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

NCT Number: NCT03315143

Document Date: SAP Version 1: 21 August 2020

21-August-2020
Version Number: 1.0

Signature Page

X

[redacted] MD

[redacted] Lexicon

X

[redacted] MS

[redacted] Lexicon

X

[redacted] PhD

[redacted] Lexicon

Statistical Analysis Plan Authors

X

[redacted] PhD

[redacted]

X

[redacted] MD, MPH

Steering Committee [redacted]

X

[redacted] MD

[redacted] Lexicon Pharmaceuticals

STATISTICAL ANALYSIS PLAN

A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Demonstrate the Effects of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes, Cardiovascular Risk Factors and Moderately Impaired Renal Function; The SCORED Trial, EFC14875

DATE OF ISSUE: 21-Aug-2020

Total number of pages: 38

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
AESI	Adverse events of special interest
BMI	Body mass index
CV	Cardiovascular
DAOH	Days alive and out of hospital
eGFR	Estimated glomerular filtration rate
EOSI	Events of special interest
HbA1c	Hemoglobin A1c
HF	Heart failure
HHF	Hospitalization for heart failure
IMP	Investigational medicinal product
ITT	Intent-to-treat
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction

PDAOH	Percent days alive and out of hospital
PT	Preferred term
SBP	Systolic blood pressure
WHF	Worsening heart failure

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 BACKGROUND

SCORED is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group, stratified study of sotagliflozin for the treatment of patients with type 2 diabetes (T2D), cardiovascular risk factors, and moderate to severely impaired renal function.

After screening, patients who met all eligibility criteria were centrally randomized via in a 1:1 ratio to sotagliflozin or placebo at the randomization visit. Randomization was stratified by region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world) and by HF-related criteria (Yes/No).

The original plan was to provide approximately 27 months of follow-up after the last patient was randomized, with treatment duration ranging from 27 to 51 months. However, the decision to close SCORED was made in March 2020 before meeting this objective.

A recent publication in the Journal of the American College of Cardiology discussed more broadly how clinical trials have been disrupted by the COVID-19 pandemic.[1] It described issues relating to recruitment, follow-up, and pharmaceutical sponsor access to capital. It referred to the sotagliflozin program as an example where clinical trials have been prematurely terminated. Recommendations included careful consideration of statistical issues relating to potential loss of power, increased variability in data, and challenges in adjudication of events. Similarly, the FDA has issued guidance specific to COVID-19 recognizing the potential for disruption of clinical trials and identifying some of the data and statistical issues that need to be addressed by investigators and sponsors.[2]

This plan describes statistical efficacy analyses to be conducted by an independent academic statistician and separately verified by the Lexicon statistical team. It addresses issues related to the early termination of SCORED. These issues have been reviewed and the recommended steps have been chosen in a blinded fashion, without the use of any unblinded interim analysis.

The termination of follow-up in SCORED did not allow enough time to amend the study protocol. Changes to the intended analysis plan are reflected in this document, rather than the protocol, and this plan takes precedence where there are differences between the two documents.

The key efficacy focus is on total (first and potentially subsequent) investigator-reported events. This focus captures the impact of treatment in actual practice. Recurrent hospitalization for heart failure, and urgent heart failure visits, as recognized and treated by the medical community, are very frequent and have a significant clinical and societal impact. In contrast, a standard assessment of time to a first event may not capture the totality of the effects of treatment.[3] The number of total investigator-reported events in SCORED is a measure of high clinical relevance, and consequently it is appropriate to summarize the effects of sotagliflozin in SCORED.

While outcomes studies have been performed on SGLT inhibition in patients with renal impairment, they have been performed with selective SGLT2 inhibitors whose efficacy is believed to be almost entirely renal dependent. In contrast, sotagliflozin inhibits both SGLT1 and SGLT2. Inhibition of SGLT1 by sotagliflozin is in the gastrointestinal tract and may be beneficial to patients regardless of the degree of renal impairment. A genomic study of reduced function variations in the SGLT1 gene found these variations were associated with less congestive heart failure and lower mortality.[4] Furthermore, a smaller study of sotagliflozin in patients with T2D and severe renal impairment was recently concluded, and it provided evidence of clinically meaningful A1C reduction at one year with sotagliflozin 400 mg compared to placebo. Therefore, sotagliflozin may be associated with efficacy and safety profiles that differ from those of approved SGLT2 inhibitors.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of the study is to compare the effect of sotagliflozin to placebo on total occurrences of cardiovascular (CV) death, hospitalization for heart failure [HHF], and urgent visit for heart failure [HF] in patients with type 2 diabetes, cardiovascular risk factors, and moderate to severely impaired renal function.

1.2.2 Secondary objectives

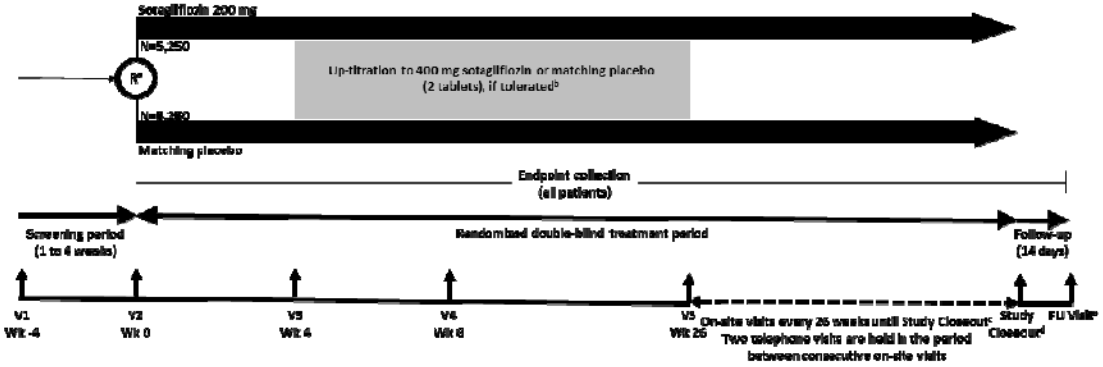
- To compare the effects of sotagliflozin to placebo on:
  - Total occurrences of HHF and urgent visit for HF
  - Occurrences of cardiovascular death
  - Total occurrences of cardiovascular death, HHF, urgent HF visit, non-fatal stroke, and non-fatal myocardial infarction
  - Total occurrences of cardiovascular death, HHF, urgent HF visit, and HF while hospitalized
  - First occurrence of a sustained ≥50% decrease in estimated glomerular filtration rate (eGFR) from baseline (for ≥30 days), chronic dialysis, renal transplant or sustained eGFR <15 mL/min/1.73m2 (for ≥30 days)
  - All-cause mortality
  - Total occurrences of cardiovascular death, non-fatal stroke, and non-fatal myocardial infarction

