebo for changes in hemoconcentration from Baseline in the total patient population

	• To compare sotagliflozin versus placebo for changes in hemoconcentration from Baseline in patients with LVEF <40% • To compare sotagliflozin versus placebo on the time to first occurrence of either of the following clinical events in subgroups of patients who started first IMP dose prior vs. after hospital discharge (or urgent care facility where appropriate): - Cardiovascular death - Hospitalization for heart failure
STUDY DESIGN	This study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in about 4000 hemodynamically stable patients with T2D who have been admitted to the hospital, a HF unit, infusion center, or Emergency Department (ED) for WHF with intravascular volume overload. The study will consist of 3 periods: • A Screening period (up to 14 days) • A Randomized, double-blind treatment period that will include an initial up-titration period • A Post-treatment period of 14 days (±4 days). The Screening and Randomization visits may be conducted on the same day. Patients who meet all eligibility criteria will be randomized 1:1 to sotagliflozin or placebo at the Randomization Visit (Visit 2 [Day 1]) that will take place prior to hospital discharge or within 3 days after discharge (from hospital, HF unit, infusion center, or ED). Randomization will be stratified by LVEF (LVEF <50% and LVEF ≥50%) and region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world). The number of patients with LVEF ≥50% will be limited to approximately 1100, to ensure sufficient number of patients (ie, approximately 2900) with LVEF <50%. The double-blind study treatment will be initiated at Visit 2 (Day 1) after the patient has been randomized (ie, after a patient is hemodynamically stable and ready to transition from intravenous [IV] to oral diuretic therapy). Patients will receive sotagliflozin 200 mg or placebo at Visit 2 and will continue this regimen once daily (qd) until the next visit. Patients will return a week later at Visit 3 (Day 8). Clinical safety and tolerability (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]) will be assessed and blood (including serum creatinine) and urine laboratory samples will be collected. Patients will continue to receive sotagliflozin 200 mg or matching placebo qd until the next visit. Patients will return a week later at Visit 4 (Day 15). Clinical safety and tolerability (including vital signs and collection of AEs, including EOSIs, AESIs, and SAEs) will be assessed and laboratory results from the prior week (including serum creatinine) will be reviewed, and new laboratory samples (blood and urine) will be collected. 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 volume depletion, symptomatic hypotension (eg,

	dizziness, lightheadedness), or other AEs intolerable to the patient such as severe polyuria or nocturia, the dose will be up-titrated to sotagliflozin 400 mg or matching placebo qd until the next visit. The patient will then return for Visits at Month 1 (Day 29), Month 4, and every 4 months thereafter until the end of the study. If the patient does not meet up-titration criteria for safety reasons (eg, hypotension), the Investigator will have the option of either continuing IMP at the dose of 200 mg or placebo, with the optional adjustment of concomitant medications, or discontinuing IMP temporarily. If the dose is not up-titrated for safety reasons, the Investigator should make all attempts to up-titrate the dose at 1 of the next 3 subsequent visits: Visit 5 (Month 1), Visit 6 (Month 4), or Visit 7 (Month 8). In patients who cannot reach the dose of 400 mg or matching placebo during the first 8 months after Randomization (Visit 7), the dose of 200 mg or matching placebo will be used throughout the study. If at any time during the study, the dose of 400 mg or placebo is not well-tolerated, the dose can be down-titrated (to 200 mg or matching placebo), 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. Sotagliflozin/metabolite levels may be analyzed via routine blood samples collected throughout the study. Throughout the course of the study, if the double-blind treatment is down-titrated or temporarily discontinued, every effort should be made to resume the higher dose of double-blind treatment as early as possible (unless there are safety concerns) so that patients are kept on the maximal tolerated study dose of double-blind treatment for as long as possible throughout the double-blind period of the trial. **This is an event-driven study.** The study will end when approximately 947 primary events have been positively adjudicated (ie, number of patients with at least 1 positively adjudicated primary event) in patients with LVEF <50%, AND approximately 1341 primary events have been positively adjudicated (ie, number of patients with at least 1 positively adjudicated primary event) in the total patient population. 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. Patients will continue taking IMP after a CV or renal endpoint occurs unless the criteria for permanent treatment discontinuation have otherwise been met.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** **At the Screening Visit** *The Screening Visit should be no more than 14 days prior to Randomization.* ***Please note: sites that plan to enroll patients who have not been hospitalized (ie, admitted for at least 24 hours) will need to be qualified by the Sponsor at the pre-site visit or a site visit to ensure the existence of appropriate facilities.***

	I 01. Either: A) Diagnosis of T2D, based on appropriate supportive documentation for patients with a diagnosis of T2D prior to the Index Event OR B) For patients diagnosed with T2D at the time of the Index Event, laboratory evidence is required as follows: • Fasting plasma glucose ≥126 mg/dL OR • Random plasma glucose ≥200 mg/dL OR HbA1c ≥6.5% I 02. Patient admitted to the hospital or had urgent HF visit to ED, HF Unit, or infusion center for WHF with intravascular volume overload (the Index Event), as determined by Investigator (based on appropriate supportive documentation) and defined by: • Presence of ≥2 of the following clinical signs and symptoms of congestion: - Dyspnea - Jugular venous distention - Pitting edema in lower extremities (>1+) - Rales heard on auscultation - Radiographic pulmonary congestion AND • Patient received treatment with IV loop diuretics I 03. Patient had a diagnosis of HF ≥3 months prior to Screening (based on appropriate supportive documentation) I 04. Prior chronic treatment (or prescription) with a loop diuretic (eg, furosemide, torsemide, bumetanide) for ≥30 days prior to the Index Event I 05. Patients with LVEF <40% should be on beta-blockers and RAAS inhibitors as per local guidelines unless contraindicated I 06. Patient or a legally acceptable representative has signed written informed consent to participate in the study in accordance with local regulations At the Randomization Visit Prior to hospital discharge if applicable, or within 3 days after discharge from hospital, ED, HF unit, or infusion center I 07. Patient is hemodynamically stable, defined as: • Systolic blood pressure ≥100 mmHg, AND • No requirement for IV inotropic therapy or IV vasodilators (except for nitrates) and no treatment with IV inotropic or IV vasodilators within 2 days prior to Randomization AND • No requirement for mechanical ventilation or oxygen therapy in the last 24 hours

	I 08. Transitioning from IV to oral diuretics defined as: • Intravenous diuretic has been discontinued, AND • Chronic oral loop diuretic has been prescribed and/or administered I 09. At least 1 of the following laboratory values between admission for the Index Event and Randomization (based on local laboratory or central laboratory): • B-type natriuretic peptide (BNP) ≥150 pg/mL (≥450 pg/mL for patients with atrial fibrillation) OR • N-terminal B-type natriuretic peptide ≥600 pg/mL (≥1800 pg/mL for patients with atrial fibrillation) **Note**: *The presence or absence of atrial fibrillation in order to determine the appropriate cut-off for a given BNP/NT-proBNP sample should be evaluated using the latest available electrocardiogram (ECG; or telemetry data) performed prior to that BNP/NT-proBNP sample.* **Exclusion criteria:** E 01. Age <18 years (or legal age for the country of participation) or >85 years at the Screening Visit E 02. Index Event (admission for worsening HF associated with intravascular volume overload – see I 02) primarily triggered by pulmonary embolism, cerebrovascular accident, or acute myocardial infarction (AMI) **Note:** Troponin elevations are frequently seen in patients with WHF and therefore are not sufficient for a diagnosis of AMI. In order to exclude patient due to AMI, concomitant objective evidence of AMI from ECG, and/or cardiac imaging and/or coronary angiography should be available. E 03. Index Event (admission for WHF – see I 02) for WHF not caused primarily by intravascular volume overload. For example, Index Event triggered by significant arrhythmia (eg, sustained ventricular tachycardia, or atrial fibrillation/flutter with sustained ventricular response >130 beats per minute, or bradycardia with sustained ventricular arrhythmia <45 beats per minute), infection severe anemia, or exacerbation of chronic obstructive pulmonary disease (COPD) E 04. Hospitalization for index event >2 weeks E 05. Acute coronary syndromes within 3 months prior to Randomization E 06. Ejection fraction not assessed by the time of Randomization (ie, no LVEF assessment performed following the Index Event and no LVEF measurement available within 12 months prior to Screening via imaging modality (such as echocardiogram, Multiple Gated Acquisition (MUGA) scan, Magnetic Resonance Imaging (MRI), positron emission tomography (PET),

		single-photo emission computed tomography (SPECT), left ventricular (LV) angiography)
	E 07.	End-stage HF defined as requiring left ventricular assist devices (LVAD), intra-aortic balloon pump (IABP), or any type of mechanical support at the time of Randomization.
	E 08.	Cardiac surgery (coronary artery bypass graft), percutaneous coronary intervention (PCI), implantation of cardiac device (including biventricular pacemaker), or cardiac mechanical support implantation within 1 month prior to Randomization or planned during the study
	E 09.	Hemodynamically significant uncorrected primary cardiac valvular disease (please note that secondary mitral regurgitation or tricuspid regurgitation due to dilated cardiomyopathy is not excluded)
	E 10.	Significant pulmonary disease contributing substantially to the patients' dyspnea such as forced expiratory volume in 1 second (FEV_1) <1 liter or need for chronic steroid therapy, or any kind of primary right heart failure such as primary pulmonary hypertension or recurrent pulmonary embolism
	E 11.	Heart failure caused by postpartum cardiomyopathy diagnosed within the past 6 months
	E 12.	Heart failure from uncorrected thyroid disease, active myocarditis, known amyloid cardiomyopathy
	E 13.	Obstructive hypertrophic cardiomyopathy
	E 14.	History of stroke within 3 months prior to Randomization
	E 15.	History of dialysis within 1 year prior to Randomization
	E 16.	History of solid organ transplant or inclusion on a transplant list (if a heart transplant, defined as status 1 transplant)
	E 17.	Use of any investigational drug(s) for 5 half-lives prior to Screening
	E 18.	Hypersensitivity to sotagliflozin active substance or to any of the excipients including those in the placebo
	E 19.	Patients who are planning to start a sodium-glucose cotransporter 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 20.	Any SGLT2 inhibitor <1 month prior to the Screening Visit, or between Screening and Randomization
	E 21.	Patients with respiratory, hepatic, neurological, 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) or patients with short life expectancy (defined as ≤1 year) that, according to the Investigator, will preclude their safe participation in this study, and will

	make implementation of the protocol or interpretation of the study results difficult
	E 22. Presence of any other conditions (eg, geographic, social) actual or anticipated, that the Investigator feels would restrict or limit the patient's participation or compliance with all HF therapy, including study medication, for the duration of the study
	E 23. Patient is the Investigator or any Subinvestigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol
	E 24. 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 25. Severe kidney disease as defined by eGFR <30 mL/min/1.73 m² at the Screening Visit by the 4 variable Modification of Diet in Renal Disease (MDRD) equation
	E 26. Any infection requiring intravenous antibiotics and/or with pyrexia (defined as temperature >38 °C [100.4 °F]) at time of Randomization
	E 27. History of diabetic ketoacidosis or nonketotic hyperosmolar coma within 3 months prior to the Screening Visit
	E 28. Lower extremity diabetic complications (such as skin ulcers, infection, osteomyelitis and gangrene) identified during the Screening period, and still requiring treatment at Randomization
	E 29. Pregnant (demonstrated by serum pregnancy test at Screening) or breastfeeding women Women of childbearing potential (WOCBP) as defined in Appendix A, 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. The Investigators may perform additional tests at their discretion or at frequency specified by local regulations
	E 30. Digoxin level >1.2 ng/mL (in a patient treated with digoxin, and based on last local or central laboratory value available prior to Randomization)*
	E 31. Laboratory findings (based on Screening value or last available value before Randomization, whichever is later)** • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN) • Total bilirubin >1.7 times the ULN (except in case of Gilbert's syndrome) • Serum potassium >5.5 mEq/L

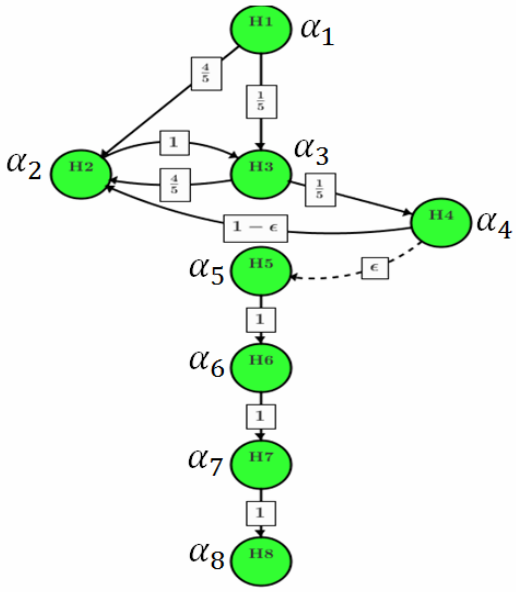
	Note: A patient should not be randomized more than once. One-time rescreening is allowed at the Investigator's medical judgment for any manageable reasons that caused the Screening failure and if the patient is likely to be eligible before the completion of enrollment. *If a patient meets exclusion criteria E 30 a one-time repeat testing is allowed for digoxin level without the need to rescreen the patient. **If a patient meets exclusion criterion E 31: • A one-time repeat testing is allowed for ALT or AST without the need to rescreen the patient • Repeat testing for serum potassium is allowed for 3 days after Screening without the need to rescreen the patient
Total expected number of patients	Approximately 4000
Expected number of sites	Approximately 800 sites
STUDY TREATMENT(s) **Investigational medicinal product(s)** **Formulation:** **Route(s) of administration:**	 Sotagliflozin and placebo Tablet Oral
Dose regimen:	**Sotagliflozin:** During the first 2 weeks: one (1) sotagliflozin 200-mg tablet qd before the first meal of the day At Week 3 and beyond: sotagliflozin 400 mg administered as two (2) 200-mg tablets qd before the first meal of the day, as tolerated. **Placebo:** During the first 2 weeks: one (1) placebo tablet qd (identical to sotagliflozin 200-mg tablets in appearance) before the first meal of the day At Week 3 and beyond: placebo administered as two (2) 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 endpoints:** • Time to first occurrence of either of the following clinical events in patients with LVEF <50%: - Cardiovascular death - Hospitalization for heart failure • Time to first occurrence of either of the following clinical events in the total patient population: - Cardiovascular death - Hospitalization for heart failure **Secondary endpoints:** • Total number (ie, including recurrent events) of the following clinical events in the total patient population: - Cardiovascular death

	- Hospitalization for heart failure - Urgent HF visit • Time to CV death in patients with LVEF <50% • Time to all-cause mortality in patients with LVEF <50% • Time to first occurrence of the composite of positively adjudicated sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, or positively adjudicated sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days) in the total patient population • Time to CV death in the total patient population • Time to all-cause mortality in the total patient population **Other endpoints:** The following endpoints are assessed in the total patient population: • Proportion of patients with HHF or urgent HF visit (see Appendix B) within 30 days of Randomization • Changes in KCCQ-12 scores from Baseline to Week 2, Month 1, Month 4, Month 8, Month 12, then annually • Time to ≥50% decrease in eGFR from Baseline • Proportion of patients with ≥1 new onset of atrial fibrillation, atrial flutter, or ventricular arrhythmia from Randomization • Time to first MI (fatal and nonfatal) • Time to first stroke (fatal and nonfatal) • Changes from Baseline to Month 1 and Month 4 for NT-proBNP • Changes from baseline in loop diuretics at day 180 and/or end of treatment visit • Changes in hemoconcentration from Baseline at Week 2, Month 1, Month 4, Month 12, and EOT • Changes from Baseline to Month 4, Month 12, and Month 24 in: - Hemoglobin A1c - Body weight • Time to first occurrence of either of the following clinical events in subgroups of patients who started first IMP dose prior vs. after hospital discharge (or urgent care facility where appropriate): - Cardiovascular death - Hospitalization for heart failure The following endpoints are assessed in subgroups of patients defined by LVEF: • Time to first occurrence of either of the following clinical events in patients with LVEF <40%:

	- Cardiovascular death - Hospitalization for heart failure • Time to first occurrence of either of the following clinical events in patients with LVEF ≥40% to <50%: - Cardiovascular death - Hospitalization for heart failure • Time to first occurrence of either of the following clinical events in patients with LVEF≥50%: - Cardiovascular death - Hospitalization for heart failure • Time to all-cause mortality in patients with LVEF <40% • Changes in hemoconcentration from Baseline at Week 2, Month 1, Month 4, Month 12, and EOT in patients with LVEF <40% • Safety endpoints: • All AEs, including AEs leading to premature treatment discontinuation, AESIs, EOSIs, and SAEs • Severe hypoglycemia (also an EOSI) • Clinical laboratory results and vital signs (including heart rate, blood pressure)
ASSESSMENT SCHEDULE	**Visits scheduled during the double-blind treatment period:** Clinic/on-site visits: Weeks 1, 2, 4, Month 4, then every 4 months until the end of the study.
STATISTICAL CONSIDERATIONS	The study will recruit approximately 4000 patients over an estimated recruitment period of 29 months with approximately 3 months of follow-up after the last patient is randomized. To ensure sufficient number of patients with LVEF <50%, the number of patients with LVEF ≥50% will be limited to approximately 1100. It is estimated to accrue approximately 947 primary events (first occurrence of CV death or HHF positively adjudicated by a Clinical Endpoint Committee [CEC]) in patients with LVEF <50% and approximately 1341 positively adjudicated primary events (first occurrence of CV death or HHF, positively adjudicated by CEC) in the total patient population, based on the following trial design characteristics and assumptions: • A recruitment period of approximately 29 months • Approximately 3 months of follow-up after the last patient is randomized • 29.2%, 39.7%, and 44.5% event rate by Month 6, Month 12, and Month 24, respectively, in the placebo group (by assuming yearly hazard rate at Months 1, 2, 3, 4, 5, 6, 12, 24, and 36 be 1.06, 0.87, 0.74, 0.62, 0.49, 0.36, 0.32, 0.08, and 0.05, respectively)

	• hazard ratio (HR) = 0.81 for sotagliflozin versus placebo for patients with LVEF <50% and for patients with LVEF ≥50% • 2% annual censoring rate This will provide: • 90% power (with α=0.05, 2-sided) to demonstrate superiority for the primary endpoint (first occurrence of CV death or HHF) comparing sotagliflozin versus placebo in patients with LVEF <50% • More than 90% power (with α=0.05, 2-sided) to demonstrate superiority for the primary CV endpoint (first occurrence of CV death or HHF) comparing sotagliflozin versus placebo in the total patient population. Analysis population: The analysis population for primary and secondary efficacy endpoints will be the intent-to-treat (ITT) population that includes all randomized patients irrespective of compliance with the study protocol and procedures. Efficacy analyses will be conducted according to the treatment assigned at the Randomization Visit irrespective of the treatment received. The safety analysis will be conducted on the safety population that includes all randomized patients who have received ≥1 dose of double-blind treatment. Safety analyses according to the treatment that the patients actually received. Primary analysis: The time to the first occurrence of CV death or HHF in patients with LVEF <50% will be analyzed by using stratified log-rank test with region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) as stratification factor. Stratified Cox proportional hazards model with region as stratification factor and treatment (sotagliflozin, placebo) as fixed effect factor will be used to provide the HR estimation between sotagliflozin and placebo along with its associated 2-sided 95% confidence interval (CI). The time to the first occurrence of CV death or HHF in the total patient population will be analyzed by using stratified log-rank test with LVEF (<50%, ≥50%) and region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) as stratification factors. Stratified Cox proportional hazards model with LVEF (<50%, ≥50%) and region as stratification factors and treatment (sotagliflozin, placebo) as fixed effect factor will be used to provide the HR estimation between sotagliflozin and placebo along with its associated 2-sided 95% CI. Kaplan-Meier curves of the cumulative incidence rate will also be provided by treatment groups. All randomized patients (irrespective of whether they experienced efficacy event[s] or whether they permanently early discontinued double-blind treatment) 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 analyses of CV efficacy endpoints will be based on the positively adjudicated CV endpoint events occurring from Randomization to the patient's end of study date, including events occurring after patients have discontinued study treatment, unless otherwise specified. Analysis of secondary endpoints: Extended Cox proportional hazards model for recurrent events with treatment (sotagliflozin, placebo), LVEF (<50%, ≥50%) and region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) as factors will be used to analyze the secondary endpoint of total number (ie, including recurrent events) of CV deaths, HHF or urgent HF visit in the total patient population. For the following secondary endpoints: • Time to CV death in patients with LVEF <50% • Time to all-cause mortality in patients with LVEF <50% • Time to first occurrence of the composite of positively adjudicated sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant or positively adjudicated sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days) in the total patient population • Time to CV death in the total patient population • Time to all-cause mortality in the total patient population Stratified log-rank test with LVEF (<50%, ≥50%) and region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) as stratification factor will be used for the analysis. Stratified Cox proportional hazards model with LVEF (<50%, ≥50%) and region as stratification factors and with treatment (sotagliflozin, placebo) as fixed effect factor will be used to provide the HR estimation between sotagliflozin and placebo along with its associated 2-sided 95% CI. The LVEF factor will not be included in the statistical model as stratification factor if the endpoint is defined in patients with LVEF <50%. For secondary endpoint analyses, all randomized patients (irrespective of whether they experienced efficacy event[s] or whether they permanently early discontinued double-blind treatment) will be followed up until death or the end of study. The secondary endpoint events occurring from Randomization to the patient's study end date, including the events that occurred after treatment discontinuation, will all be included in the analysis, unless otherwise specified. Multiplicity adjustment: The graphical approach (1) will be used to strongly control the family-wise type 1 error rate at 0.05 level. An initial graph as below will be used to control the type-1 error.



Note: ε=0.001.
In the graph, there are two primary hypotheses (H1 and H2) and six secondary hypotheses (H3, H4, H5, H6, H7, H8) defined as below:

H1: Time to first occurrence of CV death or HHF in patients with LVEF <50%

H2: Time to first occurrence of CV death or HHF in the total patient population

H3: Total number (ie, including recurrent events) of CV death, HHF, or urgent HF visit in total patient population

H4: Time to CV death in patients with LVEF <50%

H5: Time to all-cause mortality in patients with LVEF <50%

H6: Time to first occurrence of the composite of positively adjudicated sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, or positively adjudicated sustained eGFR <15 mL/min/1.73 m2 (for ≥30 days) in total patient population

H7: Time to CV death in total patient population

H8: Time to all-cause mortality in total patient population

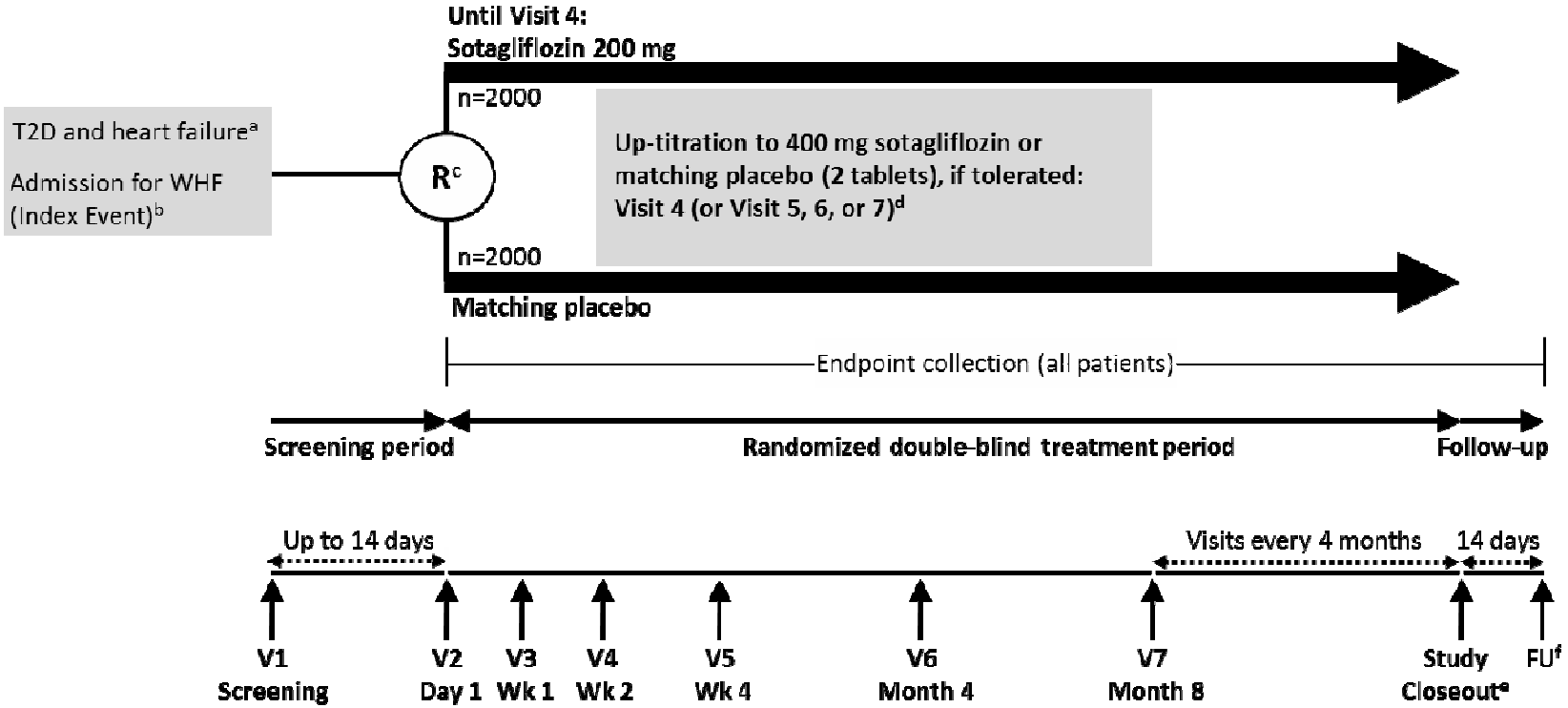
All tests will be two-sided. Significance levels $\alpha_1 = 0.05$ ($\alpha_2 = \alpha_3 = \alpha_4 = \alpha_5 = \alpha_6 = \alpha_7 = \alpha_8 = 0$) are initially defined such that they sum up to $\alpha = 0.05$.

The details of this method will be provided in the Section 11.4.2.4 and SAP (statistical analysis plan).

	Analysis of other endpoints: The analysis of other time to event endpoints will be performed using the same stratified Cox proportional hazards model as for the second primary endpoint, with LVEF (<50%, ≥50%) and region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) as stratification factors and treatment (sotagliflozin, placebo) as fixed effect factor. The LVEF factor will not be included in the statistical model as stratification factor if the endpoint is defined in subgroup of patients defined by LVEF (eg, LVEF<40%). Analysis of other endpoints will be descriptive with no statistical testing. Summary statistics at scheduled visits using observed data will be provided by each treatment group. Graphical presentations will also be used to illustrate trends over time if applicable. Analyses of Safety Data: All safety summaries will be descriptive; no statistical hypothesis 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 ≥1 dose of double-blind treatment, regardless of the amount of treatment administered.
DURATION OF STUDY PERIOD (per patient)	The estimated study duration for a given patient will be approximately 3 to 32 months, assuming approximately 29 months of recruitment, and approximately 3 months of follow-up after the last patient is randomized. All randomized patients (irrespective of whether they experienced efficacy event[s] or whether they permanently early discontinued double-blind treatment) 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.
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 Prior diagnosis of HF ≥3 months prior to Screening (based on appropriate supportive documentation).

b Index Event: Patient admitted to the hospital or had urgent HF visit to ED, Heart Failure Unit, or infusion center for WHF associated with intravascular volume overload as determined by Investigator (based on appropriate supportive documentation) and further defined in I 02.

c The Randomization Day is always Day 1.

d For titration details, please refer to Section 8.1.1

e This is an event-driven study. 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.

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

ED = Emergency Department; FU = Follow-up; HF = heart failure; IMP = investigational medicinal product; T2D = type 2 diabetes; R = Randomization; V = visit; WHF = worsening heart failure; Wk = Week.

1.2 STUDY FLOW CHART

	Screen	Randomization		Up-titration				Patients who prematurely permanently discontinue IMP		Patients who do not prematurely permanently discontinue IMP	
Visit	1	2	3	4	5	6	7 to 12				
Month	0	0	0	0	M1	M4	M8, M12, M16, M20, M24, M28	pEOT[a]	Study Closeout Visit	Study Closeout Visit	Follow-up Visit[b]
Week	-2 (after admission for Index Event)	0 (prior to hosp. discharge, if patient hospitalized, or within 3 days after discharge from hospital/ED/HF unit/infusion center)	1	2	4	16	Every 4 months until final visit				Study Closeout +14 days
Day (window in days)	within 14 days before randomization	1	8 (±3)	15 (±3)	29 (±3)	113 (±7)	(±7)	(±7)			(±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	
Medical/Surgical History	X										
Medication History	X										
Body weight (kg), height (cm)[c]	X	X	X	X	X	X	X	X	X	X	
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X
Physical Examination:											
Complete[e]	X							X	X	X	
Abbreviated[e]		X	X	X	X	X	X				X
IRT contact	X	X				X	X	X	X	X	X
Randomization[f]		X									
Dispense IMP		X				X	X				
IMP accounting[g]						X	X	X		X	
IMP compliance			X	X	X	X	X	X		X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X							X	X	X	
Echocardiogram[h]	X[h]										

	Screen	Randomization		Up-titration				Patients who prematurely permanently discontinue IMP		Patients who do not prematurely permanently discontinue IMP	
Visit	1	2	3	4	5	6	7 to 12				
Month	0	0	0	0	M1	M4	M8, M12, M16, M20, M24, M28	pEOT[a]	Study Closeout Visit	Study Closeout Visit	Follow-up Visit[b]
Week	-2 (after admission for Index Event)	0 (prior to hosp. discharge, if patient hospitalized, or within 3 days after discharge from hospital/ED/HF unit/infusion center)	1	2	4	16	Every 4 months until final visit				Study Closeout +14 days
Day (window in days)	within 14 days before randomization	1	8 (±3)	15 (±3)	29 (±3)	113 (±7)	(±7)	(±7)			(±4)
Laboratory testing[i]											
BNP and NT-proBNP (including at discharge)[j]	X	X			X	X	X (M8, M16 then annually)	X	X	X	
HbA1c		X				X	X[k]	X	X	X	
Chemistry, hematology, eGFR[l]	X[i]	X	X	X	X	X	X	X	X	X	X
Lipids		X				X		X	X	X	
Pregnancy (WOCBP)[m]	X	X			X	X	X	X	X	X	
Urinalysis[n]	X		X	X				X	X	X	
Digoxin level (if applicable)[o]	X			X							
[redacted]											
Quality of Life (KCCQ-12)		X		X	X	X	X (M8, M12 then annually)	X	X	X	
AEs/SAE/EOSIs/AESIs/ Endpoint events[r]	Throughout the study										
Severe hypoglycemia	Throughout the study										

a The pEOT Visit will only be performed for patients who discontinue treatment prior to the Study Closeout Visit. The Study Closeout Visit will be performed for all patients at the end of study. Patients will continue IMP and will continue to be followed after an event of HHF, or urgent HF visit occurs. For patients who discontinue IMP but remain in the study, the remaining visits should occur as scheduled where possible. If the patient does not agree to site visits, they will be contacted by telephone to inquire about safety status (including outcomes).

b A post-treatment safety Follow-up Visit of 14 days (±4 days) will be implemented for patients still on study treatment at the end of the study.

c Height to be measured only at Screening. Height may be collected historically if the patient is on bed rest during the hospital admission at Screening.

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

e See Section 9.2.3.1 for details of full and abbreviated physical examinations.
f Screening and Randomization visits may be conducted on the same day.
g The in-use, used and unused bottles should be brought back to the sites at Visit 6.
h If an LVEF assessment has not been performed within the last 12 months prior to Screening (Visit 1), an echocardiogram should be obtained between Screening and Randomization (Visit 2). If ECG assessment was done as standard of care, the most recent ECG collected after the Index event, can be used to formally screen the patients.
i All laboratory assessments including serum chemistry (sodium, potassium, chloride, carbondioxide, Blood urea nitrogen, creatinine, eGFR, glucose, alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase and total protein) and hematology completed at Screening (Visit 1) are to be performed at Site Local Laboratory. If sites are unable to perform laboratory tests locally, the tests can be done by central laboratory. At Randomization and at subsequent visits, laboratory assessments (with the exception of digoxin) are to be performed using central laboratory. At the Randomization Visit (Visit 2), laboratory samples will be collected prior to first dose of double-blind IMP. If the laboratory assessments were done as standard of care, the most recent results collected after the Index event may be used to formally screen the patients. However serum pregnancy testing must be collected at Screening.
j Blood samples for BNP or NT-proBNP should be collected at screening via a local laboratory, if not collected earlier following the specific Index event. After Visit 1 blood samples for NT-proBNP will be collected via a central laboratory.
k After Month 4 (Visit 6), HbA1c will be performed at Month 8 (Visit 7), Month 12 (Visit 8), Month 16 (Visit 9), Month 20 (Visit 10), and Month 24 (Visit 11).
l Sotagliflozin/metabolite levels may be analyzed via routine blood samples collected throughout the study, eGFR will be measured at the follow-up visit after discontinuation of study treatment.
m Serum pregnancy testing only at Screening (Visit 1); 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 at frequency specified by local regulations. For women of non-productive potential (Appendix A), FSH and/or estradiol levels should be tested in case the definition of postmenopausal or premenopausal can't be satisfied, eg, no medical document of hysterectomy or cessation of menses without an alternative medical cause is <12 months.
n At Visit 1 only, urinalysis will be performed by the local laboratory, for all subsequent visits urinalysis 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 urinalysis is positive for nitrite and leukocyte esterase or blood, reflexive testing will be performed (see Section 9.2.2.1).
o In patients treated with digoxin at Screening, digoxin levels may be measured in either serum or plasma at Screening (Visit 1), Week 2 (Visit 4) and 2 to 4 weeks after an up-titration has been implemented (eg, at Week 4 if up-titration occurred at Week 2, or at an unscheduled visit, if up-titration occurred after Week 2). If no up-titration is implemented, there is no requirement for digoxin level assessment beyond Week 2. Throughout the study, additional digoxin level assessments are to be performed as per Investigators' judgment. All digoxin levels will be performed at a Site Local Laboratory, if sites are unable to do the tests locally, the test should be done by central laboratory.

[redacted]

r All AEs, including AESIs, EOSIs, SAEs, and severe hypoglycemia will be collected starting with signing informed consent. All AEs that occurred during treatment should be followed for ≥30 days following the last dose of IMP or until the event has resolved, the condition has stabilized, the etiology of the event is determined to be not related to IMP, or until death.

AE adverse event; AESI adverse event of special interest; BNP b-type natriuretic peptide; BP blood pressure; CRT cardiac resynchronization therapy; DNA deoxyribonucleic acid; ECG electrocardiogram; ED Emergency Department; eGFR estimated glomerular filtration rate; EOSI events of special interest; EOT End-of-Treatment; FSH follicle-stimulating hormone; HbA1c hemoglobin A1c; HF heart failure; HHF hospitalization for heart failure; IC Infusion Center; IMP investigational medicinal product; IRT Interactive Response Technology; KCCQ-12 Kansas City Cardiomyopathy Questionnaire-12; LVEF left ventricular ejection fraction; M month; NT-proBNP N-terminal B-type natriuretic peptide; pEOT premature End-of-Teatment; SAE serious adverse event; WOCBP women of childbearing potential.