1.3 DETERMINATION OF SAMPLE SIZE

The originally assumed sample size and projected duration of follow-up were based on a hazard ratio of 0.80 for a composite of CV death and HHF, plus the aim of demonstrating superiority in the composite endpoint of CV death, non-fatal stroke, and non-fatal myocardial infarction. Given the early termination of SCORED, the study is not powered for these assumptions. However, an examination of efficacy is relevant because hazard ratios less than 0.80 have been reported with SGLT inhibition in cardiovascular outcomes studies, and the profile of sotagliflozin (with gastrointestinal SGLT1 inhibition in addition to SGLT2 inhibition) may differ from that of selective SGLT2 inhibitors.[4] Analyses are therefore conducted without any new sample size calculations.

1.4 STUDY PLAN

The following figure presents graphically the study design.


Sotagliflozin 200 mg
N=5,250
R*
Up-titration to 400 mg sotagliflozin or matching placebo
(2 tablets), if tolerated[b]
N=5,250
Matching placebo
Endpoint collection
(all patients)
Screening period
(1 to 4 weeks)
Randomised double-blind treatment period
Follow-up
(14 days)
V1
Wk -4
V2
Wk 0
V3
Wk 4
V4
Wk 8
V5
Wk 26
On-site visits every 26 weeks until Study Closeout[c]
Two telephone visits are held in the period
between consecutive on-site visits
Study
Closeout[d]
FU Visit[e]

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The Baseline eGFR, hemoglobin A1c (HbA1c), and other laboratory parameter values for each patient are 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 investigational medicinal product (IMP) or the last available value on or before the day of randomization for patients who were randomized but never exposed to IMP.

Demographic characteristics

Key demographic variables include:

- Age (years)
- Sex (Male, Female)
- Race (Asian, Black or African American, White, Other)
- Region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world)

Medical history

The patient's medical/surgical history was collected and coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at the time of database lock.

Medical history and CV risk factors:

- Duration of diabetes (years)
- Number (n) and % with any major CV risk factor, and n (%) with each
    - Hospitalization for HF during previous 2 years
    - LVEF category ≤40%
    - Diagnosis of LVH by electrocardiogram or echocardiogram
    - Coronary artery calcium (CAC) score ≥300 Agatston Units
    - NT-proBNP ≥400 pg/ml
    - Elevated high-sensitivity troponin T (by sex and for overall population meeting criteria): >15.0 pg/mL for men and >10.0 pg/mL for women
    - High-sensitivity C-reactive protein >3 mg/L
    - Urinary albumin-to-creatinine ratio ≥300 mg/g [macroalbuminuria]
- N (%) of each minor CV risk factor in the overall population, and among those with no major CV risk factor, n (%) who have age≥55 years with at least 2 minor CV risk factors

- BMI≥35
- Dyslipidemia despite maximally tolerated statin therapy (for overall population meeting criteria, for LDL, for HDL in overall population, and for HDL by sex): LDL >130 mg/dL, or HDL<40 mg/dL for men or <50 for women
- Currently smoking tobacco
- Coronary artery calcium (CAC) score >100 and <300 Agatston Units
- UACR ≥30 to 300 [microalbuminuria]
- Systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg despite antihypertensive therapy at the Screening visit
- Family history of premature heart disease (defined as MI or coronary revascularization procedure) in a first-degree relative,

- Cardiovascular history:
  - Prior myocardial infarction
  - Prior stroke
  - Prior coronary revascularization
  - Peripheral vascular disease
  - Heart failure
  - Atrial fibrillation

Disease characteristics at baseline

- Mean LVEF result (%), and n(%) for LVEF category (<40%, ≤40 to <50%, ≥50%)
- eGFR (mL/min/1.7m^2), and n(%) for each eGFR category: <15 (end stage renal disease), ≥15 to <30 (severe decrease in GFR), ≥30 to <45, and ≥45
- UACR (mg/g), and n(%) for each UACR category: <30 [normal], ≥30 to 300 [microalbuminuria], ≥300 [macroalbuminuria]
- HbA1c (%), and n(%) for each HbA1c category: <7, ≥7 to <8, ≥8 to <9, ≥9 to <10, ≥10

Other characteristics at baseline

- Body mass index (BMI) ((weight in kg)/(height in m)^2)
- SBP (mmHg)
- Heart rate
- Median NT-proBNP (IQR) — pg/ml

2.1.2 Baseline medication and device

Baseline medications are those with a start date prior to randomization (or a missing start date) and an end date after randomization or no end date during the study (use classified as ongoing).

The numbers and proportions by treatment group of the following medications are to be described:

Heart failure medications

Diuretic, ACE inhibitor, ARB, Sacubitril–valsartan, Beta-blocker, Mineralocorticoid receptor antagonist, Digitalis

Diabetes medications

Biguanide, Sulfonylurea, DPP-4 inhibitor, GLP-1 receptor agonist, Insulin, TZD

Other cardiovascular medications

Statins, any non-statin lipid lowering medication

Heart failure device

ICD/CRT

2.1.3 Efficacy endpoints

Efficacy endpoint events with onset date prior to randomization will not be included in efficacy analysis. These events will be considered pre-treatment adverse events.

In the analyses of time to a first event or the total occurrences (first and subsequent) of an event:

- Deaths not included among the events in the endpoint will be treated as competing events
- Patients alive at the end of the study will be right censored on the date they were last known to be alive
- Event types and dates included in the analyses will be those as reported by the investigators
- In the case where the exact date of occurrence of an event is not known, the date will be imputed as described in Appendix A Calculation/Derivation of time-to-event endpoints.

2.1.3.1 Primary efficacy endpoint(s)

The primary endpoint is the total occurrences (first and potentially subsequent) after randomization of CV death, HHF, and urgent HF visit.