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3 LIST OF ABBREVIATIONS

ACE-i:	angiotensin-converting enzyme inhibitor
AE:	adverse event
AESI:	adverse event of special interest
AHA:	American Heart Association
ALT:	alanine aminotransferase
AMI:	acute myocardial infarction
ARB:	angiotensin receptor blocker
ARNI:	angiotensin receptor/neprilysin inhibitor
AST:	aspartate aminotransferase
BHB:	beta-hydroxybutyrate
bid:	twice daily
BNP:	b-type natriuretic peptide
BP:	blood pressure
CEC:	Clinical Endpoint Committee
CI:	confidence interval
COPD:	chronic obstructive pulmonary disease
CRT:	cardiac resynchronization therapy
CSR:	clinical study report
CV:	cardiovascular
CVD:	cardiovascular disease
DILI:	drug-induced liver injury
DKA:	diabetic ketoacidosis
DMC:	Data Monitoring Committee
DRF:	discrepancy resolution form
EC:	Executive Committee
ECG:	electrocardiogram
e-CRF:	electronic case report form
ED:	emergency department
eGFR:	estimated glomerular filtration rate
EOSI:	event of special interest
ESC:	European Society of Cardiology
FDA:	Food and Drug Administration
FEV_1:	forced expiratory volume in 1 second
GCP:	good clinical practice
GI:	gastrointestinal
GLP-1:	glucagon-like peptide-1
GP:	general practitioner
HbA1c:	hemoglobin A1c
HF:	heart failure
HFmEF:	heart failure with mid-range ejection fraction
HFpEF:	heart failure with preserved ejection fraction

HHF:	hospitalization for heart failure
HLGT:	high-level grouped term
HLT:	high-level term
HR:	hazard ratio
HRrEF:	heart failure with reduced ejection fraction
IABP:	intra-aortic balloon pump
IB:	Investigator's Brochure
ICD:	implantable cardioverter-defibrillator
ICF:	informed consent form
IEC:	independent ethics committee
IMP:	investigational medicinal product
IRB:	institutional review board
IRT:	interactive response technology
ITT:	intent-to-treat
IV:	intravenous
KCCQ-12:	Kansas City Cardiomyopathy Questionnaire-12
LV:	left ventricular
LVAD:	left ventricular assist device
LVEF:	left ventricular ejection fraction
MDRD:	modification of diet in renal disease
MI:	myocardial infarction
MRA:	mineralocorticoid receptor antagonist
MRI:	Magnetic Resonance Imaging
MUGA:	MUltiple Gated Acquisition
NHE3:	sodium-hydrogen exchanger 3
NT-proBNP:	N-terminal B-type natriuretic peptide
PCI:	percutaneous coronary intervention
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamics
pEOT:	premature End-of-Treatment
PET:	positron emission tomography
PK:	pharmacokinetics
PRO:	patient-reported outcome
PT:	preferred term
PYY:	peptide YY
qd:	once daily
RAAS:	renin-angiotensin-aldosterone system
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	Steering Committee
SD:	standard deviation
SGLT1:	sodium-glucose cotransporter 1
SGLT2:	sodium-glucose cotransporter 2
SMQ:	standardized Medical Dictionary for Regulatory Activities query
SOC:	system organ class
SPECT:	single-photo emission computed tomography

SUSAR:	suspected unexpected severe adverse reaction
T1D:	type 1 diabetes
T2D:	type 2 diabetes
TEAE:	treatment-emergent adverse event
UGE:	urinary glucose excretion
ULN:	upper limit of normal
US:	United States
WHF:	worsening heart failure
WOCBP:	women of childbearing potential

4 INTRODUCTION AND RATIONALE

4.1 BACKGROUND: DISEASE AND PRELIMINARY THERAPEUTIC OBSERVATIONS

Heart failure (HF), the most common cause of hospitalization of patients over the age of 65, encompasses a wide spectrum of diseases and results from any structural or functional impairment of ventricular filling or ejection of blood. Classic symptoms include dyspnea and fatigue (2). Prevalence is approximately 5.7 million in the United States (US; ≥20 years age) and over 23 million worldwide. In the US, prevalence is projected to increase 46% from 2012 to 2020 to 8 million (≥18 years of age) (3, 4). Outpatient care has improved significantly with therapies such as angiotensin-converting enzyme inhibitors (ACE-i), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and implantable cardioverter-defibrillator (ICD)/cardiac resynchronization therapy (CRT) devices. However, mortality and readmission rates remain high (5).

Among patients aged ≥55 years, the average incidence of hospitalization for heart failure (HHF) is 11.6 per 1000 people per year; and recurrent hospitalized HF is 6.6 per 1000 people per year (6). Readmission for HF within 30 days of discharge occurs in approximately 24% of cases (7). The total cost for HF in 2012 was estimated at approximately 30.7 billion dollars and is projected to increase by almost 127% to 69.7 billion dollars (from 2012 to 2030) (2). Recognizing this burden on the US health care system, readmission for HF is a focus of pay for performance initiatives. In the US, the Patient Protection and Affordable Care Act, enacted in 2010, imposed financial penalties for hospitals with the highest readmission rates during the first 30 days after discharge (8).

In addition, the European Medicines Agency has recently recognized that patients hospitalized due to acute decompensation of chronic HF and stabilized by standard therapy are usually excluded from clinical trials investigating new therapies for acute or chronic HF. Hence the condition known as “post-worsening HF” represents a specific unmet medical need, particularly in patients with type 2 diabetes (T2D), since the rates of hospitalization for HF in patients with diabetes is substantially higher compared to HF patients without diabetes (9, 10, 11, 12).

Heart failure can be divided into 2 or 3 main categories, depending on the region, based on measurement of the left ventricular ejection fraction (LVEF): HF with preserved ejection fraction (HFpEF; EF ≥50%); heart failure with mid-range ejection fraction (HFmEF; LVEF ≥40 and <50%); and heart failure with reduced ejection fraction (HRrEF; <40%). Heart failure with mid-range ejection fraction is becoming a category of interest and was recently referenced in the 2016 European Society of Cardiology (ESC) Heart Failure Guidelines (9). The American Heart Association (AHA) guidelines refer to an intermediate category but do not label it HFmEF (10). A 2016 analysis of 99 825 admissions between January 2005 and September 2013 from 305 hospitals in the Get with the Guidelines-HF database showed the prevalence of HF as follows: 49% with HFrEF; 13% with HFmEF; and 38% with HFpEF (11).

The diagnosis of HF can be challenging in some patients since symptoms are nonspecific. Echocardiogram can help establish the diagnosis if the LVEF is <40%, classifying the patient into

the HFrEF category. HFmEF and HFpEF are more challenging to diagnose and elevated levels of natriuretic peptides (both b-type natriuretic peptide [BNP] and N-terminal B-type natriuretic peptide [NT-proBNP]) can aid in establishing the diagnosis. B-type natriuretic peptide and NT-proBNP are natriuretic peptides found in the heart. In response to volume overload and subsequent myocardial stretch, proBNP is secreted and then cleaved to NT-proBNP and BNP (12). The natriuretic peptides have been shown to predict clinical outcomes in clinical trials and have been used as surrogate markers of cardiovascular (CV) function. In a recent trial conducted in 149 patients with LVEF >45%, the PARAMOUNT trial, changes in NT-proBNP were used to compare the effect of sacubitril/valsartan with valsartan alone. The study showed that sacubitril/valsartan reduced NT-proBNP levels to a significantly greater extent (783 pg/mL at Baseline and 605 pg/mL at 12 weeks) compared with valsartan alone (862 pg/mL at Baseline and 835 pg/mL at 12 weeks) over 12 weeks (13).

Although ACE-i, beta-blockers, and MRAs are recommended in patients with HFrEF to reduce the risk of HF hospitalization and death, they have failed to reduce mortality in patients with HFmEF and HFpEF. Of note, diuretics are used to treat symptoms in all HF patients, regardless of LVEF status. In addition, both the AHA and ESC HF Guidelines discuss the use of new compound sacubitril/valsartan, the first in the class of angiotensin receptor neprilysin inhibitors (ARNIs) in HFrEF (9, 10).

There have been 2 clinical trials done to date in the post-worsening heart failure population. ASTRONAUT was conducted in HHF patients with reduced LVEF, randomized to either aliskiren or placebo a median of 5 days after admission (14). EVEREST was conducted in HHF patients with reduced LVEF, randomized to either tolvaptan or placebo (for a minimum of 60 days) within 48 hours of admission (15). The mechanism of action of these 2 drugs differs from each other and SGLT2 inhibitors, and neither drug reduced CV death or HHF (at 6 or 12 months after discharge for ASTRONAUT and for a median follow-up of 9.9 months for EVEREST). Both trials were conducted in patients both with and without diabetes.

Type 2 diabetes is a growing epidemic worldwide that is associated with a high incidence of macrovascular and microvascular complications (16). The Emerging Risk Factors Collaboration has recently reported that patients with T2D have a doubled risk of CV death compared to patients without diabetes (17). Cardiovascular complications of diabetes include myocardial infarction (MI), stroke, and HF (18). In patients with diabetes the prevalence of HF is much higher compared to the general population and increases with age (19, 20, 21). One in 5 patients with diabetes aged over 65 years suffers from HF (21). 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 (21, 22, 23, 24). Despite these compelling data, HF is often omitted from the list of diabetes complications because its pathogenesis is multifactorial, including coronary artery disease, hypertension, diabetic cardiomyopathy, and extracellular fluid volume expansion; hence it does not fit into the traditional classification of diabetes complications as either microvascular or macrovascular.

Recent data indicate that sodium-glucose cotransporter 2 (SGLT2) inhibitors may reduce HF morbidity and mortality in patients with T2D. These antihyperglycemic agents lower blood glucose levels, in part, through the inhibition of renal glucose reabsorption thereby enhancing renal glucose excretion (25). In 2015, the EMPA-REG OUTCOME trial showed that the SGLT2

inhibitor, empagliflozin, when added to standard of care, reduced the risk of CV death (a component of the primary composite endpoint) and HHF in patients with T2D and established CV disease (CVD), including 10% with HF at screening (26). In 2017, the CANVAS program showed that canagliflozin, when added to standard of care, reduced the risk of a composite outcome of CV death, nonfatal MI or nonfatal stroke in patients with T2D and established CVD or at high risk for CV events (27). Of note, the FDA recently approved empagliflozin for reducing the risk of CV death in adult patients with T2D and established CVD (28).

The mechanisms supporting the CV benefit of SGLT2 inhibitors have not been fully elucidated, but several experts have speculated that the hemodynamic effect of SGLT2-inhibition is the main driver. Sodium-glucose cotransporter 2 inhibitors may affect volume status via either or both of the following mechanisms: sodium and volume reduction and/or a decrease in arterial pressure. The diuresis and beneficial effect on maladaptive renal arteriolar responses may have led to improvement in both systolic and diastolic function, thereby lowering HHF and sudden cardiac death. Sodium-glucose cotransporter 2 inhibitors induce a considerable diuresis with early loss of urinary glucose and sodium. However, in contrast to regular diuretics, SGLT2 inhibitors induce a sustained reduction in plasma volume, not accompanied by electrolyte imbalance, or rebound activation of the renin-angiotensin system to the degree that would be expected given the large reduction in volume (29, 30, 31). In EMPA-REG OUTCOME (32), empagliflozin resulted in an approximate 4% increase in the hematocrit. In patients with HF, impaired 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 or CANVAS study population was not characterized, but it has been suggested that a substantial proportion of the trials' population might have had mild HF or some form of preclinical HF or diabetic cardiomyopathy at Baseline (31, 32). The beneficial CV effects of empagliflozin and canagliflozin were consistent across subgroups including patients with versus without HF at Baseline (32, 27).

In addition to inhibition of SGLT2 in the proximal tubules, SGLT2 inhibitors also down-regulate sodium-hydrogen exchanger 3 (NHE3), which is primarily responsible for tubular sodium reuptake following filtration and that is markedly upregulated in experimental models of HF (33). Cardiorenal protection has also been postulated to be linked to decreased sodium reabsorption by inhibition of intestinal NHE3 by sodium-glucose cotransporter 1 (SGLT1) inhibition (34).

In addition to the hemodynamic hypothesis, another hypothesis has been postulated to explain the CV benefit of empagliflozin. Under conditions of mild, persistent hyperketonemia, such as those that prevail during treatment with SGLT2 inhibitors, β-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 (35).

Sodium-glucose cotransporter 2 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 (36). Type 2 diabetes is associated with upregulation of the SGLT2 tubular transporters. Sodium-glucose cotransporter 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 tubule-glomerular feedback, afferent glomerular arteriolar vasoconstriction, and subsequent reduction in glomerular capillary pressure and decreased hyperfiltration. This renal effect may contribute to cardioprotection by minimizing volume overload, neurohormonal activation, and proinflammatory pathways, which are all contributors to the cardiorenal syndrome (37).

4.2 BACKGROUND: SOTAGLIFLOZIN

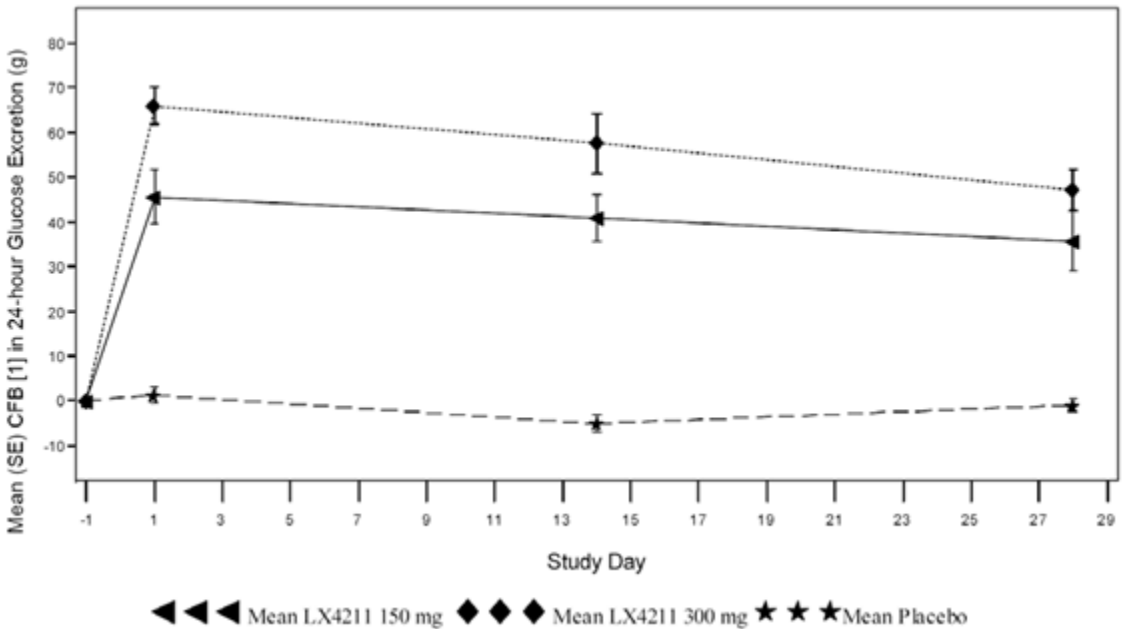
Sotagliflozin, a dual inhibitor of SGLT2 and SGLT1, is in clinical development for the treatment of type 1 diabetes (T1D) and T2D (38). In addition to this heart failure outcomes trial, another outcomes trial will be conducted in parallel in patients with T2D, renal impairment and high CV risk. Sodium-glucose cotransporter 1 receptors are expressed predominantly in the gastrointestinal (GI) tract and are 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 (39), pharmacologic inhibition of SGLT1 by sotagliflozin has not produced these effects in preclinical models or patients with T1D or T2D.

Increased renal glucose excretion and therefore osmotic diuresis, one of the main hypotheses of the mechanism of action on HF, has been seen in patients with T2D who have received sotagliflozin.

In Study LX4211.202, a Phase 2 study of sotagliflozin in combination with metformin in T2D patients, mean urinary glucose excretion (UGE) was increased over Baseline to Week 12 by a mean of 47.7 g/day and 58.9 g/day at 200 mg and 400 mg doses per day (40).

In Study LX4211.1.201, a Phase 2 study in T2D patients, both sotagliflozin dose groups (150 and 300 mg) had statistically significant increased 24-hour total UGE compared to the placebo group, and the greatest treatment effect was observed on Day 1 post-treatment. The increases in UGE in the sotagliflozin 300 mg dose group were consistently higher than in the sotagliflozin 150 mg dose group, suggesting a possible dose-response relationship in the treatment effect on 24-hour total UGE. The UGE increases were maintained throughout the course of the study in both dose groups, although they diminished slightly over 28 days of treatment, possibly due to improved glycemic control. These trends are considered a result of the pharmacologic activity of sotagliflozin on SGLT2 inhibition. Figure 1 illustrates the mean change from Baseline in UGE over time (41).

Figure 1 - Study LX4211.1-201-T2DM - Mean (+/- SE) Change from Baseline in 24-hour urinary glucose excretion by treatment on Days 1, 14, and 28 (Efficacy population)



Source: CSR Figure 14.2.1.1

4.3 BENEFIT/RISK PROFILE

Studies with sotagliflozin have shown that this agent produces significant UGE in preclinical animal models, healthy human volunteers, and patients with T2D.

No significant safety concerns have been identified in the sotagliflozin clinical program, and sotagliflozin has been generally 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, the majority of these events were mild to moderate in intensity, with most resolving spontaneously. Overall, no imbalance was observed in the events of hypoglycemia in the sotagliflozin clinical program, and there have been no events of severe hypoglycemia or SAEs related to hypoglycemia in the completed studies. However, concomitant use of sulfonylurea and insulin may increase the risk for hypoglycemia.

Single- and multiple-dose administration of sotagliflozin to healthy human subjects has resulted in dose-dependent increases in UGE. Multiple-dose (up to 12 weeks) administration in patients with T1D and T2D produced improvements in several metabolic parameters, including levels of fasting glucose, postprandial glucose, glycosylated hemoglobin A1c (HbA1c), GLP-1, hemoglobin, and PYY. Sotagliflozin also enabled patients with T1D to control their daily glucose levels while decreasing their daily insulin doses in 1 of the Phase 1 studies implemented to date (42). These data suggest that sotagliflozin will be of therapeutic benefit to patients with T1D and T2D.

Overall, the potential benefits of sotagliflozin therapy for patients with T1D and T2D outweigh the potential risks. In Phase 1 and 2 studies, sotagliflozin has been generally safe and well-tolerated in patients with T1D and in patients with T2D with and without renal impairment. The favorable benefit-risk assessment to date supports the further development.

Benefit-risk in patients with type 2 diabetes and heart failure

Heart failure is a common comorbidity and complication of T2D. Patients with HF have particularly poor outcomes and 5-year survival rates of <25% (43). The condition known as post-worsening heart failure (WHF) represents a specific unmet medical need in patients with T2D, since the rates of hospitalization for HF in patients with diabetes are substantially higher compared to those for HF patients without diabetes (9, 10, 11, 12).

Recent data point to the beneficial effects of SGLT2 inhibitors in reducing CV death and HF in patients with T2D. The EMPA-REG OUTCOME trial (26) showed that empagliflozin, when added to standard of care, reduced the risk of CV death and HF requiring hospitalization in patients with T2D and established CVD, including 10% with HF at screening. The CANVAS program (27) showed that canagliflozin, when added to standard of care, reduced the risk of a composite outcome of CV death, nonfatal MI or nonfatal stroke in patients with T2D and established CVD or at high risk for CV events (19). Finally, the real-world database study CVD-REAL, conducted in more than 300 000 T2D patients, showed that treatment with a SGLT2 inhibitor (canagliflozin, dapagliflozin, or empagliflozin) was associated with a decreased risk of HHF (hazard ratio [HR]=0.61; 95% confidence interval [CI]: 0.51 to 0.73; p<0.001) and all-cause death (HR=0.49; 95% CI: 0.41 to 0.57; p<0.001) (44).

Taken together, the CV benefits observed to date in T2D patients treated with SGLT2 inhibitors and the high unmet medical need of post-WHF support the development of sotagliflozin in patients with T2D and post-WHF.

Overall, the potential benefits of sotagliflozin therapy for patients with T2D and HF outweigh the potential risks.

More information on the safety of sotagliflozin and on the clinical program can be found in the Investigator's Brochure (IB).

4.4 RATIONALE FOR CURRENT STUDY

The main objectives of the study are to demonstrate whether sotagliflozin reduces the composite of CV death and HHF as compared to placebo in diabetic patients after admission for WHF.

In all patients, double-blind treatment (sotagliflozin or placebo) will be added to the standard of care, evidence-based background therapies for their underlying diabetes and HF conditions.

The randomization will be stratified according to LVEF (<50% or ≥50%) since they represent 2 distinct forms of HF. However, both forms lead to significant congestion and have the potential to be improved by an agent such as sotagliflozin.

Although ACE-i, beta-blockers and MRAs are recommended in patients with HFrEF to reduce the risk of HHF and death, they have failed to reduce mortality in patients with HF and preserved EF. Therefore, in order to evaluate the effect of sotagliflozin on patients across the spectrum of LVEF values, there are 2 primary endpoints. The first in patients with a LVEF <50% and the second in the total patient population. The cut-off of 50% was chosen to group HFrEF and HFmEF patients (a very small subgroup, 13% [11]) together, since HFmEF patients are a category of interest.

In order to do a robust analysis of the potential improvement in patients with LVEF <50%, recruitment will begin with all patients (LVEF <50% and LVEF ≥50%). Enrollment of patients with LVEF ≥50% will be capped at ~27% of the total patient population and enrollment of patients with LVEF <50% will continue to reach the total patient population. In addition, since an intermediate category has recently emerged (LVEF between 40% and 49%) for which little information on outcome is available, an exploratory subgroup analysis will also be performed using the 3 categories (<40%, 40 to 49% and ≥50%).

In addition, since this patient population is burdened with repeated hospitalizations and visits to the emergency department (ED) or HF acute unit (where available) with major financial consequences for healthcare systems and utilization of public health care resources, the study will also assess, in addition to the occurrence of a primary event, the occurrence of the total number of CV deaths and HHF or urgent HF visits (see Appendix B) throughout the course of the study. Finally, the effect of sotagliflozin on CV death alone and all-cause mortality will be analyzed.

4.4.1 Rationale for selection of dose

In healthy subjects, sotagliflozin was well-tolerated following single doses up to 2000 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 2000 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.

Both dosages (the starting dose of sotagliflozin [200 mg once daily [qd] and the maintenance dose [400 mg qd]) are currently undergoing evaluation in Phase 3 glucose-control studies. For the clinical development of sotagliflozin in patients with diabetes the dose selected was 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 (bid), and 400 mg qd were tested over a 12-week, double-blind period. At 12 weeks, the 200 mg 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 0.14%. The overall incidence of AEs on sotagliflozin 200 mg and 400 mg qd doses were similar to placebo, hence the 200 mg dose was less effective than the 400 mg dose and did not present clear advantages in safety or tolerability.

The mechanism(s) supporting the decreased risk of CV death and HHF observed in patients with T2D treated with SGLT2 inhibitors are still under investigation, but the CV benefit does not appear to be related to the glucose lowering effect of these medications. In fact, a major role has been speculated to be played by their hemodynamic effects (29, 30, 31) since these compounds decrease plasma volume and reduce blood pressure (BP) likely resulting in improved systolic and diastolic function. It should be noted that in EMPA-REG OUTCOME (26) 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. 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.

In Study LX4211.1 202 DM (40) 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 bid 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 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 bid and 400 mg qd, respectively versus (0.273) -0.04 g/dL in the placebo arm. The mean change (SD) in hemoglobin from Baseline to Week 12 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 bid 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 systolic BP 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 cardiovascular outcomes, the dose of 400 mg was chosen as the proposed maintenance dose for the study.

Sotagliflozin induces an acute, but modest, decrease in estimated glomerular filtration rate (eGFR). Since the study population includes 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.

4.4.2 Rationale for study design and control groups

This study is a pivotal, randomized, double-blind, placebo-control Phase 3, outcomes trial planned to be conducted in the post WHF population with T2D. A placebo control group, in addition to standard of care, has been selected since no treatment is indicated or has been proven to be safe and effective in patients with diabetes and a recent admission for WHF. In addition to receiving double-blind treatment, all patients in the study will receive background evidence-based, standard of care treatment for their underlying diabetes and HF conditions, as per Investigator's discretion. The study will be an event-driven study and will continue until approximately 947 positively

adjudicated primary events (ie, number of patients with at least 1 positively adjudicated primary event) have been observed in patients with LVEF <50%, AND approximately 1341 positively adjudicated primary events (ie, number of patients with at least 1 positively adjudicated primary event) have been observed in the total patient population.

5 STUDY OBJECTIVES

5.1 PRIMARY

- To demonstrate that sotagliflozin reduces CV mortality and morbidity (composite of CV death or HHF) compared to placebo in hemodynamically stable patients with T2D and HF with LVEF <50%, after admission for WHF
- To demonstrate that sotagliflozin reduces CV mortality and morbidity (composite of CV death or HHF) compared to placebo in hemodynamically stable patients with T2D and HF, irrespective of LVEF, after admission for WHF (total patient population)

5.2 SECONDARY

- To demonstrate that, when compared to placebo, in the total patient population, sotagliflozin reduces the total number (ie, including recurrent events) of the following clinical events:
  - Cardiovascular death, HHF, or urgent HF visit (see Appendix B)
- To demonstrate that, when compared to placebo, sotagliflozin reduces:
  - Cardiovascular death in patients with LVEF <50%
  - All-cause mortality in patients with LVEF <50%
  - The composite of positively adjudicated sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant or positively adjudicated sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days) in the total patient population
  - Cardiovascular death in the total patient population
  - All-cause mortality in the total patient population
- To demonstrate the safety and tolerability of sotagliflozin in the total patient population

5.3 OTHER

- To compare sotagliflozin versus placebo on the occurrence of the following events in the total patient population:
  - Hospitalization for heart failure or urgent HF visit (see Appendix B) within 30 days of Randomization
  - At least 50% decrease in eGFR from Baseline (for ≥30 days)
  - Myocardial infarction (fatal and nonfatal)
  - Stroke (fatal and nonfatal)
- To compare sotagliflozin versus placebo with respect to the proportion of patients with ≥1 new onset of atrial fibrillation, atrial flutter, or ventricular arrhythmia from Randomization in the total patient population

- To demonstrate that sotagliflozin reduces CV mortality and morbidity (composite of CV death or HHF) compared to placebo in hemodynamically stable patients with T2D and HF with LVEF <40%, after admission for WHF
- To demonstrate that sotagliflozin reduces CV mortality and morbidity (composite of CV death or HHF) compared to placebo in hemodynamically stable patients with T2D and HF with LVEF ≥40% to <50%, after admission for WHF
- To demonstrate that sotagliflozin reduces CV mortality and morbidity (composite of CV death or HHF) compared to placebo in hemodynamically stable patients with T2D and HF with LVEF ≥50% after admission for WHF
- To demonstrate that, when compared to placebo, sotagliflozin reduces all-cause mortality in patients with LVEF <40%
- To compare sotagliflozin versus placebo in the total patient population with respect to change from Baseline in the following endpoints:
  - Hemoglobin A1c
  - Body weight
- To compare sotagliflozin versus placebo with respect to changes in Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12) scores from Baseline in the total patient population
- To compare sotagliflozin versus placebo with respect to changes in NT-proBNP from Baseline in the total patient population
- To compare sotagliflozin versus placebo with respect to changes in loop diuretics from Baseline in the total patient population
- To compare sotagliflozin versus placebo for changes in hemoconcentration from Baseline in the total patient population
- To compare sotagliflozin versus placebo for changes in hemoconcentration from Baseline in patients with LVEF <40%
- To compare sotagliflozin versus placebo on the time to first occurrence of either of the following clinical events in subgroups of patients who started first IMP dose prior vs. after hospital discharge (or urgent care facility where appropriate):
  - Cardiovascular death
  - Hospitalization for heart failure

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in about 4000 hemodynamically stable patients with T2D who have been admitted to the hospital, a HF unit, infusion center, or ED for WHF with intravascular volume overload. The study will consist of 3 periods:

- A Screening period (up to 14 days)
- A randomized, double-blind treatment period that will include an initial up-titration period
- A Post-treatment period of 14 days (±4 days)

6.1.1 Screening period

The Screening period will last up to 14 days. The Screening period duration provides sites the ability to collect the data required to establish whether the patient satisfies the inclusion/exclusion criteria. Patients will have been admitted to hospital, HF unit, infusion center, or ED for WHF associated with intravascular volume overload (Index Event; see Section 7.1.1 for definition) prior to the Screening Visit (Visit 1).

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.

Blood samples for BNP or NT-proBNP should be collected by the local laboratory at Screening before Randomization, if not collected earlier following the specific Index event.

6.1.2 Randomized double-blind treatment period

Patients who meet all eligibility criteria during the Screening period will have Randomization Visit (Visit 2) up to 14 days later and, if they are still eligible for the study, they will be randomized 1:1 to sotagliflozin or placebo. The Screening and Randomization visits may be conducted on the same day.

The Randomization Visit (Visit 2; Day 1) should occur prior to hospital discharge if applicable, or within 3 days after discharge from hospital, ED, HF unit, or infusion center. A blood sample for NT-proBNP will be collected and sent to the central laboratory at Randomization before taking IMP. The sample for NT-proBNP will be sent to the central laboratory for all other subsequent visits.

Patients will be stratified by LVEF (LVEF <50% and LVEF ≥50%) and region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world). The number of patients with LVEF ≥50% will be limited to approximately 1100, to ensure sufficient number of patients (ie, approximately 2900) with LVEF <50%.

The double-blind study treatment will be initiated at Visit 2 (Day 1) after the patient has been randomized (ie, after patient is hemodynamically stable and ready to transition from intravenous [IV] to oral diuretic therapy). Patients will receive sotagliflozin 200 mg or placebo at that visit and will continue this regimen qd until the next visit. If the randomization visit occurs after the patient has had their first meal of the day, the patient is allowed to take the first dose the following day, before the first meal.

Patients will return a week later at Visit 3 (Day 8). Clinical safety and tolerability (including vital signs and collection of AEs, including events of special interest [EOSIs], adverse events of special interest [AESIs], and SAEs) will be assessed and blood (including serum creatinine) and urine laboratory samples will be collected. Patients will continue to receive sotagliflozin 200 mg or matching placebo qd until the next visit.

Patients will return a week later at Visit 4 (Day 15). Clinical safety and tolerability (including vital signs and collection of AEs, including EOSIs, AESIs, and SAEs) will be assessed and laboratory results from the prior week (including serum creatinine) will be reviewed, and new laboratory samples (blood and urine) will be collected. 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 volume depletion, symptomatic hypotension (eg, dizziness, lightheadedness), or other AEs intolerable to the patient such as severe polyuria or nocturia, the dose will be up-titrated to sotagliflozin 400 mg or matching placebo qd until the next visit.

The patient will then return for Visits at Month 1 (Day 29), Month 4, and every 4 months thereafter until the end of the study.

If the patient does not meet up-titration criteria for safety reasons (eg, hypotension), the Investigator will have the option of either continuing IMP at the dose of 200 mg or placebo, with the optional adjustment of concomitant medications, or discontinuing IMP temporarily. If the dose is not up-titrated for safety reasons, the Investigator should make all attempts to up-titrate the dose at 1 of the next 3 subsequent visits: Visit 5 (Month 1), Visit 6 (Month 4), or Visit 7 (Month 8). In patients who cannot reach the dose of 400 mg or matching placebo during the first 8 months after Randomization (Visit 7), the dose of 200 mg or matching placebo will be used throughout the study. If at any time during the study, the dose of 400 mg or placebo is not well-tolerated, the dose can be down-titrated (to 200 mg or matching placebo), 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.

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).

This is an event-driven study. The study will end when approximately 947 primary events have been positively adjudicated (ie, number of patients with at least 1 positively adjudicated primary event) in patients with LVEF <50%, AND approximately 1341 primary events have been positively adjudicated (ie, number of patients with at least 1 positively adjudicated primary event) in the total patient population. 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 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 (this repeat renal assessment may occur beyond the last planned visit per protocol). 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 (see Appendix E). Patients will continue with IMP treatment after a CV or renal endpoint occurs unless 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 will participate in a Screening period of up to 14 days. The study observation period starts at Randomization and lasts until the end of the study (the last study visit [eg, Follow-up Visit for patients who complete study treatment per protocol, or Study Closeout Visit for patients who prematurely permanently discontinue study treatment] of patient). The study is event-driven, therefore the duration will be determined as described in Section 6.1.2.

The estimated study duration will be approximately 3 to 32 months, assuming approximately 29 months of recruitment, and approximately 3 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 947 primary events have been positively adjudicated (ie, number of patients with at least 1 positively adjudicated primary event) in patients with LVEF <50%, AND approximately 1341 primary events have been positively adjudicated (ie, number of patients with at least 1 positively adjudicated primary event) in the total patient population. 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

No interim analysis is planned.

6.4 STUDY COMMITTEES

6.4.1 Executive Committee

The Executive Committee (EC) will oversee the 2 sotagliflozin outcome trials, ie, the present HF trial, and the other CV outcomes trial that will be conducted in parallel in patients with T2D, renal impairment and high CV risk. 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. The SC is also responsible for addressing and resolving 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, selected CV and renal events, diabetic ketoacidosis (DKA), and bone fractures in a treatment-blinded manner.

6.4.5 Safety events requiring ongoing monitoring

Two independent committees will review safety events to ensure timing of protocol amendments in case a safety signal is identified. These events are: 1) potential cases of drug-induced liver injuries (DILI), and 2) AEs leading to amputations.

The 2 independent committees will review the cases in a treatment-blinded manner and will present their assessment to the DMC.

The 2 committees' composition and roles/responsibilities will be described in a charter.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

7.1.1 At the Screening Visit

The Screening Visit should be no more than 14 days prior to Randomization.

Please note: sites that plan to enroll patients who have not been hospitalized (ie, admitted for at least 24 hours) will need to be qualified by the Sponsor at the pre-site visit or a visit to ensure the existence of appropriate facilities.

I 01. Either:

A) Diagnosis of T2D, based on appropriate supportive documentation for patients with a diagnosis of T2D prior to the Index Event

OR

B) For patients diagnosed with T2D at the time of the Index Event, laboratory evidence is required as follows:

- Fasting plasma glucose ≥126 mg/dL

  OR

- Random plasma glucose ≥200 mg/dL OR HbA1c ≥6.5%

I 02. Patient admitted to the hospital or had urgent HF visit to ED, Heart Failure Unit, or infusion center for WHF associated with intravascular volume overload (the Index Event), as determined by Investigator (based on appropriate supportive documentation) and defined by:

- Presence of ≥2 of the following clinical signs and symptoms of congestion:
  - Dyspnea
  - Jugular venous distention
  - Pitting edema in lower extremities (>1+)
  - Rales heard on auscultation
  - Radiographic pulmonary congestion

  AND

- Patient received treatment with IV loop diuretics

I 03. Patient had a diagnosis of HF ≥3 months prior to Screening (based on appropriate supportive documentation)

I 04. Prior chronic treatment (or prescription) with a loop diuretic (eg, furosemide, torsemide, bumetanide) for ≥30 days prior to the Index Event

I 05. Patients with LVEF <40% should be on beta-blockers and RAAS inhibitors as per local guidelines unless contraindicated

I 06. Patient or a legally acceptable representative has signed written informed consent to participate in the study in accordance with local regulations

7.1.2 At the Randomization Visit

Prior to hospital discharge if applicable, or within 3 days after discharge from hospital, ED, HF unit, or infusion center.

I 07. Patient is hemodynamically stable, defined as:

- Systolic blood pressure ≥100 mmHg, AND
- No requirement for IV inotropic therapy or IV vasodilators (except for nitrates) and no treatment with IV inotropic or IV vasodilators within 2 days prior to Randomization AND
- No requirement for mechanical ventilation or oxygen therapy in the last 24 hours

I 08. Transitioning from IV to oral diuretics defined as:

- Intravenous diuretic has been discontinued, AND
- Chronic oral loop diuretic has been prescribed and/or administered

I 09. At least 1 of the following laboratory values between admission for the Index Event and Randomization (based on local or central Laboratory):

- B-type natriuretic peptide ≥150 pg/mL (≥450 pg/mL for patients with atrial fibrillation)

  OR

- N-terminal B-type natriuretic peptide ≥600 pg/mL ≥1800 pg/mL for patients with atrial fibrillation)

Note: *The presence or absence of atrial fibrillation in order to determine the appropriate cut-off for a given BNP/NT-proBNP sample should be evaluated using the latest available electrocardiogram (ECG) or telemetry data performed prior to that BNP/NT-proBNP sample.*

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 2 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Age <18 years (or legal age for the country of participation) or >85 years at the Screening Visit

E 02. Index Event (admission for WHF associated with intravascular volume overload – see I 02) primarily triggered by pulmonary embolism, cerebrovascular accident, acute myocardial infarction (AMI)

Note: *Troponin elevations are frequently seen in patients with WHF and therefore are not sufficient for a diagnosis of AMI. In order to exclude patient due to AMI, concomitant objective evidence of AMI from ECG, and/or cardiac imaging and/or coronary angiography should be available.*

E 03. Index Event (admission for WHF – see I 02) for WHF not caused primarily by intravascular volume overload. For example, Index Event triggered by significant arrhythmia (eg, sustained ventricular tachycardia, or atrial fibrillation/flutter with sustained ventricular response >130 beats per minute, or bradycardia with sustained ventricular arrhythmia <45 beats per minute), infection, severe anemia, or exacerbation of chronic obstructive pulmonary disease (COPD)

E 04. Hospitalization for index event >2 weeks

E 05. Acute coronary syndromes within 3 months prior to Randomization

E 06. Ejection fraction not assessed by the time of Randomization (ie, no LVEF assessment performed following the Index Event and no LVEF measurement available within 12 months prior to Screening via imaging modality (such as echocardiogram, MUGA scan, MRI, PET, SPECT, LV angiography)

E 07. End-stage HF defined as requiring left ventricular assist devices (LVADs), intra-aortic balloon pump (IABP), or any type of mechanical support at the time of Randomization.