2.1.3.2 Secondary efficacy endpoint(s)

- Total occurrences of HHF and urgent HF visits after randomization
- Occurrence of CV death after randomization
- Total occurrences after randomization of CV death, HHF, non-fatal stroke, and non-fatal myocardial infarction

- Total occurrences after randomization of CV death, HHF, urgent HF visit, and HF while hospitalized
- First occurrence after randomization of the composite of sustained ≥50% decrease in eGFR from baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73m^2 (for ≥30 days) in the total patient population
- Occurrence of all-cause mortality after randomization
- Total occurrences after randomization of CV death, non-fatal stroke, and non-fatal myocardial infarction

The primary analysis of renal events will be based on the following definition, based on investigator-reported outcomes.

Endpoint definitions of renal events for renal endpoint analysis

Event	Endpoint definition
Sustained ≥50% decrease in eGFR from baseline	confirmed ≥50% decrease in eGFR for ≥30 days OR with no repeat eGFR ≥30 days as recorded in eCRF "eGFR decrease"
Sustained eGFR <15 mL/min/1.73 m2	confirmed eGFR <15 mL/min/1.73 m2 for ≥30 days OR with no repeat eGFR ≥30 days as recorded in eCRF "eGFR decrease"
Chronic dialysis	(a) dialysis lasted for ≥90 days (e.g. end date – start date+ 1 ≥90) as recorded in eCRF "Renal Event – Dialysis", OR (b) answered Yes to the question ". Does the subject meet the criteria for ESRD".
Renal transplant	"Renal transplant" captured in eCRF "Other procedure form". PTs of Renal transplant, Renal and pancreas transplant, Renal and liver transplant based on MedDRA v23.0.

2.1.3.3 Other efficacy endpoints

- First occurrence of CV death, HHF, or urgent HF visit after randomization
- First occurrence of CV death, HHF, urgent HF visit, or hospitalization with HF after randomization
- The total occurrences of HHF after randomization
- First occurrence of CV death, HHF, nonfatal MI, or nonfatal stroke
- First occurrence of CV death, nonfatal MI, or nonfatal stroke
- First occurrence of MI (fatal and non-fatal)
- First occurrence of stroke (fatal and non-fatal)
- First occurrence of atrial fibrillation or atrial flutter (adverse events [AEs] with preferred terms [PT] of atrial fibrillation or atrial flutter)
- First occurrence of severe hypoglycemia

- Total occurrences of the following hypoglycemia categories
  - Severe hypoglycemia
  - Hypoglycemia with documented glucose value <54 mg/dL
  - Hypoglycemia with documented glucose value <70 mg/dL
- First occurrence after randomization of the composite of sustained ≥40% decrease in eGFR from baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73m^2 (for ≥30 days) in the total patient population
- First occurrence after randomization of the composite of sustained ≥30% decrease in eGFR from baseline (for ≥30 days), chronic dialysis, renal transplant, or sustained eGFR <15 mL/min/1.73m^2 (for ≥30 days) in the total patient population
- The rate of decline in eGFR after Week 4 (mL/min/1.73m^2) to the end of the study
- Days alive and out of hospital (DAOH) and percent DAOH (PDAOH)
- Changes from baseline in
  - NT-proBNP in the overall population
  - NT-proBNP among those with baseline NT-proBNP ≥400 pg/ml
  - Hematocrit
  - Hemoglobin A1c
    - In the overall population, and in subgroups defined by baseline eGFR (<30, ≥30 to <45, ≥45 to <60, and ≥30 to <60)
  - Body weight
  - UACR
    - In the overall population, and in subgroups defined by baseline UACR (<30 mg/g [normal], ≥30 to 300 [microalbuminuria], ≥300 [macroalbuminuria])
    - And in subgroups defined by baseline eGFR<30 mL/min/1.73m^2, ≥30 to <45, ≥45 to <60, and ≥30 to <60
  - Systolic blood pressure
    - In the overall population, and in subgroups defined by baseline SBP (<130 mmHg, ≥130, <140, ≥140)

All time-to-event endpoints are assessed based on investigator-reported events.

Cardiovascular death includes death of undetermined cause.

2.1.4 Safety endpoints

The period of safety observation starts from the time when the patient gives informed consent and is divided into three periods:

- Pre-treatment period: defined from the signed informed consent up to the first dose of double-blind IMP

- Treatment-emergent adverse event (TEAE) period: defined as the time from the first dose of double-blind IMP to the last dose of double-blind IMP dose + 10 days (1 day for severe hypoglyemcia)

- Post-treatment period: defined as the time starting the day after the end of the TEAE period

2.1.4.1 Adverse event variables

Occurrences of AEs (including serious adverse events [SAEs], and AEs of special interest [AESIs] are recorded from the time of signed informed consent until the end of the study.

All AEs will be coded to a Lowest Level Term (LLT), PT, HIhg Level Term (HLT), High Level Group Term (HLGT), and associated primary System Organ Class (SOC) using the version of MedDRA currently in effect at the time of the database lock.

Adverse event observation periods:

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

- Treatment-emergent AEs are adverse events that developed or worsened or became serious during the TEAE period;

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

Adverse events of special interest

- 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

- Symptomatic overdose (serious or nonserious) with IMP

- ALT ≥3 x ULN (if Baseline ALT < ULN) or ALT ≥2 times the Baseline value (if Baseline ALT ≥ ULN)

Events of special Interest

- 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
- 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 candida balanitis in males)
- Urinary tract infections
- Diarrhea
- Clinically relevant volume depletion and events related/possibly related to volume depletion
- Fournier's gangrene

EOSI will be identified based on criteria in the following table. Of note, drug-induced liver injury is not listed as an EOSI, but it will be described in the same manner, with a presentation of the number and percentage of events in each treatment group. Severe hypoglycemia is a EOSI that will be analyzed in the group of other endpoints.