E 08. Cardiac surgery (coronary artery bypass graft), percutaneous coronary intervention (PCI), implantation of cardiac device (including biventricular pacemaker), or cardiac mechanical support implantation within 1 month prior to Randomization or planned during the study

E 09. Hemodynamically significant uncorrected primary cardiac valvular disease (please note that secondary mitral regurgitation or tricuspid regurgitation due to dilated cardiomyopathy is not excluded)

E 10. Significant pulmonary disease contributing substantially to the patients' dyspnea such as forced expiratory volume in 1 second (FEV_1) <1 liter or need for chronic steroid therapy, or any kind of primary right heart failure such as primary pulmonary hypertension or recurrent pulmonary embolism

E 11. Heart failure caused by postpartum cardiomyopathy diagnosed within the past 6 months

E 12. Heart failure from uncorrected thyroid disease, active myocarditis, known amyloid cardiomyopathy

E 13. Obstructive hypertrophic cardiomyopathy

E 14. History of stroke within 3 months prior to Randomization

E 15. History of dialysis within 1 year prior to Randomization

E 16. History of solid organ transplant or inclusion on a transplant list (if a heart transplant, defined as status 1 transplant)

E 17. Use of any investigational drug(s) for 5 half-lives prior to Screening

E 18. Hypersensitivity to sotagliflozin active substance or to any of the excipients including those in the placebo

E 19. 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 20. Any SGLT2 inhibitor <1 month prior to the Screening Visit, or between Screening and Randomization

E 21. Patients with respiratory, hepatic, neurological, 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) or patients with short life expectancy (defined as ≤1 year) that, according to the Investigator, will preclude their safe participation in this study, and will make implementation of the protocol or interpretation of the study results difficult

E 22. Presence of any other conditions (eg, geographic, social) actual or anticipated, that the Investigator feels would restrict or limit the patient's participation or compliance with all HF therapy, including study medication, for the duration of the study

E 23. Patient is the Investigator or any Subinvestigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol

E 24. 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)

7.2.2 Exclusion criteria related to the current knowledge of sotagliflozin

E 25. Severe kidney disease as defined by eGFR <30 mL/min/1.73 m² at the Screening Visit by the 4 variable Modification of Diet in Renal Disease (MDRD) equation

E 26. Any infection requiring intravenous antibiotics and/or with pyrexia (defined as temperature >38 °C [100.4 °F]) at time of Randomization

E 27. History of DKA or nonketotic hyperosmolar coma within 3 months prior to the Screening Visit

E 28. Lower extremity diabetic complications (such as skin ulcers, infection, osteomyelitis and gangrene) identified during the Screening period, and still requiring treatment at Randomization

E 29. Pregnant (demonstrated by serum pregnancy test at Screening) or breastfeeding women.

WOCBP as defined in Appendix A, 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. The Investigators may perform additional tests at their discretion or at frequency specified by local regulations

E 30. Digoxin level >1.2 ng/mL (in a patient treated with digoxin, and based on last local or central laboratory value available prior to Randomization)*

E 31. Laboratory findings (based on Screening value or last available value before Randomization, whichever is later):**

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN)
- Total bilirubin >1.7 times the ULN (except in case of Gilbert's syndrome)
- Serum potassium >5.5 mEq/L

Note: A patient should not be randomized more than once. 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 completion of enrollment. * If a patient meets exclusion criteria E 30, a one-time repeat testing is allowed for digoxin level without the need to rescreen the patient.

** If a patient meets exclusion criterion E 31:

- A one-time repeat testing is allowed for ALT or AST without the need to rescreen the patient
- Repeat testing for serum potassium is allowed for 3 days after Screening without the need to rescreen the patient

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCTS

IMPs are tablets of sotagliflozin 200 mg and matching placebo. Patients will be provided with 70-tablet bottles of sotagliflozin 200 mg or matching placebo included in 1 box. 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 placebo.

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[b] of the day	1 or 2 tablets (depending on visit number and dose titration status[a]), taken orally once daily, before first meal[b] of the day
Duration of treatment	The estimated study treatment duration will be approximately 3 to 32 months	The estimated study treatment duration will be approximately 3 to 32 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)

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

b If the randomization visit occurs after the patient has had their first meal of the day, the patient is allowed to take the first dose the following day, before the first meal.

IMP: investigational medicinal product

8.1.1 Dose up-titration and adjustments

8.1.1.1 Dose up-titration

Patients will receive sotagliflozin 200 mg or placebo from Visit 2 and will continue this regimen qd until the next visit.

Patients will return a week later at Visit 3 (Day 8). Clinical safety and tolerability (including vital signs and collection of AEs, including EOSIs, AESIs, and SAEs) will be assessed and blood (including serum creatinine) and urine laboratory samples will be collected. Patients will continue to receive sotagliflozin 200 mg or matching placebo qd until the next visit.

Patients will return a week later at Visit 4 (Day 15). Clinical safety and tolerability (including vital signs and collection of AEs, including EOSIs, AESIs, and SAEs) will be assessed and laboratory results from the prior week (including serum creatinine) will be reviewed, and new

laboratory samples (blood and urine) will be collected. If, in the opinion of the Investigator the patient's clinical condition is satisfactory and the patient has tolerated the IMP well without evidence of volume depletion, symptomatic hypotension (eg, dizziness, lightheadedness), or other AEs intolerable to the patient such as severe polyuria or nocturia, the dose will be up-titrated to sotagliflozin 400 mg or matching placebo qd until the next visit.

If the patient does not meet up-titration criteria for safety reasons (eg, hypotension), the Investigator will have the option of either continuing IMP at the 200 mg dose or placebo, with the optional adjustment of concomitant medications, or discontinuing IMP temporarily. If the dose is not up-titrated for safety reasons, the Investigator should make all attempts to up-titrate the dose at 1 of the next 3 subsequent visits: Visit 5 (Month 1), Visit 6 (Month 4), or Visit 7 (Month 8). In patients who cannot reach the dose of 400 mg or matching placebo during the first 8 months after Randomization (Visit 7), the dose of 200 mg or matching placebo will be used throughout the study. If at any time during the study, the 400 mg dose or placebo is not well-tolerated, the dose can be down-titrated (to 200 mg or matching placebo), 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.

8.1.1.2 Dose adjustments

If at any time during the study, the 400 mg dose or placebo is not well-tolerated, the dose can be down-titrated (to 200 mg or matching placebo), temporarily discontinued, or if medically necessary, permanently discontinued.

Throughout the course of the study, if the double-blind treatment is down-titrated or temporarily discontinued, every effort should be made to resume the higher dose of double-blind treatment as early as possible (unless there are safety concerns) so that patients are kept on the maximal tolerated study dose of double-blind treatment for as long as possible throughout the double-blind period of the trial.

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 PRODUCT(S)

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 the 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 treatment-blinded manner. The two safety committees will review potential cases of DILI and AEs leading to amputation in a treatment-blinded manner.

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 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 LVEF (<50% or ≥50%) and region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world).

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]

[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.

8.5 INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING

Packaging is 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 10.4.7).

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 6 and all subsequent on-site visits up to the Study Closeout Visit (or pEOT if patient prematurely permanently discontinues study treatment).

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 Visit 6.
- 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, 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 Visit 6.

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). The IMP includes sotagliflozin and placebo.

All concomitant medications should be documented on the Medications page of the e-CRF. This includes all treatments that are taken by the patients at any time during the clinical trial, beginning at Visit 1. Additionally, all medications taken in the month prior to Visit 1 and prior use of SGLT2 inhibitors should be reported.

8.8.1 Management of glycemia and diabetes complications

During the double-blind study treatment period, the management of glycemia and diabetes complications will be left to the physician's judgment, informed by clinical guidelines. While participating in this study, the patient should continue regularly scheduled visits with the physician (ie, diabetologist or internist) who manages their diabetes.

Investigators will monitor the glycemic status, potassium levels, and diabetic complications (including DKA) of patients throughout the study and should consult with relevant experts (eg diabetologists or nephrologists) as appropriate.

Diabetic ketoacidosis, including atypical (euglycemic) DKA, is the most serious emergency in patients with T1D and T2D. It is possible that GI or other AEs occurring with sotagliflozin may mask presenting symptoms of DKA. Because sotagliflozin lowers blood glucose by insulin independent SGLT1 and SGLT2 inhibition, it is possible for DKA to be present with normal or low blood glucose. Therefore, the Investigator must still consider a DKA event even if blood glucose is low or normal. Please refer to Appendix F for further details regarding DKA.

For patients with HbA1c <7.5% at time of Screening, and who are 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.

Patients should be instructed regarding careful attention to foot care and proper management of foot injuries in order to prevent ulcer formation. (Refer to Section 9.2.3.2 for further details).

8.8.2 Management of blood pressure and renal function

During the double-blind study treatment period, the management of BP (in hypertensive patients), potassium, and renal function (in patients with chronic kidney disease) will be left to the Investigator's judgment, informed by clinical guidelines; the Investigator should consult with relevant experts (eg nephrologists) as appropriate.

For patients with a systolic blood pressure <110 mmHg at Randomization, the doses of any 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 ACE-i/ARB, which should be at optimum / maximally tolerated doses. If a patient who is on an ACE-i/ARB does not tolerate the combination of the ACE-i/ARB with IMP due to hypotension/volume

depletion, and one of the two agents (either the ACE-i/ARB or IMP) needs to be withheld, the ACE-i/ARB should be maintained and the IMP should be withheld (temporarily if possible).

If clinically significant volume depletion occurs during coadministration of IMP with loop diuretics, or in vulnerable populations, consideration should be given to first reducing or discontinuing the loop diuretic, prior to temporarily withholding IMP administration.

8.8.3 Management of heart failure

Throughout the duration of the study, patients should be treated with drugs and devices for their HF condition, as per local guidelines.

In patients with HFrEF (LVEF <40%), several medications are considered lifesaving (ie, have been shown to reduce CV morbidity and mortality). These include RAAS inhibitors (ACE-i, ARB, ARNIs, MRAs, direct renin inhibitors) and beta-blockers. As a consequence, almost all patients with HFrEF (LVEF <40%) should receive 1 or several lifesaving medications at an optimal or maximal tolerated dose. The Investigator will confirm that patient is receiving the optimal or maximally tolerated dose, or otherwise record the reason for taking a lower dose. Every effort should be made to maintain such treatments at optimal or maximal tolerated doses throughout the duration of the trial.

In rare instances, patients could be enrolled without using concomitant lifesaving drugs. In such cases, the e-CRF will collect reasons for not using such treatments.

In all patients, change in doses of lifesaving drugs and use of devices (eg, ICD, CRT) will also be collected in the e-CRF. If a device is indicated per guidelines and not implanted, the reasons for not using the device will be collected.

8.8.4 Prohibited medications

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

- Any SGLT2 inhibitor
- Investigational drugs other than sotagliflozin

8.8.5 Other medications

For patients who are taking digoxin or P glycoprotein substrates and labels of P glycoprotein substrates, 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 inhibitor and increases systemic exposure to 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 Subinvestigator), he/she should be informed about this potential interaction. In patients treated with digoxin, digoxin levels may be measured using either serum or plasma at Screening and at Visit 4 (Week 2). If sites are unable to perform the test locally the assessment will be done by central laboratory. 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 4. Throughout the study, additional digoxin level assessments to be performed as per Investigators' judgment. Other medications that are unlikely to interfere with the pharmacokinetics (PK) or pharmacodynamics (PD) 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

The primary efficacy endpoints are:

- Time to first occurrence of either of the following clinical events in patients with LVEF <50%:
  - Cardiovascular death
  - Hospitalization for heart failure
- Time to first occurrence of either of the following clinical events in the total patient population:
  - 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).

Detailed outcome definitions will be 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 database 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 database lock of this study.

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.

9.1.2 Secondary efficacy endpoints

- Total number (ie, including recurrent events) of the following clinical events in the total patient population:
  - Cardiovascular death
  - Hospitalization for heart failure
  - Urgent HF visit
- Time to CV death in patients with LVEF <50%
- Time to all-cause mortality in patients with LVEF <50%
- Time to first occurrence of the composite of positively adjudicated sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, or

positively adjudicated sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days) in the total patient population

- Time to CV death in the total patient population
- Time to all-cause mortality in the total patient population

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 is defined as the value assessed by the central laboratory at 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 (this repeat renal assessment may occur beyond the last planned visit per protocol). 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 (see Appendix E).

9.1.3 Other efficacy endpoints

All the following endpoints are assessed in the total patient population:

- Proportion of patients with HHF or urgent HF visit (see Appendix B) within 30 days of Randomization
- Changes in KCCQ-12 scores from Baseline to Week 2, Month 1, Month 4, Month 8, Month 12, then annually
- Time to ≥50% decrease in eGFR from Baseline
- Proportion of patients with ≥1 new onset of atrial fibrillation, atrial flutter, or ventricular arrhythmia from Randomization
- Time to first MI (fatal and nonfatal)
- Time to first stroke (fatal and nonfatal)
- Changes from Baseline to Month 1 and Month 4 for NT-proBNP
- Changes from baseline in loop diuretics at day 180 and/or end of treatment visit
- Changes in hemoconcentration from Baseline at Week 2, Month 1, Month 4, Month 12, and EOT
- Changes from Baseline to Month 4, Month 12, and Month 24 in:
  - Hemoglobin A1c
  - Body weight

- Time to first occurrence of either of the following clinical events in subgroups of patients who started first IMP dose prior vs. after hospital discharge (or urgent care facility where appropriate):
  - Cardiovascular death
  - Hospitalization for heart failure

The following endpoints are assessed in subgroups of patients defined by LVEF:

- Time to first occurrence of either of the following clinical events in patients with LVEF <40%:
  - Cardiovascular death
  - Hospitalization for heart failure
- Time to first occurrence of either of the following clinical events in patients with LVEF ≥40% to <50%:
  - Cardiovascular death
  - Hospitalization for heart failure
- Time to first occurrence of either of the following clinical events in patients with LVEF ≥50%:
  - Cardiovascular death
  - Hospitalization for heart failure
- Time to all-cause mortality in patients with LVEF <40%
- Changes in hemoconcentration from Baseline at Week 2, Month 1, Month 4, Month 12, and EOT in patients with LVEF <40%

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 Kansas City Cardiomyopathy Questionnaire-12

The Kansas City Cardiomyopathy Questionnaire is a validated questionnaire assessing the health-related quality of life of patients with congestive HF (45). A 12-item version of this questionnaire (KCCQ-12) will be used in this study, capturing symptom frequency (4 items), physical (4 items) and social limitations (3 items), and quality of life impairment (2 items) as a result of HF (46). An overall summary score as well as 4 domain scores can be calculated ranging from 0 to 100 where 100 denotes the highest health status.

The KCCQ-12 will be completed by all patients as described in the Study Flow Chart (Section 1.2). The KCCQ-12 should take less than 10 minutes for patients to complete (see Appendix C).

The patients will be requested to complete the KCCQ-12 questionnaire by themselves during the selected clinical visits, independently from Investigator, site staff and any help from friends or relatives. In case patients are too weak to complete the KCCQ-12 by themselves, it could be interviewer-administered. In this case, interviewers will be allowed to help patients completing the KCCQ-12 by reading each question aloud and strictly recording the patient's responses without influencing or interpreting them. If the patient is unable to give a response verbally or by pointing, the questionnaire should be considered as missing.

For validity purposes, patients will be asked to answer all the questions of the questionnaires at the start of the visits before any other procedures or tests, in a quiet place, and while on site to return the completed questionnaires to the Investigator or his/her designee on the same day.

In case of premature permanent IMP discontinuation, the KCCQ-12 will be completed by patients at the visit planned for the last dosing day with IMP and afterwards as normally planned.

9.1.3.3 Concomitant medications by class

All concomitant medications (eg, beta-blockers, loop diuretics, ACE inhibitors, direct renin inhibitors, ARNis, ARBs, MRAs) are collected as described in Section 8.8. Details of the analysis will be included in the statistical analysis plan (SAP).

9.2 SAFETY ENDPOINTS

- All AEs including AESIs, EOSIs, and SAEs
- Severe hypoglycemia (also an EOSI)
- Clinical laboratory results including vital signs (including heart rate, BP)

9.2.1 Adverse events

Adverse events including AEs leading to premature treatment discontinuation, 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 10.4.7, 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 laboratory values obtained at the local laboratory will be used for screening purposes and for safety review and will not be included for analysis. 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 frequency specified by local regulations. For women of non-productive potential (Appendix A), follicle stimulating hormone and/or estradiol levels should be tested in case the definition of postmenopausal or premenopausal cannot be satisfied, eg, no medical document of hysterectomy or cessation of menses without an alternative medical cause is <12 months.

Table 2 - Chemistry parameters

Serum clinical chemistry	Serum hematology	Serum lipid profile	Digoxin
Sodium	Complete blood count (CBC)	Total cholesterol (TC)	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			
Phosphorus			
Total protein			
Albumin			
Magnesium			
Creatine phosphokinase (CPK)			
Lactic acid dehydrogenase (LDH)			

a In patients treated with digoxin at Screening, digoxin levels should be measured at Screening and at Visit 4 (Week 2). 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 4. Throughout the study, additional digoxin level assessments to be performed in either serum or plasma as per Investigators' judgment. If applicable, digoxin level assessment should be performed via a local laboratory, if sites are unable to perform the test locally, the test should be done by central 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

At Visit 1 only, urinalysis will be performed by the local laboratory. For all subsequent visits the urinalysis 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

urinalysis is positive for nitrite and leukocyte esterase or blood, reflexive testing will be performed at the local laboratory at Visit 1, and at the central laboratory for subsequent visits. Reflexive testing includes microscopy and urine culture (microscopy includes detection of formed cellular elements, casts, bacteria, yeast, parasites, and crystals in centrifuged urine sediment).

If the urine dipstick is positive for nitrite and leukocyte esterase or blood, 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).

9.2.3 Vital signs

Vital signs (sitting BP and heart rate) measurements will be made at every on-site visit and should be measured in a seated position.

9.2.3.1 Physical examinations

- A complete physical examination will be performed as per clinical practice in order to assess the health status of the participant at Screening and evaluate the inclusion/exclusion criteria, and at pEOT (if applicable) and Study Closeout Visits.
- At all other on-site visits, an abbreviated physical examination focused on any affected body area or organ system and other symptomatic or related organ system(s) will be performed.
- All physical examinations, including abbreviated physical examinations, will include 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 and this examination should be documented on the e-CRF. Lower extremity complications (such as skin ulcers, infection, osteomyelitis, and gangrene) requiring treatment should lead to temporary discontinuation of IMP.

9.2.3.2 Foot care

Patients should be instructed regarding careful attention to foot care and proper management of foot injuries in order to prevent ulcer formation (47, 48, 49).

Patients or caregivers should be instructed to perform daily foot inspection. Gentle cleansing should be performed regularly with soap and water, followed by liberal use of moisturizers in order to help maintain healthy skin and help resist skin breakdown and injury.

Care should be taken to ensure that shoes fit properly. Patients may benefit from the use of thick absorbent socks and custom shoes in certain cases (such as those with foot deformities).

Minor foot injuries (such as cuts, scrapes, blisters) and infections (such as tinea pedis) can be unintentionally exacerbated by use of some home remedies. Patients should be instructed to discuss any use of such therapies with their healthcare provider. Patients should avoid hot soaks, heating pads and certain harsh topical therapies such as hydrogen peroxide, iodine (eg, betadine) and astringents (eg, witch hazel). Gentle cleansing of minor wounds along with a topical antibiotic to maintain a moist environment can help to prevent ulcer formation. Any minor wound that does not heal rapidly should be immediately brought to the attention of the healthcare provider. Patients should be instructed to regularly trim their toenails and to take care not to injure surrounding skin by cutting straight across and filing any rough edges with a nail file. Referral to a podiatrist should be considered for proper foot care management (such as for corn or callus management, for treatment of onychomycosis, or to trim toenails if the patient cannot safety do so on their own).

The importance of daily foot inspection, treating lesions (even if minor), and seeking medical attention for lesions that do not heal cannot be overemphasized.

9.2.4 Electrocardiogram variables

A 12-lead ECG record is performed locally at Screening (Visit 1), the pEOT Visit (if patient prematurely discontinues study treatment), and the Study Closeout Visit. The 12-lead ECG should be performed after ≥10 minutes in the supine position. If ECG assessment was done as standard of care, the most recent ECG collected after the Index event, may be formally used to screen patients.

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.

9.3 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 discussed in Section 4, HF is a common comorbidity and complication of T2D with particularly poor outcomes. Because HF patients admitted to the hospital with WHF carry a high risk of CV death and HHF (~30% at 6 months), the main objectives of this study are to

demonstrate whether sotagliflozin reduces the composite of CV death and HHF as compared to placebo in diabetic patients after hospitalization for WHF. In order to further evaluate the effect of sotagliflozin on patients across the spectrum of LVEF values, there are 2 primary endpoints. The first endpoint is in patients with a LVEF <50% and the second in the total patient population.

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 6 on-site visits in the first 4 months. Subsequently, on-site visits are every 4 months until the Study Closeout Visit.

The visit windows for Visits 3, 4, and 5 are ±3 days. The window for Visits 6 to 12 and, if applicable, the pEOT Visit, is ±7 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 Subinvestigators who are qualified in the treatment of T2D and are trained on the study.

10.1.1 Screening period

The Screening period will be up to 14 days in duration, and includes Visit 1 (Week -2). The Screening period duration provides sites the ability 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).

Blood samples for BNP or NT-proBNP should be collected by the local laboratory at Screening before Randomization, if not collected earlier following the specific Index event.

In cases where a patient fails Screening due to reasons expected to change during Screening period, 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 -2) Screening Visit

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

- Obtaining the informed consent (for main study [redacted]):
  - 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 [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 (as applicable, to be recorded in source documents). Alternate contact information for patients (ie, relative or friend) should also be collected as a backup
- 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 complete physical examination, including lower extremities (see Section 9.2.3)
- 12-lead ECG. If ECG assessment was done as standard of care, the most recent ECG collected after the Index event, may be formally used to screen patients
- IRT to be contacted (for allocation of patient ID, registration of Screening, and IP allocation)
- Prior and concomitant medications, including for 1 month prior to Screening
- Echocardiogram (if not performed within the last 12 months)
- The following laboratory testing will be collected locally:
  - BNP or NT-proBNP
  - Hematology
  - Chemistry (including eGFR)

- Serum pregnancy testing for WOCBP
- Urinalysis (dipstick)
- Digoxin (if applicable, see Section 9.2.2)

  Note: If the laboratory assessments were done as standard of care, the historical data collected after the Index event may be used for Screening. However, serum pregnancy test must be collected at Screening. If sites are unable to perform the screening tests locally, the assessment can be done by central laboratory.

- An appointment will be made for Visit 2

10.1.2 Randomized double-blind treatment period

The Screening and randomization visits may be conducted on the same day. 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 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.

A blood sample for NT-proBNP will be collected by the central laboratory at Randomization before taking IMP, and for any subsequent visits when NT-proBNP is scheduled to be collected.

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.

Sotagliflozin/metabolite levels may be analyzed via routine blood samples collected throughout the study. Fasting is not necessary before the blood draw for laboratory assessments from Visit 2.

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 (this repeat renal assessment may occur beyond the last planned visit per protocol). 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 Randomization Visit should occur prior to hospital discharge if applicable, or within 3 days after discharge from hospital, ED, HF unit, or infusion center.

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)
- Abbreviated physical examination, including lower extremities
- IRT to be contacted and Randomization will occur if the patient is eligible for the study
- IMP is dispensed
- 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, ARNIs, MRAs, direct renin inhibitors, loop diuretics, and beta-blockers should be collected **at Baseline and at all study visits**. Where patients are receiving RAAS inhibitors, ARNIs, MRAs, loop diuretics, and/or beta-blockers at lower than the optimal/ 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 (as applicable, to be recorded in source documents). Alternate contact information for patients (ie, relative or friend) should also be reviewed as a backup
- The following laboratory testing:
  - NT-proBNP (before administration of study drug)
  - HbA1c
  - Hematology
  - Chemistry (including eGFR)
  - Lipids
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
  - [redacted]
  - [redacted]

- KCCQ-12 questionnaire
- An appointment for Visit 3 will be made

10.1.2.2 On-site Visits 3 (Week 1) and 4 (Week 2)

The following procedures/assessments will be performed at Visits 3 and 4 (Weeks 1 and 2):

- 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)
- Abbreviated physical examination, including lower extremities
- IMP compliance
- 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 (as applicable, to be recorded in source documents). Alternate contact information for patients (ie, relative or friend) should also be reviewed as a backup
- The following laboratory testing:
  - Hematology
  - Chemistry (including eGFR)
  - Sotagliflozin/metabolite levels may be analyzed via routine blood samples collected at these visits
  - Urinalysis (dipstick)
- The following laboratory testing (by local laboratory):
  - Digoxin (Visit 4 **ONLY**) (if applicable, see Section 9.2.2). If sites are unable to perform the test locally the assessment will be done by central laboratory.
- KCCQ-12 questionnaire (Visit 4 **ONLY**)
- An appointment for Visit 4 will be made at Visit 3

10.1.2.3 On-site Visit 5 (Week 4)

The following procedures/assessments will be performed at Visit 5 (Month 1):

- 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)
- Abbreviated physical examination, including lower extremities
- IMP compliance
- 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 (as applicable, to be recorded in source documents). Alternate contact information for patients (ie, relative or friend) should also be reviewed as a backup
- The following laboratory testing:
  - Hematology
  - Chemistry (including eGFR)
  - NT-proBNP
  - Sotagliflozin/metabolite levels may be analyzed via routine blood samples collected at this visit
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
- KCCQ-12 questionnaire
- An appointment for Visit 6 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 6).

10.1.2.4 On-site Visit 6 (Month 4)

The following procedures/assessments will be performed at Visit 6 (Month 4):

- 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)
- Abbreviated physical examination, including lower extremities
- IRT contact
- IMP is dispensed
- IMP accounting and compliance
- 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 (as applicable, to be recorded in source documents). Alternate contact information for patients (ie, relative or friend) should also be reviewed as a backup
- The following laboratory testing:
  - NT-proBNP
  - HbA1c
  - Hematology
  - Chemistry (including eGFR)
  - Lipids
  - Sotagliflozin/metabolite levels may be analyzed via routine blood samples collected at this visit
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
- KCCQ-12 questionnaire
- An appointment for Visit 7 will be made

10.1.2.5 On-site Visits 7 to 12 (Months 8, 12, 16, 20, 24, 28)

The following procedures/assessments will be performed (except when noted) at on-site Visits 7 (Month 8), 8 (Month 12), 9 (Month 16), 10 (Month 20), 11 (Month 24), and 12 (Month 28), up until the end of study:

- 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)
- Abbreviated physical examination, including lower extremities
- IRT contact
- IMP is dispensed
- IMP accounting and compliance
- 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 (as applicable, to be recorded in source documents). Alternate contact information for patients (ie, relative or friend) should also be reviewed as a backup

- The following laboratory testing:
  - NT-proBNP (at Visits 7 and 9 [Months 8 and 16], then annually)
  - HbA1c (will be performed at Visit 7 [Month 8], Visit 8 [Month 12], Visit 9 [Month 16], Visit 10 [Month 20], and Visit 11 [Month 24])
  - Hematology
  - Chemistry (including eGFR)
  - Sotagliflozin/metabolite levels may be analyzed via routine blood samples collected at these visits
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
  - [redacted]
- KCCQ-12 questionnaire (at Visits 7 [Month 8] and 8 [Month 12], then annually)
- An appointment for the next Visit will be made

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 (see Section 10.3.2 for further details of contact).

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 10.3.4 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)
- 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)
- Complete physical examination, including lower extremities

- IRT contact
- IMP accounting and compliance
- 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 (as applicable, to be recorded in source documents). Alternate contact information for patients (ie, relative or friend) should also be reviewed as a backup
- 12-lead ECG
- The following laboratory testing:
  - NT-proBNP
  - HbA1c
  - Hematology
  - Chemistry (including eGFR)
  - Lipids
  - Sotagliflozin/metabolite levels may be analyzed via routine blood samples collected at this visit
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
  - Urinalysis (dipstick)
  - [redacted]
- KCCQ-12 questionnaire

10.1.4 Study Closeout

All randomized patients will be asked to return to the study site for a Study Closeout Visit as described in Section 6.1.2. 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 10.1.4.2).

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)

- 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)
- Complete physical examination, including lower extremities
- IRT contact
- IMP accounting and compliance
- 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 (as applicable, to be recorded in source documents). Alternate contact information for patients (ie, relative or friend) should also be reviewed as a backup
- 12-lead ECG
- The following laboratory testing:
  - NT-proBNP
  - HbA1c
  - Hematology
  - Chemistry (including eGFR)
  - Lipids
  - Sotagliflozin/metabolite levels may be analyzed via routine blood samples collected at this visit
  - Urine pregnancy testing for WOCBP (any positive urine test results must be confirmed by a serum pregnancy test)
  - Urinalysis (dipstick)
  - [redacted]
- KCCQ-12 questionnaire
- 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)

- 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)
- Complete physical examination, including lower extremities
- IRT contact
- Concomitant medications are assessed
- 12-lead ECG
- The following laboratory testing:
  - NT-proBNP
  - 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)
- KCCQ-12 questionnaire

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:

- Vital signs (sitting BP, heart rate)
- Abbreviated physical examination, including lower extremities
- Measurement of eGFR
- IRT contact
- 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)

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 until the Study Closeout Visit 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 must be fully documented in the e-CRF. In any case, the patient should remain in the study and be 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 products

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. This is in part due to the fact that a patient is expected to participate in the study for a period potentially lasting several years. 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 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.

If DKA is suspected or confirmed, study treatment should be stopped immediately and should not be re-started unless another cause for the ketoacidosis is identified and resolved.

In addition, IMP administration should be stopped in patients admitted to the hospital for major surgical procedures or due to serious illness.

If a patient who is on an ACE-i/ARB does not tolerate the combination of the ACE-i/ARB with IMP due to hypotension/volume depletion, and one of the two agents (either the ACE-i/ARB or IMP) needs to be withheld, the ACE-i/ARB should be maintained, and the IMP should be withheld (temporarily if possible).

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 responsibility of the IMP in the occurrence of the concerned event was unlikely.

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.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

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 ≥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

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reason(s) for treatment discontinuation and this should be documented in the e-CRF.

Patients who report a CV or renal endpoint as described in Section 10.4.1.4 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 or ECG parameter will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the 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.

10.3.5 Procedure and consequence for patient withdrawal from study

The 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.

The Investigators should discuss with them key visits to attend. The value of all their 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 patient contacts should be distinguished from withdrawal of consent for non-patient contact follow-up, medical records check. The site should document any case of withdrawal of consent.

For patients who fail to return to the site, unless the patient withdraws consent for contact, the Investigator must make the best effort to recontact the patient, and to determine his/her 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 Closeout 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 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, independent ethics committee (IECs)/institutional review boards (IRBs), 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 10.4.1.4) 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
- 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 ED 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 (Please refer to related flowchart in Appendix E)
  - 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 aggravated during the study
  - 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
  - Adverse events leading to amputation(s)
  - Diabetic ketoacidosis

10.4.1.3 Adverse event of special interest

An **adverse event of special interest** (AESI) is an AE (serious or nonserious) 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 AESIs 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 be qualified 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 (see Appendix A).
- Symptomatic overdose (serious or nonserious) with IMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as administration of more than twice the intended daily dose of IMP within a 24-hour period..
  - Of note, asymptomatic overdose has to be reported as a standard AE.
- ALT ≥3 ULN (if baseline ALT < ULN) or ALT ≥2 times the baseline value (if baseline ALT ≥ ULN) (Please refer to related flowchart in Appendix D).

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 EOSIs for this study are:

- Venous thrombotic events to include deep venous thrombosis and thromboembolism (to include pulmonary embolism)
- Pancreatitis
- Bone fractures
- Adverse events leading to amputation(s)
- Diabetic ketoacidosis (see Section 10.4.7 for further details)

- 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.

All Cardiovascular events 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 all CV events 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 all CV events will be waived:

- Cardiovascular death
- Any MI
- Unstable angina
- Any stroke
- Heart failure leading to hospitalization
- Urgent HF visit (as defined in Appendix B)

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, 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 progression has been stabilized, 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. At the prespecified study end-date, patients who experience an ongoing SAE or an AESI should be followed until resolution, stabilization, or death and related data will be collected.
- 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:
  - 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

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 monitoring team 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 representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. 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 management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix D. 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 2 study visits** should be followed up as described in Appendix E.

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 E)

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

10.4.7 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).

Whenever AE data is collected or the patient reports DKA or intercurrent illness (including infections), generalized weakness, increased weight loss, GI symptoms including nausea, vomiting, or abdominal pain or other symptoms or signs that the Investigator believes may be consistent with DKA, the site will determine if an assessment for DKA, such as assessing blood beta-hydroxybutyrate level (BHB), is appropriate. If BHB or other laboratory testing confirms the presence of metabolic acidosis, then the "Possible DKA" e-CRF will be completed.

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 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 ≥3 ULN (if baseline ALT < ULN) or ALT ≥2 times the baseline value (if baseline ALT ≥ ULN) (Please refer to related flowchart in Appendix D).

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, IV 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.

If the event fulfills SAE criteria, the severe hypoglycemia will also be reported as an SAE. 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 (50, 51).

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 by primary endpoints of time to first occurrence of CV death or HHF in patients with LVEF <50%, and in the total patient population. In order to achieve the target number of events of 947 first occurrence of CV death/HHF in patients with LVEF <50% and 1341 first occurrences of CV death/HHF in the total patient population, it is estimated that approximately 4000 patients will be randomized over an estimated 29 months of recruitment period with approximately 3 months of follow-up after the last patient is randomized.

The sample size calculation is based on the following trial design assumptions:

- A recruitment period of approximately 29 months
- Approximately 3 months of follow-up after the last patient is randomized
- 29.2%, 39.7% and 44.5% event rate by Month 6, Month 12, and Month 24, respectively, in the placebo group (by assuming yearly hazard rate at Months 1, 2, 3, 4, 5, 6, 12, 24, and 36 be 1.06, 0.87, 0.74, 0.62, 0.49, 0.36, 0.32, 0.08, and 0.05, respectively)
- Hazard ratio (HR) = 0.81 for sotagliflozin versus placebo for patients with LVEF <50% and for patients with LVEF ≥50%
- 2% annual censoring rate

This will provide:

- 90% power (with α=0.05, 2-sided) to demonstrate superiority of the primary endpoint (first occurrence of CV death or HHF) comparing sotagliflozin versus placebo in patients with LVEF <50%.
- More than 90% power (with α=0.05, 2-sided) to demonstrate superiority of the primary CV endpoint (first occurrence of CV death or HHF) comparing sotagliflozin versus placebo in the total patient population.

This is an event-driven study. Therefore, the study will continue until approximately 947 primary events (first occurrence of CV death or HHF) have been positively adjudicated in patients with LVEF <50%, AND approximately 1341 primary events (first occurrence of CV death or HHF) have been positively adjudicated in total patient population, and ≥3 months follow-up for the last randomized patient.