Identification criteria for EOSI

AE Grouping	Criteria
Bone Fractures	Investigator's opinion: eCRF form "Adverse Events" and its associated complementary form "Bone Fracture";
Diabetic ketoacidosis	Investigator's opinion: eCRF form "Adverse Events" and its associated complementary form "METABOLIC ACIDOSIS/SUSPECTED DKA"
Venous thrombotic events	Identified by using MedDRA preferred terms listed in Appendix B
Pancreatitis	Identified by using MedDRA preferred terms listed in Appendix B
Malignancies of special interest (breast, etc)	Breast cancer: Narrow search on "Breast neoplasms, malignant and unspecified (SMQ)" [20000149] Prostate cancer: Narrow search on "Prostate neoplasms, malignant and unspecified (SMQ)" [20000152] Leydig-cell cancer: PTs in Appendix B Thyroid cancer: PTs in Appendix B Renal cell cancer: PTs in Appendix B Pancreatic cancer: PTs in Appendix B Bladder cancer: PTs in Appendix B
Genital mycotic infections	Identified by using MedDRA preferred terms listed in Appendix B
Urinary tract infection	Identified by using MedDRA preferred terms listed in Appendix B
Diarrhea	Narrow search on "Noninfectious diarrhoea (SMQ)" plus the following PTs (MedDRA v23.0): Gastroenteritis, Antidiarrhoeal supportive care, Enteritis, Enteritis leukopenic, Enterocolitis, Enterocolitis haemorrhagic
Volume depletion	Identified by using MedDRA preferred terms listed in Appendix B

AE Grouping	Criteria
Severe hypoglycemia	Finish eCRF form "Hypoglycemia event information" and meet the criteria: To the question "Assistance Required", ticked the option "Required assistance because subject was not capable of helping self", and To the question "Were Symptoms Present", ticked "Yes".
EOSI AE related with amputation (non-traumatic)	
Amputation (non-traumatic)	Identified on the eCRF 'Other procedures related to Amputation'
AE leading to amputation (non-traumatic)	'AE correction' as the reason for amputation in eCRF 'Other procedures related to Amputation'
Potential cases of Fournier's Gangrene	
Potential cases of Fournier's gangrene[a]	Identified by using MedDRA preferred terms listed in Appendix B

*Search terms will be updated using the MedDRA version currently in effect at the time of database lock for EOSI identified for them.

a Potential cases of Fournier's gangrene: not an EOSI per protocol; analyzed due to a warning released by health authorities in 3Q 2018 about rare occurrences of a serious infection of the genital area with FDA-approved SGLT2 inhibitors for diabetes.

2.1.4.2 Laboratory safety variables

The clinical laboratory data to be analyzed include measures of hematology, clinical chemistry, renal function, liver function, and lipids. Clinical laboratory values will be analyzed in conventional units.

2.1.4.3 Vital signs variables

Vital signs include weight, heart rate, and systolic and diastolic blood pressure in sitting position.

2.2 DISPOSITION OF PATIENTS

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

Randomized patients consist of all patients with a signed informed consent form who have had a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used. These patients form the randomized 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. Patients who are not randomized will not be in the safety population.

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

- Screened patients
- Screen failure patients and reasons for screen failure
- Nonrandomized but treated patients
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who complete the study treatment period as per protocol (as per e-CRF treatment status form)

  Note: patients who die while on treatment will be treated as treatment completers
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation (as per e-CRF treatment status form)
- Patients who complete the study as scheduled (i.e. subject status is death or completed on the Completion of end of study eCRF form or a study close-out visit was performed through alternative contact during the study close-out period)
- Patients who did not complete the study as scheduled and the reasons for study discontinuation
- Status at last study contact (as per e-CRF Subjects Status form)
- Patients who had known vital status during the study close-out period

Patients randomized but not treated will be included in the efficacy analysis.

The number (%) of patients who prematurely discontinued the study for primary efficacy events will be summarized. The main reason for study discontinuation will be summarized overall and according to whether or not the patients had a primary efficacy endpoint confirmed by CEC prior to study discontinuation. A patient will be considered as having discontinued the study for CV death and HHF if the date of the last information on efficacy endpoints (presence or absence) is before his/her scheduled Study Closeout Visit.

Duration of patient in study (Study duration regardless of on treatment or not) is defined as end study visit date – randomization date + 1 day. The study duration will be summarized according to mean, median, and range for each treatment group and for the overall population.

Additionally, the analysis populations for safety and efficacy will be summarized in a table by number of patients on the randomized population.

- Randomization population
- Efficacy population: intent-to-treat (ITT) population
- Safety population

2.3 ANALYSIS POPULATIONS

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

2.3.1 Randomized population

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

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population.

2.3.2 Efficacy populations

The primary efficacy analysis population will be the ITT population.

2.3.3 Safety population

The safety population is defined as the randomized population who actually received at least 1 dose or part of a dose of the IMP, analyzed according to the treatment actually received

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Parameters will be summarized on the randomized population by treatment group and overall using descriptive statistics.

Unless otherwise specified, parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized. Similar analyses will be done on the safety population and will be included in the appendices if the size of the safety population is different (>10%) from the size of the randomized population for any treatment group.

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

2.4.2 Concomitant medications

Baseline medications and devices will be presented for the randomized populations and summarized by treatment group.

2.4.3 Extent of investigational medicinal product exposure and dose titration

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

Duration of IMP exposure in days, regardless of intermittent discontinuations, is defined as:

Last dose of double-blind IMP – first dose of double-blind IMP +1

The number (%) of patients with an up-titration to 400 mg overall (at Visit 5 [Week 26]) will also be summarized in the sotagliflozin group.

2.4.4 Analyses of efficacy endpoints

All efficacy analyses will be performed based on the ITT approach that will include events occurring, for a given patient, from the date of randomization to their date last known alive, including events that occur after the patient has discontinued the study IMP.

2.4.4.1 Analyses of primary efficacy endpoint

The analysis of the primary efficacy endpoint will be the comparison between the two treatments using a Wald test stratified by region (North America, Latin America, Western Europe, Eastern Europe, and rest of world) and HF-related criteria (yes/no). This primary comparison will be a 2-sided test at the 0.05 type 1 error level for the following hypotheses:

H0: HR =1 versus H1: HR ≠1

The estimates of the hazard ratio (HR) and corresponding 2-sided 95% confidence interval (CI) will be provided by a marginal Cox proportional hazard model stratified by region and ejection fraction, with non-cardiovascular (non-CV) death treated as a competing event. By using a robust sandwich covariance matrix estimate, the model allows for the possibility of multiple events within a given patient. If a given patient has more than one event on a given day, the event times will be varied by 0.1 day so that every event time is unique.

To determine whether the treatment effect on the primary endpoint is different before and after 180 days (the last opportunity for up-titration in SCORED), a marginal proportional hazards model that allows the treatment HR to vary before and after 180 days will be compared with the model in which the treatment HR is assumed constant over time, to test whether a nonconstant HR provides a better fit to the observed data.