Calculations were based log-rank test with user defined survival, accrual and drop-out rates by using EAST 6.4.

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 database, 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 actually received.

11.3.1.1 Intent–to-treat /modified intent-to-treat population

Intent-to-treat (ITT) population: all randomized patients 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 ≥1 dose of double-blind IMP (regardless of the amount of treatment administered).

Patients will be analyzed for safety 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 with the longest duration.

11.3.3 Patient-reported outcome analysis populations

The patient-reported outcome (PRO) KCCQ-12 evaluation will be based on patients included in the efficacy population who have Baseline PRO assessment, at least 1 IMP administration, and at least 1 post-baseline PRO assessment.

11.4 STATISTICAL METHODS

Continuous data will be summarized by treatment group using the number of observations available, mean, SD, minimum, median, and maximum.

Categorical data will be summarized by treatment group using count and percentage (%).

In general, descriptive statistics of quantitative efficacy and safety parameters (result and change from Baseline) by scheduled visits will be provided on observed cases (OC), ie, inclusion of patients having non-missing assessments at a specific visit only.

Baseline for eGFR is defined as the value assessed by the central laboratory at 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.

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received for 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 for 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 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, minimum, and maximum). The percentage of patients with compliance <80% will be summarized.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoints

The time to the first occurrence of CV death or HHF in patients with LVEF <50% will be analyzed by using stratified log-rank test with region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) as stratification factor. Stratified Cox proportional hazards model with region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) as stratification factor and treatment (sotagliflozin, placebo) as fixed effect factor will be used to provide the HR estimation between sotagliflozin and placebo along with its associated 2-sided 95% confidence interval (CI).

The time to the first occurrence of CV death or HHF in the total patient population will be analyzed by using stratified log-rank test with LVEF (<50%, ≥50%) and region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) as stratification factors. Stratified Cox proportional hazards model with LVEF (<50%, ≥50%) and region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) as stratification factors and treatment (sotagliflozin, placebo) as fixed effect factor will be used to provide the HR estimation between sotagliflozin and placebo along with its associated 2-sided 95% CI.

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 complete the study), or date of non-CV death, or date of last contact when information on efficacy endpoints has been retrieved (for patients who discontinue the study). Underlying assumptions of the Cox proportional hazards model will be checked using graphical methods. If proportionality is not observed, further sensitivity analysis will be performed (details will be specified in the SAP).

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 up to study completion (whichever is later), but not beyond the patient's end of study date (Follow-up Visit for patient completed study or Study Closeout Visit for patient prematurely permanently discontinued study), using the same stratified log-rank test and stratified Cox proportional hazards model described above.

Subgroup analysis

Subgroup analyses will be conducted for the primary endpoints with respect to LVEF (for second primary endpoint only), region, age, gender, race, ethnicity, Baseline eGFR, and Baseline BMI group. Additional subgroups and analysis details will be provided in the SAP.

11.4.2.2 Analyses of secondary efficacy endpoints

The total number (ie, including recurrent events) of CV death, HHF, or urgent HF visit will be analyzed using the Andersen-Gill approach (52), a generalization of the Cox proportional hazards model for recurrent events with treatment, LVEF, and region as factors. For standard errors in the Andersen-Gill model, a robust variance estimator will be used (53).

Secondary time to event endpoints will be analyzed using the same stratified log-rank test with LVEF (<50%, ≥50%) and region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) as stratification factors. Stratified Cox proportional hazards model with LVEF (<50%, ≥50%) and region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) as stratification factors and with treatment (sotagliflozin, placebo) as fixed effect factor will be used to provide the HR estimation between sotagliflozin and placebo along with its associated 2-sided 95% CI. The LVEF factor will not be included in the statistical model as stratification factor if the endpoint is defined in patients with LVEF <50%. Kaplan-Meier curves of the cumulative incidence rates will be provided by treatment groups.

11.4.2.3 Other endpoints

Other time to event endpoints will be analyzed using the same stratified Cox proportional hazards model described for the second primary endpoint with LVEF and region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) as stratification factors and treatment as fixed effect factor. The LVEF will not be included in the statistical model as stratification factor if the endpoint is defined in a subgroup of patients by LVEF, eg, LVEF<40%.

Number (%) of patients with at least 1 new onset of atrial fibrillation, atrial flutter, or ventricular arrhythmia since Randomization will be summarized by treatment group. For other endpoint of changes in concomitant loop diuretic medications, summary tables will be provided.

Analysis of other endpoints will be descriptive with no statistical testing. Summary statistics at scheduled visits using observed data will be provided by treatment group. Graphical presentations will also be used to illustrate trends over time if applicable.

11.4.2.4 Multiplicity considerations

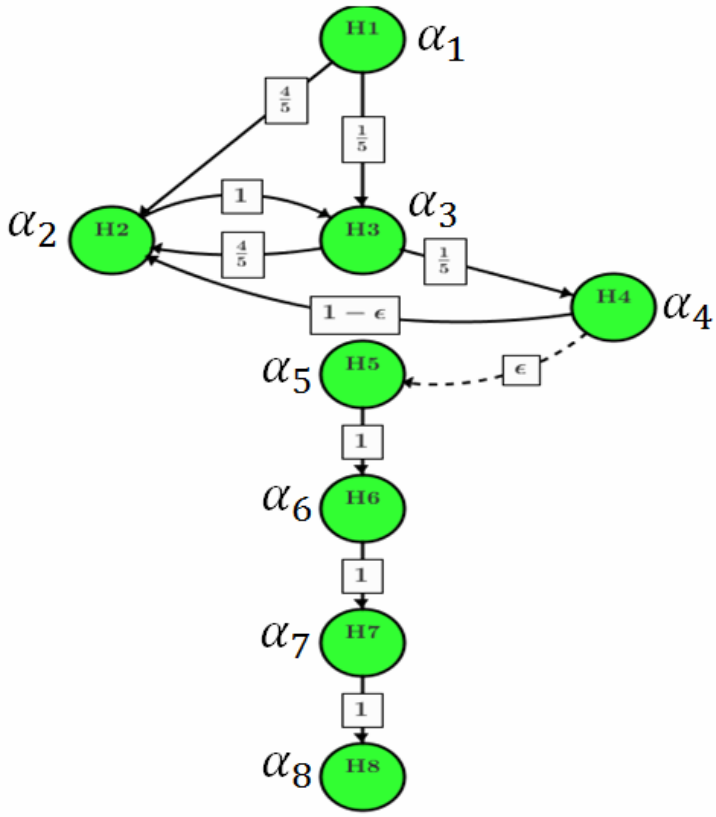
The graphical approach (1) will be used to control the family-wise type 1 error rate at 0.05 levels.

In graphical approach, the testing procedure is fully determined by an initial weighted graph where the elementary hypotheses are represented by vertices with associated weights representing the local significance levels. The weight associated with a directed edge between any two vertices indicates the fraction of the (local) significance level at the initial vertex (tail) that is added to the

significance level at the terminal vertex (head) if the hypothesis at the tail is rejected. Together with the algorithm as specified by Bretz et al (1) for sequentially updating the graph after rejection of a hypothesis, this approach controls the family-wise type I error rate strongly at level α.

As shown by Bretz et al., (1) the test decisions are independent of the order of rejection. If in a step of the algorithm more than one hypothesis can be rejected, the choice of the hypothesis Hi does not influence the total set of hypotheses that eventually can be rejected. The initial graph and the algorithm unequivocally define the testing strategy.

Initial Graph:



Note: ε=0.001.

There are two primary hypotheses and six secondary hypotheses will be included in the multiple testing procedure as below:

Primary hypotheses:

H1: Time to first occurrence of CV death or HHF in patients with LVEF <50%

H2: Time to first occurrence of CV death or HHF in the total patient population

Secondary Hypotheses

H3: Total number (ie, including recurrent events) of CV death, HHF, or urgent HF visit in total patient population

H4: Time to CV death in patients with LVEF <50%

H5: Time to all-cause mortality in patients with LVEF <50%

H6: Time to first occurrence of the composite of positively adjudicated sustained ≥50% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis, renal transplant, or positively adjudicated sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days) in total patient population

H7: Time to CV death in total patient population

H8: Time to all-cause mortality in total patient population

All tests will be two-sided. Significance levels $\alpha_1 = 0.05$

($\alpha_2 = \alpha_3 = \alpha_4 = \alpha_5 = \alpha_6 = \alpha_7 = \alpha_8 = 0$) are initially defined such that they sum up to

$\alpha = 0.05$.

The procedure is as follows: Test the hypotheses H_i, i=1, 2, …. 8, each at its local significance

level α_i. If a hypothesis H_i can be rejected, reallocate its level to other hypotheses according to a pre-specified rule represented by the initial weighted graph. Update the reallocation weights in the reduced graph and repeat the testing step for the remaining, non-rejected hypotheses with the updated local significance levels. This possibility leads to further rejected null hypotheses with the updated local significance levels. The procedure is repeated until no further hypothesis can be rejected.

The reallocation of the local alpha levels is fully determined by the initial graph of the multiple testing strategy.

No further multiplicity adjustments will be made for other efficacy endpoints or subgroup analyses for which nominal p-values may be provided for descriptive purpose only.

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 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. Potentially clinically significant abnormality criteria for parameters not cited in the protocol as safety parameters will not be analyzed.
- The 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.

Please note that the same observation period will be used for all safety observations (ie, AE and death).

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

- The Screening period is defined as the time from signed informed consent to Randomization.
- 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).
- On-study observation period is defined as the time from randomization until the end of the study.

11.4.3.1 Analysis of adverse events

Pre-treatment AEs are AEs that developed or worsened or became serious during the time between date of informed consent and the first dose of double-blind IMP.

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 10.4.1.4.

All adverse events

The number (%) of patients with at least 1 AE will be tabulated 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 by treatment group. Multiple occurrences of the same event for the same patient will be counted only once in the tables within a treatment period. The denominator for computation of percentages is number of patients within each treatment arm in the safety population.

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 (%) 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

Deaths and treatment-emergent SAEs will be summarized and presented as number (%) of patients by treatment group.

The following deaths will be summarized by treatment received for the safety population:

- Number (%) of patients died by study period (on-study and on-treatment) and the adjudicated death reason.
- Death in nonrandomized patients or randomized but not treated patients.
- Number (%) of patients with 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, sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.
- Number (%) of patients with 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, presenting 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

All TEAEs leading to permanent treatment discontinuation will be summarized and presented as number (%) of patients in each treatment group.

11.4.3.2 Analysis of severe hypoglycemia

The number (%) of patients and rate in patient-year (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 will be 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 interests 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 Medical Dictionary for Regulatory Activities 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 variable

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.

Liver tests

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 post-baseline visit by Baseline status will be displayed by treatment group for each parameter.

The proportion of patients with PCSA values at any post-baseline 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 by 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. For each vital sign parameter, its value and change from Baseline will be summarized for visit and the last on-treatment value by treatment group. Tabular and graphical methods may be used to present the results for parameters of interest. Listings will be provided with flags indicating PCSA values.

11.4.4 Analyses of patient reported outcomes (health-related quality of life/health economics variables)

Summary statistics of KCCQ-12 scores will be provided at scheduled visits by treatment group. Graphical presentations will also be used to illustrate trends over time. Further details will be provided in the SAP.

11.5 INTERIM ANALYSIS

No formal interim analysis for efficacy is planned for this study. The study will not be terminated early for excellent efficacy.

An independent DMC was formed to monitor the safety data and benefit/risk in the entire Phase 3 (outcome and non-outcome) Sotagliflozin program, including this trial. The DMC will regularly review the safety data provided by an independent statistical group. Related details are available in separate documents (DMC charter and DMC 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 Subinvestigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Council for Harmonisation 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.

[redacted]

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, IB 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 IB 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 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 Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators 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 informed consent form 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 Subinvestigator 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 IB, 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 Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators 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 /Subinvestigator 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 Subinvestigators 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 database shall be treated in compliance with all applicable laws and regulations including General Data Protection Regulation.
- 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 databases, 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, good clinical practice, 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 Subinvestigator, 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 thirty (30) 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 informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

16 BIBLIOGRAPHIC REFERENCES

1. Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine. 2009;28:586-604.

2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013 Oct 15;128(16):e240-327.

3. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart Disease and Stroke Statistics -- 2016 Update: A report from the American Heart Association. Circulation. 2016 Jan 26;133(4):e38-360.

4. Roger VL. Epidemiology of heart failure. Circ Res. 2013 Aug 30;113(6):646-59.

5. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: problems and perspectives. J Am Coll Cardiol. 2013 Jan 29;61(4):391-403.

6. Krumholz HM, Merrill AR, Schone EM, Schreiner GC, Chen J, Bradley EH, et al. Patterns of hospital performance in acute myocardial infarction and heart failure 30-day mortality and readmission. Circ Cadriovasc Qual Outcomes. 2009 Sep;2(5):407-13.

7. Desai A, Stevenson L. Rehospitalization for heart failure: predict or prevent? Circulation. 2012 Jul 24;126(4):501-06.

8. An act entitled “The Patient Protection and Affordable Care Act”. Pub L 111-148 (2010).

9. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016 Aug;18(8):891–975.

10. American College of Cardiology Foundation/American Heart Association. 2013 ACCF/AHA Guideline for the Management of Heart Failure. Circulation. 2013 Oct 15;128:000–000.

11. Kapoor JR, Kapoor R, Ju C, Heidenreich PA, Eapen ZJ, Hernandez AF, et al. Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. JACC Heart Fail. 2016 Jun;4(6):464-72.

12. Wilkins MR, Redondo J, Brown LA. The natriuretic-peptide family. Lancet. 1997 May 3;349(9061):1307-10.

13. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a Phase 2 double-blind randomised controlled trial. Lancet. 2012 Oct 20;380(9851):1387-95.

14. Gheorghiade M, Böhm M, Greene SJ, Fonarow GC, Lewis EF, Zannad F, et al. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial. JAMA. 2013 Mar 20;309(11):1125-35.

15. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: The EVEREST outcome trial. JAMA. 2007 Mar 28;297(12):1319-31.

16. 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 Jun 26;375(9733):2215-22.

17. 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 Jul 7;314(1):52-60.

18. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. Lancet Diabetes Endocrin. 2015 Feb;3(2):105-13.

19. 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 Mar;28(3):612-16.

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

21. 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 Mar;27(3):699-703.

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

23. Carr AA, Kowey PR, Devereux RB, Brenner BM, Dahlöf B, Ibsen H, et al. Hospitalizations for new heart failure among subjects with diabetes mellitus in the RENAAL and LIFE studies. Am J Cardiol. 2005 Dec 1;96(11):1530-36.

24. 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 Jul;10(4):330-36.

25. 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 Jul;59(7):1333-39.

26. 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 Nov 26;373(22):2117-28.

27. 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].

28. U.S. Food and Drug Administration. FDA approves Jardiance to reduce cardiovascular death in adults with type 2 diabetes. Available from URL: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm531517.htm. [Accessed 05 December 2016.

29. 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 May;39(5):717-25.

30. McMurray J. EMPA-REG - the “diuretic hypothesis”. J Diabetes Complications. 2016 Jan-Feb;30(1):3-4.

31. Raz I and Cahn A. SGLT2 inhibitors and heart failure -- clinical implications. Nat Rev Cardiol. 2016 Apr;13(4):185-86.

32. 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 May 14;37(19):1526-34.

33. Inoue BH, dos Santos L, Pessoa TD, Antonio EL, Pacheco BP, Savignano FA, et al. Increased NHE3 abundance and transport activity in renal proximal tubule of rats with heart failure. Am J Physiol Regul Integr Comp Physiol. 2012 Jan 1;302(1):R166-174.

34. Spencer AG, Labonte ED, Rosenbaum DP, Plato CF, Carreras CW, Leadbetter MR, et al. Intestinal inhibition of the Na+/H+ exchanger 3 prevents cardiorenal damage in rats and inhibits Na+ uptake in humans. Sci Transl Med. 2014 Mar 12;6(227):227ra36.

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

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

37. Sha S, Devineni D, Ghosh A, Polidori D, Hompesch M, Arnolds S, et al. Pharmacodynamic effects of canagliflozin, a sodium glucose co-transporter 2 inhibitor, from a randomized study in patients with type 2 diabetes. PLoS One. 2014 Aug 28;9(8):e105638.

38. Lapuerta P, Zambrowicz B, Strumph P, Sands A. Development of sotagliflozin, a dual sodium-dependent glucose transporter 1/2 inhibitor. Diab Vasc Dis Res. 2015 Mar;12(2):101-10.

39. Wright EM. Glucose galactose malabsorption. Am J Physiol. 1998 Nov;275(5 Pt 1):G879-82.

40. LX4211.1-202-DM: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Safety and Efficacy of LX4211 in Combination with Metformin in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin Monotherapy. Lexicon Pharmaceuticals. 03 June 2014.

41. LX4211.1.201: A Phase 2, Single-center, Randomized, Double-blind, Placebo-controlled, Multiple-dose Study to Determine the Safety and Efficacy of Orally Administered LX4211 in Subjects with Type 2 Diabetes Mellitus. Lexicon Pharmaceuticals. 30 July 2010.

42. 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 Jul;38(7):1181-88.

43. Weatherley BD, Milo-Cotter O, Felker GM, Uriel N, Kaluski E, Vered Z, et al. Early worsening heart failure in patients admitted with acute heart failure–a new outcome measure associated with long-term prognosis? Fundam Clin Pharmacol. 2009;23(5):633–639.

44. Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, et al. Lower risk of heart failure and death in patients initiated on SGLT2 inhibitors versus other glucose-lowering drugs: The CVD-REAL Study. Circulation. 2017;136:249-59.

45. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol. 2000;35(5):1245-1255.

46. Spertus JA, Jones PG. Development and Validation of a Short Version of the Kansas City Cardiomyopathy Questionnaire. Circ Cardiovasc Qual Outcomes. 2015;8(5):469-476.

47. Armstrong DG, Lavery LA. Diabetic foot ulcers: prevention, diagnosis and classification. Am Fam Physician. 1998 Mar 15;57(6):1325-32, 1337-8.

48. American Diabetes Association. Foot Care. 2014. Available at: http://www.diabetes.org/living-with-diabetes/complications/foot-complications/foot-care.html [accessed December 2017]

49. International Diabetes Federation. IDF Clinical Practice Recommendations on the Diabetic Foot – 2017.

50. 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.