As a sensitivity analysis, an on-treatment analysis will be performed for the primary endpoint, using the same method above but only including events through 30 days after last dose. Another on-treatment sensitivity analysis will include only events through 7 days after last dose.

The cumulative incidence function (CIF) will also be constructed to estimate the primary efficacy endpoint rate by treatment group. [5] The absolute risk reduction (ARR) will be estimated by the

difference between treatment groups in the number of events per 100 patient-years of follow-up. Results will be provided for both the primary efficacy endpoint overall and its individual components (CV death, HHF, urgent HF visit). In addition, a figure summarizing the numbers of first and subsequent events will be constructed. Bars for sotagliflozin and placebo will be provided for the numbers of first events, second events, third events, and a category of "fourth and subsequent events."[5] Within each bar the number of CV death, HHF, and urgent HF visit events will be separated by color.

Proportional hazards model for the primary endpoint will be constructed for subgroups defined by the following:

- Presence/absence of HF-related criteria
  - HF-related criteria are present when a patient meets at least 1 of: EF ≤40% documented within the past year, or hospitalization for HF during the previous 2 years
- LVEF in two categories (<50%, ≥50%)
- LVEF in three categories (<40%, ≥40% <50%, ≥50%)
- LVEF in two categories (<50%, ≥50%) among those with HF-related criteria
- LVEF in three categories (<40%, ≥40% <50%, ≥50%) among those with HF-related criteria
- Presence/absence of major CV risk factor
- History of CVD (defined as myocardial infarction, stroke, coronary revascularization, or peripheral vascular disease)
- Region (North America, Latin America, Europe, Rest of the world)
- Age (<65, ≥65)
- Gender (male, female)
- Race/ethnicity (Asian, black or African American, White, Hispanic, other)
- Baseline eGFR (<30 mL/min/1.73m^2, ≥30 to <45, ≥45 to <60)
- Baseline category of UACR (<30 mg/g, ≥30 mg/g)
- Baseline BMI group (<30, ≥30 kg/m^2)
- NT-proBNP (≤Median, >Median)
- MRA at Baseline (among those with HF-related criteria)
- GLP-1 receptor agonist at Baseline
- Sacubitril-valsartan at Baseline (among those with HF-related criteria)
- ICD/CRT at Baseline
- Insulin at Baseline
- Atrial fibrillation or flutter at Baseline
- Left ventricular hypertrophy (LVH) at Baseline
- Main cause of heart failure (ischemic vs. non-ischemic or unknown)

For each factor, a marginal Cox proportional hazard model stratified by region and HF-related criteria (note that when region is the subject of the analysis stratification will only be by HF-related criteria; similarly when HF-related criteria is the subject of the analysis, stratification will only be by region) with non-CV death as a competing event will be constructed, including the treatment, the factor, and the treatment-by-factor interaction terms as covariates. The treatment

HF and CI will be estimated from this Cox model for each subgroup. P-values for interaction terms will be provided, and those <0.05 will be considered statistically significant and therefore suggestive of heterogeneity in the treatment effect. Results will be also presented by a forest plot.

2.4.4.2 Analyses of secondary efficacy endpoints

Methods for controlling the overall type-1 error rate when testing the secondary efficacy endpoints are described in the Section Multiplicity issues.

Time-to-event secondary efficacy endpoints will be analyzed using the same statistical methodology as for the primary endpoint. Deaths that are not part of a given endpoint will be treated as competing events.

2.4.4.3 Multiplicity issues

In order to handle multiple main secondary endpoints, the overall type-1 error will be controlled by the use of a sequential inferential approach. Statistical significance of the primary endpoint is required before drawing inferential conclusions about the first secondary endpoint at the 0.05 2-sided alpha level. Inferential conclusions about successive secondary endpoints require statistical significance of the prior one. The order of tests is detailed in Section 2.1.3.2. This fixed hierarchical approach will ensure a strong control of the overall type-1 error rate at the required 0.05 2-sided level.

2.4.4.4 Additional efficacy analysis(es)

Other efficacy endpoints that are total occurrences of events or the time to a first event will be analyzed using the same statistical methodology as for the primary endpoint. If the endpoint concerns the first event, then only the first event experienced by a given patient will be included in the analysis. Deaths that are not part of a give endpoint will be treated as competing events.

For the analyses of DAOH and PDAOH, total potential follow-up time for each patient is defined as the number of days from date of randomization until the patient's date last known alive, or May 1, 2020 (the date sites were instructed to complete end of study contacts with patients; patients known to have died after this date will be censored as alive on May 1, 2020) if the patient died. The total number of days spent in hospital will be derived from the investigator reports. If a patient died, the number of days dead will be calculated as the time interval between their date of death and May 1, 2020. DAOH will be calculated by subtracting days in hospital and days dead from total potential follow-up time; if a patient survived without hospitalization, DAOH will be equal to the potential follow-up time for that patient.

DAOH, days dead, and days in hospital will be compared between treatment groups by rate ratios (RRs) from a Poisson regression model with a log link function and Pearson χ^2 scaling of standard errors to account for potential overdispersion. In addition to treatment group, the logarithm of potential follow-up time will be used as an offset variable in the model. Given the expectation that a fraction of patients will survive without hospitalization until the end of follow-up (i.e., PDAOH=100%), PDAOH will be compared between treatment groups with one-inflated beta

regression. In this application the model will jointly estimate the treatment odds ratio (OR) of surviving until the end of the study without hospitalization (i.e., PDAOH=10)%) and the treatment oR of higher mean PDAOH among the subset of patients who died or had at least one hospitalization or died during follow-up ((i.e. pDAOH<100%). Plots of the distribution of DAOH will be constructed, as well as summaries of reasons for hospitalizations (e.g. HF, other efficacy event, non-efficacy adverse event, etc.).

Changes from baseline in NT-proBNP, hematocrit, HbA1c, UACR, body weight, and SBP will be analyzed using the same methods as for change in eGFR.

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group. All safety analysis will be performed on the safety population.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.3, unless otherwise specified, using the following common rules:

- The baseline value (with the exception of lab parameters, like eGFR and HbA1C) is defined as the last available value before the first dose of double-blind IMP. Baseline eGFR, HbA1C and other lab parameters values are the values assessed by the central laboratory at randomization visit.
- There will be no imputation of missing values for clinical laboratory test results, vital sign measurements in the safety analyses and there will be no hypothesis testing for results from safety analyses.