51. 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

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

53. Lin DY, Wei LJ. The robust inference for the Cox proportional-hazards model. J Am Stat Assoc 1989;84:1074–1078.

54. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). Circulation. 2015 Jul 28;132(4):302-61.

55. European Medicines Agency. SGLT2 inhibitors: PRAC makes recommendations to minimise risk of diabetic ketoacidosis. 2016. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/02/news_detail_002470.jsp&mid=WC0b01ac058004d5c1 Accessed November 2017

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 Definition of urgent heart failure visit

An urgent HF Visit is defined as an event that meets all of the following (in accordance with the 2014 Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials guidance document [54]):

1. The patient has an urgent, unscheduled office/practice or ED visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization
2. The following signs and symptoms for HF hospitalization (ie, symptoms, physical examination findings/laboratory evidence of new or worsening HF) must be met:

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

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

   B) Decreased exercise tolerance

   C) Fatigue

   D) Other symptoms of worsened end-organ perfusion or volume overload (must be specified and described by the protocol

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

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

      a) Peripheral edema

      b) Increasing abdominal distention or ascites (in the absence of primary hepatic disease)

      c) Pulmonary rales/crackles/crepitations

      d) Increased jugular venous pressure and/or hepatojugular reflux

      e) S3 gallop

      f) 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:

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

      b) Radiological evidence of pulmonary congestion

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

OR

d) 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

3. The patient receives initiation or intensification of treatment specifically for HF, including at least one of the following (**NOTE**: augmentation of oral diuretic therapy will not be considered sufficient):

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

   B) Mechanical or surgical intervention, including:

      a) Mechanical circulatory support (eg, intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)

      b) Mechanical fluid removal (eg, ultrafiltration, hemofiltration, dialysis)

Appendix C Kansas City Cardiomyopathy Questionnaire-12

Kansas City Cardiomyopathy Questionnaire (KCCQ-12)

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
a. Showering/bathing	O	O	O	O	O	O
b. Walking 1 block on level ground	O	O	O	O	O	O
c. Hurrying or jogging (as if to catch a bus)	O	O	O	O	O	O
	1	2	3	4	5	6

2. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O
1	2	3	4	5

3. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O	O	O
1	2	3	4	5	6	7

4. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O	O	O
1	2	3	4	5	6	7

5. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O
1	2	3	4	5

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6. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
O	O	O	O	O
1	2	3	4	5

7. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
O	O	O	O	O
1	2	3	4	5

8. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Activity	**Severely** Limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
a. Hobbies, recreational activities	O	O	O	O	O	O
b. Working or doing household chores	O	O	O	O	O	O
c. Visiting family or friends out of your home	O	O	O	O	O	O
	1	2	3	4	5	6

Appendix D General guidance for the follow-up of laboratory abnormalities by Sanofi

NEUTROPENIA

Neutrophils < 1500/mm³ or according to ethnic group

Repeat immediately a full blood count if value close to 1500/mm³

Neutrophils < 1500/mm³ confirmed with signs of infection	Neutrophils < 1500/mm³ confirmed with no signs of infection
1. **DISCONTINUE** Investigational Medicinal Product, hospitalization should be considered 2. **PERFORM** biological investigations for infection	1. **DISCONTINUE** Investigational Medicinal Product 2. **INVESTIGATE** for infection

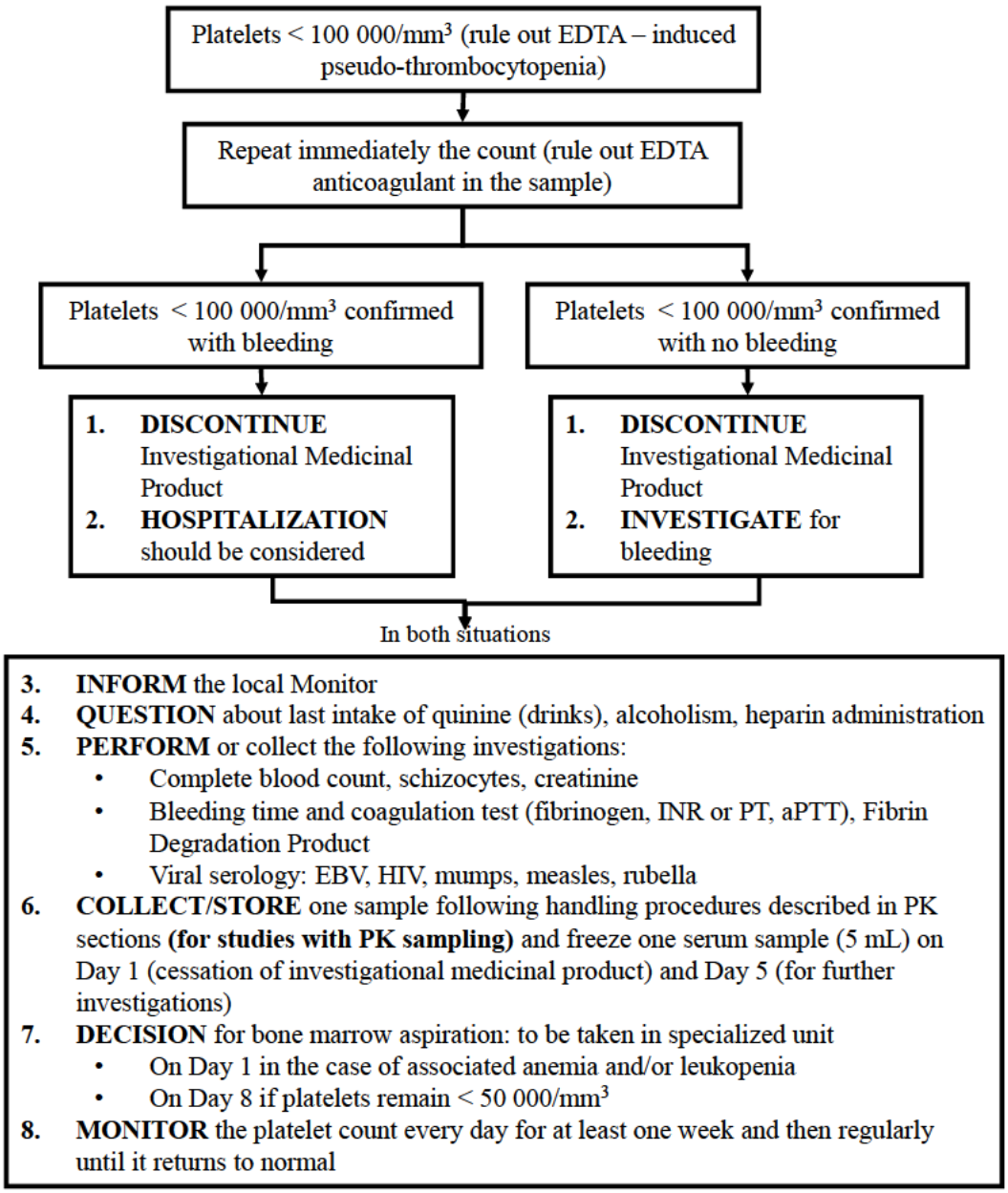
In both situations

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 adverse events in Section 10.4.3 is met.

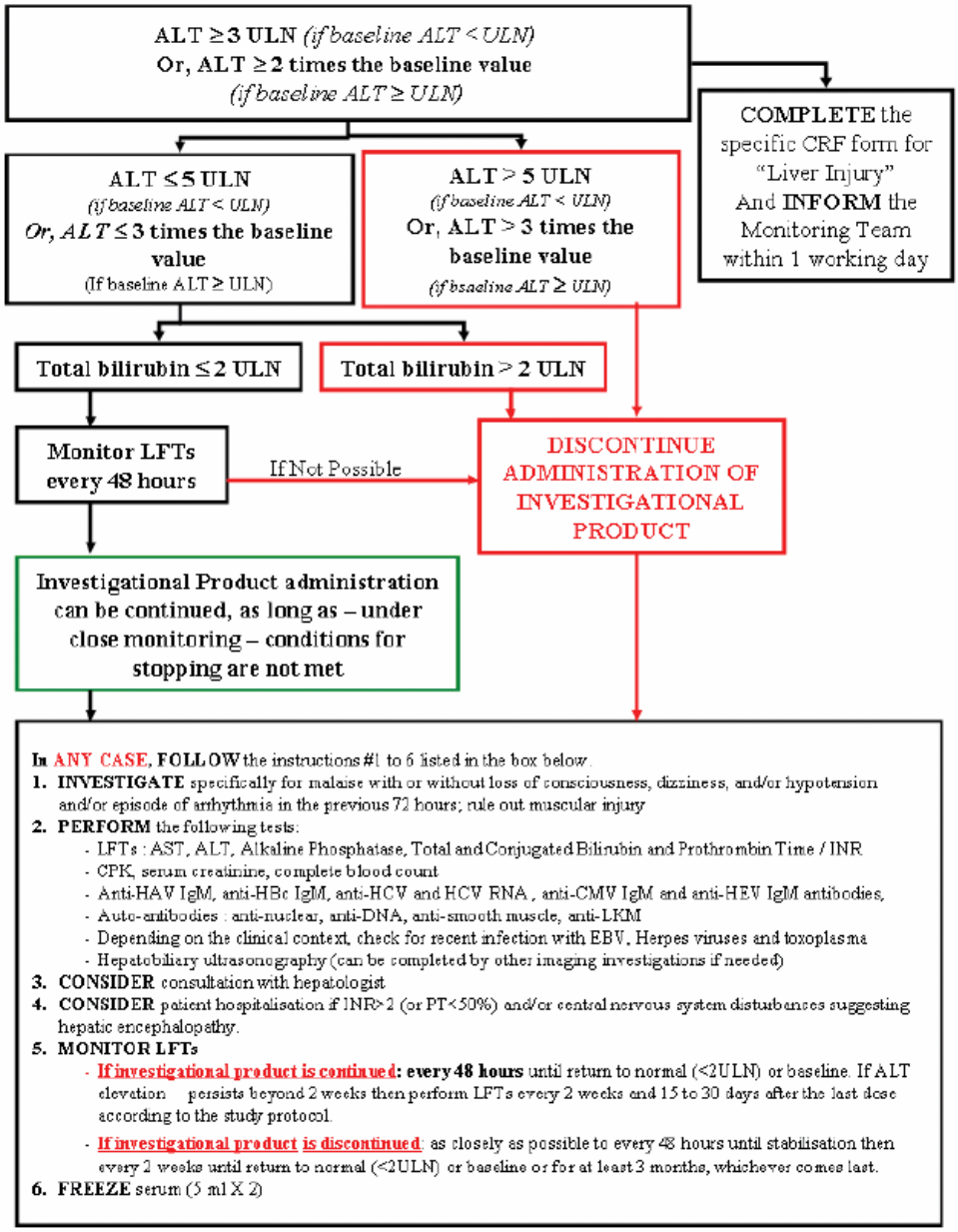
THROMBOCYTOPENIA



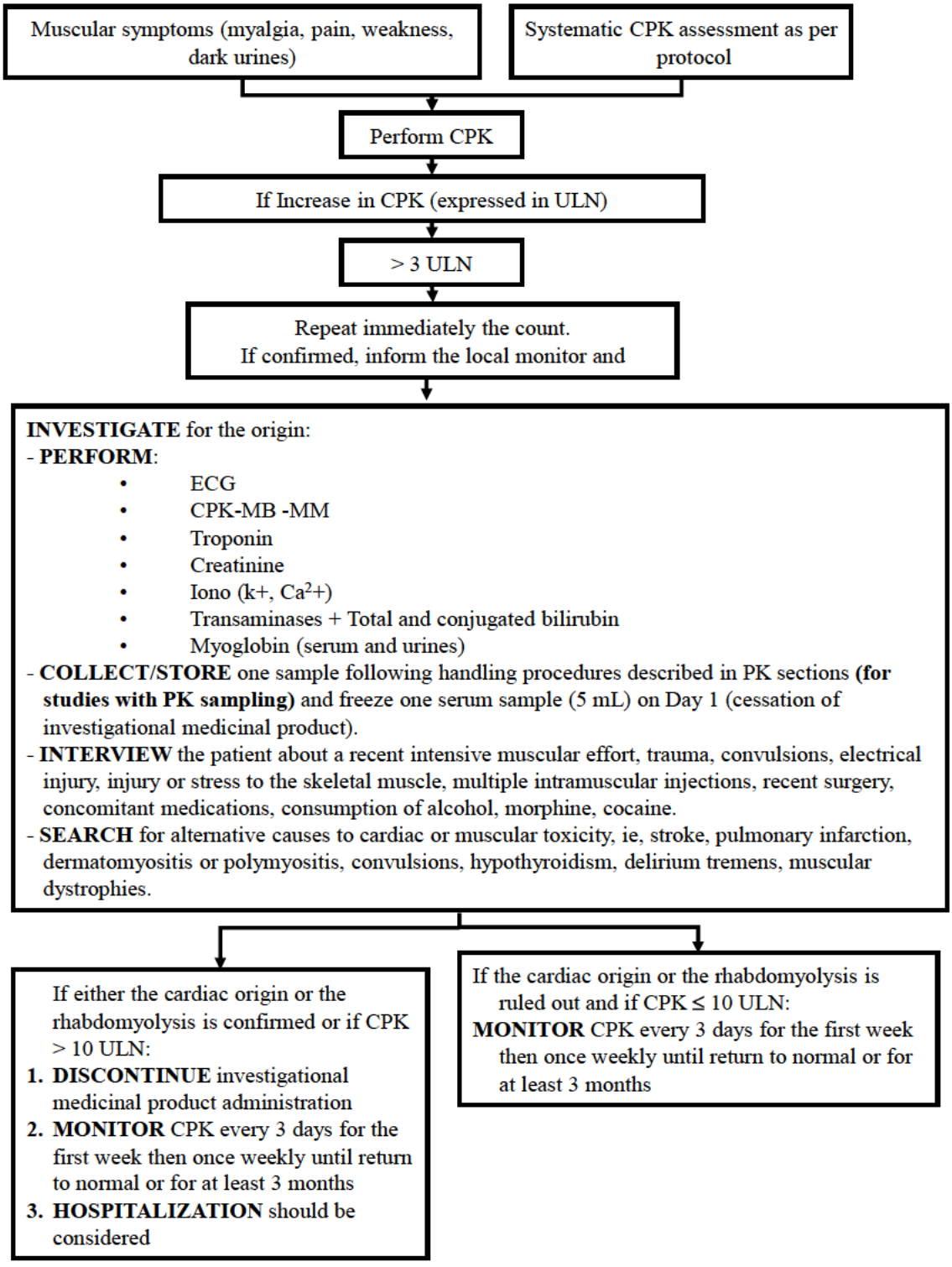
Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

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

INCREASE IN ALT



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



Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting adverse events in Section 10.4.3 is met.

Appendix E 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 2 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 (this repeat renal assessment may occur beyond the last planned visit per protocol). 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/1.73 m^2 that has been confirmed on repeated testing and in the absence of a reversible cause (see protocol Section 10.3.3).

Appendix F Diabetic ketoacidosis

Recognizing diabetic ketoacidosis

Diabetic ketoacidosis, including atypical (euglycemic) DKA, is the most serious emergency in patients with T1D and T2D. Common precipitating factors include infections, intercurrent illnesses, psychological stress and noncompliance with insulin therapy. Clinical features of DKA at presentation can be nonspecific; however most patients complain of polydipsia and polyuria for several days before onset of DKA. Symptoms of DKA include rapid weight loss, nausea or vomiting, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odor to urine or sweat (55).

It is possible that GI or other AEs occurring with sotagliflozin may mask presenting symptoms of DKA. Because sotagliflozin lowers blood glucose by insulin independent SGLT1 and SGLT2 inhibition, it is possible for DKA to be present with normal or low blood glucose. Therefore, the Investigator must still consider a DKA event even if blood glucose is low or normal.

More information can be found in the sotagliflozin IB.

If DKA is suspected or confirmed, study treatment should be stopped immediately and should not be re-started unless another cause for the ketoacidosis is identified and resolved.

Caution should be exercised in patients with risk factors for ketoacidosis and patients should be informed of the risk factors. These include low reserve of insulin-secreting cells, conditions that restrict food intake or can lead to severe dehydration, a sudden reduction in insulin or an increased requirement for insulin due to illness, surgery or alcohol abuse.

In addition, IMP administration should be stopped in patients in hospital for major surgical procedures or due to serious illness.

Whenever AE data is collected or the patient reports DKA or intercurrent illness (including infections), generalized weakness, increased weight loss, GI symptoms including nausea, vomiting, or abdominal pain or other symptoms or signs that the Investigator believes may be consistent with DKA, the site will determine if an assessment for DKA, such as assessing blood BHB, is appropriate. If BHB or other laboratory testing confirms the presence of metabolic acidosis, then the “Possible DKA” e-CRF will be completed.

Patient communication cards will be printed with the following:

“If you have any of these symptoms on the list, then contact your study site immediately for assistance with managing your diabetes:

- Inability to maintain oral intake
- Generalized weakness

- Abdominal (belly) pain
- Increased weight loss
- Fever
- Frequent urination, including at night
- Fruity-scented breath
- Confusion
- Acute illness
- Consistently elevated blood glucose
- Feeling very thirsty or drinking a lot
- Nausea or vomiting
- Having trouble thinking clearly or feeling tired.

It is possible to have DKA even if your blood glucose is not elevated. Regardless of your blood glucose level, if you have any of these symptoms on the list, then contact your study site regarding the need to be evaluated for possible DKA, which will include specific blood testing. If your study site is closed and your study doctor is not available, go to the nearest emergency room for evaluation.

If you are scheduled for a procedure or surgery that requires you to not take any food or liquids, please contact your study doctor for instructions on continuing study drug. In such cases your study doctor may advise you NOT to take your study drug from the day prior to the procedure or surgery until after the procedure or surgery is complete, and you are taking food and liquids as you normally do."

EFC15156 16.1.1 Amended protocol 01

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	18-Dec-2018 14:01 GMT+0100
	Clinical Approval	18-Dec-2018 14:26 GMT+0100
	Regulatory Approval	18-Dec-2018 22:58 GMT+0100