2.4.5.1 Analyses of adverse events

Generalities

Analysis of adverse events

The following summaries of treatment emergent adverse events will be generated for the safety population.

- Overview of TEAE, summarizing number (%) of patients by treatment group with any
  - TEAE
  - Serious TEAE
  - TEAE leading to death
  - TEAE leading to permanent treatment discontinuation
- All TEAEs by primary SOC
- All TEAEs related to IMP by primary SOC

Analysis of treatment-emergent serious adverse events

- All treatment-emergent SAEs by primary SOC
- All treatment-emergent SAEs related to IMP by primary SOC

Analysis of treatment-emergent adverse events leading to permanent discontinuation

- All TEAEs leading to permanent discontinuation by primary SOC
- All TEAES leading to death by primary SOC and preferred term

Analysis of events of special interest

The selection of PTs will be based on standardized MedDRA query (SMQ) for each corresponding item.

An overview table of EOSI, summarizing number (%) of patients with any of following categories will be provided:

- At least one TEAE EOSI by category of severe hypoglycemia, genital mycotic infection, urinary tract infection, volume depletion and events related/possible related to volume depletion, diarrhea, pancreatitis, bone fracture, venous thrombotic event, amputation, diabetic, ketoacidosis, malignancy of special interest

Drug-induced liver injury

These events will be presented in the same manner as EOSI.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The date of the last dose of IMP is equal to the last date of administration reported on the IMP administration case report form page.

The following formulas will be used for computation of parameters.

Renal function formulas

The estimated GFR (mL/min/1.73 m^2) will be calculated using the 4 variable Modification of Diet in Renal Disease (MDRD) formula:

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

2.5.2 Data handling conventions for secondary efficacy variables

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

2.5.3 Missing data

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

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

Handling of missing or incomplete dates of time-to-event efficacy endpoints

Rules for imputation are detailed in Section 2.1.3.

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

Date/time of first administration is the first non-missing start date/time of double-blind IMP completed in the e-CRF 'First dose IMP' form.

For a patient who was randomized and dispensed a double-blind treatment kit:

- If the date of first IMP is missing, the date of the first IMP administration will be set to the date of randomization.
- If the date of first administration is partially missing with the month and year present, the day will be set to the date of randomization if randomization was in the same month. If randomization was in the month prior to the first drug administration the missing day will be imputed as the first day of the month.

A patient who is randomized but not exposed is identified by 'Not taken' ticked in the e-CRF 'First dose IMP' form.

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

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment, the adverse event will be classified as occurring after treatment initiation. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only. There is no imputation for date/time of adverse event resolution.

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

When the date and time of the first IMP administration is missing, adverse events will be considered to occur after treatment initiation if they occurred on or after the day of randomization.

Baseline definition for efficacy data

The baseline for a given parameter is defined as the last available measurement, including unscheduled assessments, assessed prior to the first administration of double-blind IMP or the last available value before randomization if not treated with double-blind IMP.

2.5.4 Windows for time points

Data analyzed by time point (laboratory safety data, vital signs) will be summarized using the time windows given the table below. These time windows will be applicable for all analyses, and they are defined to provide more homogeneous data for time point-specific analyses that the visit windows specified in the protocol. If multiple values of a parameter are available in a time window, the last will be used in a given analysis.

Time windows definitions

Time point	Targeted study day	Time window
Date of Randomization	1	n/a
Week 4	28	21 to 35
Week 8	56	46 to 66
Week 26	182	168 to 196
Month 12	364	336 to 392
Month 14	427	399 to 455
Month 16	490	462 to 518

REFERENCES

1. Bagiella E, Bhatt DL, Gaudino M. The Consequences of the COVID-19 Pandemic on Non-COVID-19 Clinical Trials. *J Am Coll Cardiol*. 2020 Jul 21; 76(3): 342–345. Published online 2020 May 26. doi: 10.1016/j.jacc.2020.05.041

2. U.S. Food and Drug Administration. FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency. Guidance document. March 2020. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidanceconduct-clinical-trials-medical-products-duringcovid-19-pandemic. Accessed July 23, 2020.

3. Szarek M, White HD, Schwartz GG et al. Alirocumab Reduces Total Nonfatal Cardiovascular and Fatal Events: The ODYSSEY OUTCOMES Trial. J Am Coll Cardiol. 2019 Feb 5;73(4):387-396. doi: 10.1016/j.jacc.2018.10.039. Epub 2018 Nov 11

4. Seidelmann SB, Feofanova E, Yu B et al. Genetic Variants in SGLT1, Glucose Tolerance, and Cardiometabolic Risk. *J Am Coll Cardiol.* 2018 Oct 9;72(15):1763-1773. doi: 10.1016/j.jacc.2018.07.061

5. Szarek M, Amarenco P, Callahan A et al. Atorvastatin Reduces First and Subsequent Vascular Events Across Vascular Territories: The SPARCL Trial. *J Am Coll Cardiol*. 2020 May 5;75(17):2110-2118. doi: 10.1016/j.jacc.2020.03.015. Epub 2020 Mar 16.

APPENDIX A CALCULATION/DERIVATION OF TIME-TO-EVENT ENDPOINTS

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

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

Date of event – start date + 1

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

Date of censoring – start date + 1

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

Start date

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

- AE (including AE, AESI, EOSI)

Onset of event (date of event)

For composite outcomes, e.g. time to CV death and HHF, the earliest onset date of the corresponding components will be used.

For events, which are included as a fatal and non-fatal component into a composite endpoint (applies only to MI and stroke), the onset of the event is considered for the derivation of time to first occurrence, not the date of death.

For all other CV death types (e.g. sudden death) the date of death is used.

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

For events with multiple episodes, such as severe hypoglycemia, the onset date of the first episode will be used. The same applies to time-to-AE analysis.

Censoring

The underlying rule for censoring is that the censoring date should be the last date the patient is known to be free of the event endpoint (free of each component for composite endpoint).

a. General censoring rule for primary efficacy endpoint:

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

- Patients who completed the study will be censored at their last study visit date (study close-out visit date or final follow-up visit date, whichever later).
  Note: If there are CV events happening after the patient's last study visit and the event's prior/related event's onset date is on or before the patient's last study visit date, in this case, this CV events will be included in efficacy analysis.

  Another example, for a HHF, if the onset date of its HF is before last study visit and its resulted hospitalization is after last study visit, this HHF will be included in efficacy analysis.

- Patients who died without discontinuing the study before death (ie Death reported on the 'Completion of End of Study') will be censored at their date of Non-CV death

- Patients who discontinued the study will be censored at their later of study discontinuation date or latest date with cardiovascular efficacy endpoint information (MI/UA, heart failure, cerebrovascular event, or coronary procedure, admission to hospital/emergency room, cardiac biomarkers) collected

b. Specific censoring rule for all-cause mortality

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

c. Specific censoring rule for eGFR endpoint only

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

Patients who already fulfill the respective condition at baseline or without post-baseline laboratory measurements will be censored at Day 1.

d. Specific censoring rule for composite renal endpoints

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

Patients who already fulfil the respective condition at baseline or without post-baseline laboratory measurements will be censored at Day 1.

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

To keep the analysis of severe hypoglycemia consistent with the overall AE analysis, a patient without an adverse event will be considered censored at the date of last IMP taken + 10 days or date of death, if earlier. For severe hypoglycemia, a patient without a severe hypoglycemia will be considered censored at the date of last IMP taken + 1 day or date of death, whichever earlier.

Handling of missing or incomplete dates

If the onset dates of time-to-event endpoints is missing (complete or partial), then the partial missing onset date will be imputed by using the following algorithm, with the reference date being the randomization date.

- If only month of the event is known, then the 15th day of this month will be imputed for a missing day and year of the start date will be imputed as the year, or
- If only the year of the event is known, then 1st of July will be imputed for the missing day and month, or

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

APPENDIX B LIST OF PTS FOR SELECTED EOSI (MEDDRA V23.0)

EOSI	Preferred Term
Genital Mycotic Infections	Balanitis candida
Genital Mycotic Infections	Candida cervicitis
Genital Mycotic Infections	Fungal balanitis
Genital Mycotic Infections	Genital candidiasis
Genital Mycotic Infections	Genital infection fungal
Genital Mycotic Infections	Urogenital infection fungal
Genital Mycotic Infections	Vulvovaginal candidiasis
Genital Mycotic Infections	Vulvovaginal mycotic infection
Urinary tract infections	Nephritis bacterial
Urinary tract infections	Bacterial pyelonephritis
Urinary tract infections	Bacterial urethritis
Urinary tract infections	Bladder candidiasis
Urinary tract infections	Cystitis
Urinary tract infections	Cystitis bacterial
Urinary tract infections	Cystitis escherichia
Urinary tract infections	Cystitis glandularis
Urinary tract infections	Cystitis helminthic
Urinary tract infections	Cystitis klebsiella
Urinary tract infections	Cystitis pseudomonal
Urinary tract infections	Cystitis viral
Urinary tract infections	Cytomegalovirus urinary tract infection
Urinary tract infections	Emphysematous cystitis
Urinary tract infections	Emphysematous pyelonephritis
Urinary tract infections	Escherichia pyelonephritis
Urinary tract infections	Escherichia urinary tract infection
Urinary tract infections	Fungal cystitis
Urinary tract infections	Genitourinary chlamydia infection
Urinary tract infections	Genitourinary tract gonococcal infection
Urinary tract infections	Genitourinary tract infection
Urinary tract infections	Kidney infection
Urinary tract infections	Pyelitis
Urinary tract infections	Pyelocystitis
Urinary tract infections	Pyelonephritis
Urinary tract infections	Pyelonephritis acute
Urinary tract infections	Pyelonephritis chronic
Urinary tract infections	Pyelonephritis fungal
Urinary tract infections	Pyelonephritis mycoplasmal
Urinary tract infections	Pyelonephritis viral
Urinary tract infections	Pyonephrosis
Urinary tract infections	Renal abscess
Urinary tract infections	Renal cyst infection
Urinary tract infections	Streptococcal urinary tract infection
Urinary tract infections	Tuberculosis of genitourinary system
Urinary tract infections	Tubulointerstitial nephritis
Urinary tract infections	Ureter abscess
Urinary tract infections	Ureteritis
Urinary tract infections	Urethral abscess
Urinary tract infections	Urethritis
Urinary tract infections	Urethritis chlamydial
Urinary tract infections	Urethritis gonococcal
Urinary tract infections	Urethritis mycoplasmal
Urinary tract infections	Urethritis ureaplasmal
Urinary tract infections	Urinary bladder abscess
Urinary tract infections	Urinary tract abscess
Urinary tract infections	Urinary tract infection
Urinary tract infections	Urinary tract infection bacterial
Urinary tract infections	Urinary tract infection enterococcal
Urinary tract infections	Urinary tract infection fungal
Urinary tract infections	Urinary tract infection pseudomonal

Urinary tract infections	Urinary tract infection staphylococcal
Urinary tract infections	Urinary tract infection viral
Urinary tract infections	Urinary tract inflammation
Urinary tract infections	Urogenital infection bacterial
Urinary tract infections	Urogenital infection fungal
Urinary tract infections	Urogenital trichomoniasis
Urinary tract infections	Urosepsis
Volume depletion	Blood osmolarity increased
Volume depletion	Blood pressure ambulatory decreased
Volume depletion	Blood pressure decreased
Volume depletion	Blood pressure diastolic decreased
Volume depletion	Blood pressure immeasurable
Volume depletion	Blood pressure orthostatic decreased
Volume depletion	Blood pressure systolic decreased
Volume depletion	Blood pressure systolic inspiratory decreased
Volume depletion	Capillary nail refill test abnormal
Volume depletion	Central venous pressure decreased
Volume depletion	Circulatory collapse
Volume depletion	Decreased ventricular preload
Volume depletion	Dehydration
Volume depletion	Diastolic hypotension
Volume depletion	Distributive shock
Volume depletion	Dizziness postural
Volume depletion	Femoral pulse decreased
Volume depletion	Hypoperfusion
Volume depletion	Hypotension
Volume depletion	Hypovolaemia
Volume depletion	Hypovolaemic shock
Volume depletion	Left ventricular end-diastolic pressure decreased
Volume depletion	Mean arterial pressure decreased
Volume depletion	Orthostatic heart rate response increased
Volume depletion	Orthostatic hypotension
Volume depletion	Orthostatic intolerance
Volume depletion	Peripheral circulatory failure
Volume depletion	Peripheral pulse decreased
Volume depletion	Postural orthostatic tachycardia syndrome
Volume depletion	Prerenal failure
Volume depletion	Presyncope
Volume depletion	Pulmonary arterial pressure decreased
Volume depletion	Pulmonary arterial wedge pressure decreased
Volume depletion	Pulse absent
Volume depletion	Pulse pressure decreased
Volume depletion	Pulse volume decreased
Volume depletion	Radial pulse decreased
Volume depletion	Shock
Volume depletion	Syncope
Volume depletion	Thirst
Volume depletion	Tilt table test positive
Volume depletion	Urine flow decreased
Volume depletion	Urine output decreased
Volume depletion	Venous pressure decreased
Volume depletion	Venous pressure jugular decreased
Volume depletion	Volume blood decreased
Pancreatitis	Alcoholic pancreatitis
Pancreatitis	Autoimmune pancreatitis
Pancreatitis	Grey Turner's sign
Pancreatitis	Haemorrhagic necrotic pancreatitis
Pancreatitis	Hereditary pancreatitis
Pancreatitis	Ischaemic pancreatitis
Pancreatitis	Oedematous pancreatitis
Pancreatitis	Pancreatic abscess
Pancreatitis	Pancreatic haemorrhage
Pancreatitis	Pancreatic necrosis
Pancreatitis	Pancreatic phlegmon
Pancreatitis	Pancreatic pseudocyst
Pancreatitis	Pancreatic pseudocyst drainage

Pancreatitis	Pancreatitis
Pancreatitis	Pancreatitis acute
Pancreatitis	Pancreatitis chronic
Pancreatitis	Pancreatitis haemorrhagic
Pancreatitis	Pancreatitis helminthic
Pancreatitis	Pancreatitis necrotizing
Pancreatitis	Pancreatitis relapsing
Pancreatitis	Pancreatorenal syndrome
Pancreatitis	Traumatic pancreatitis
Venous thrombotic events	Arteriovenous fistula thrombosis
Venous thrombotic events	Arteriovenous graft thrombosis
Venous thrombotic events	Axillary vein thrombosis
Venous thrombotic events	Brachiocephalic vein thrombosis
Venous thrombotic events	Budd-Chiari syndrome
Venous thrombotic events	Cavernous sinus thrombosis
Venous thrombotic events	Cerebral venous thrombosis
Venous thrombotic events	Deep vein thrombosis
Venous thrombotic events	Deep vein thrombosis postoperative
Venous thrombotic events	Embolism venous
Venous thrombotic events	Hepatic vein embolism
Venous thrombotic events	Hepatic vein thrombosis
Venous thrombotic events	Intracranial venous sinus thrombosis
Venous thrombotic events	Jugular vein thrombosis
Venous thrombotic events	Mesenteric vein thrombosis
Venous thrombotic events	Metastatic pulmonary embolism
Venous thrombotic events	Ophthalmic vein thrombosis
Venous thrombotic events	Ovarian vein thrombosis
Venous thrombotic events	Paget-Schroetter syndrome
Venous thrombotic events	Pelvic venous thrombosis
Venous thrombotic events	Penile vein thrombosis
Venous thrombotic events	Portal vein thrombosis
Venous thrombotic events	Portosplenomesenteric venous thrombosis
Venous thrombotic events	Post procedural pulmonary embolism
Venous thrombotic events	Post thrombotic syndrome
Venous thrombotic events	Postoperative thrombosis
Venous thrombotic events	Pulmonary embolism
Venous thrombotic events	Pulmonary microemboli
Venous thrombotic events	Pulmonary thrombosis
Venous thrombotic events	Pulmonary venous thrombosis
Venous thrombotic events	Renal vein embolism
Venous thrombotic events	Renal vein thrombosis
Venous thrombotic events	Retinal vein thrombosis
Venous thrombotic events	Splenic vein thrombosis
Venous thrombotic events	Subclavian vein thrombosis
Venous thrombotic events	Superior sagittal sinus thrombosis
Venous thrombotic events	Thrombophlebitis
Venous thrombotic events	Thrombophlebitis migrans
Venous thrombotic events	Thrombophlebitis superficial
Venous thrombotic events	Thrombosed varicose vein
Venous thrombotic events	Thrombosis corpora cavernosa
Venous thrombotic events	Transverse sinus thrombosis
Venous thrombotic events	Vena cava embolism
Venous thrombotic events	Vena cava thrombosis
Venous thrombotic events	Venous thrombosis
Venous thrombotic events	Venous thrombosis limb
Venous thrombotic events	Visceral venous thrombosis
Thyroid cancer	Anaplastic thyroid cancer
Thyroid cancer	Familial medullary thyroid cancer
Thyroid cancer	Follicular thyroid cancer
Thyroid cancer	Huerthle cell carcinoma
Thyroid cancer	Medullary thyroid cancer
Thyroid cancer	Papillary thyroid cancer
Thyroid cancer	Poorly differentiated thyroid carcinoma
Thyroid cancer	Thyroid B-cell lymphoma
Thyroid cancer	Thyroid cancer
Thyroid cancer	Thyroid cancer metastatic

Thyroid cancer	Thyroid cancer recurrent
Thyroid cancer	Thyroid cancer stage 0
Thyroid cancer	Thyroid cancer stage I
Thyroid cancer	Thyroid cancer stage II
Thyroid cancer	Thyroid cancer stage III
Thyroid cancer	Thyroid cancer stage IV
Thyroid cancer	Thyroid neoplasm
Renal cell cancer	Clear cell renal cell carcinoma
Renal cell cancer	Hereditary leiomyomatosis renal cell carcinoma
Renal cell cancer	Metastatic renal cell carcinoma
Renal cell cancer	Papillary renal cell carcinoma
Renal cell cancer	Renal cancer
Renal cell cancer	Renal cancer metastatic
Renal cell cancer	Renal cancer recurrent
Renal cell cancer	Renal cancer stage I
Renal cell cancer	Renal cancer stage II
Renal cell cancer	Renal cancer stage III
Renal cell cancer	Renal cancer stage IV
Renal cell cancer	Renal cell carcinoma
Renal cell cancer	Renal cell carcinoma recurrent
Renal cell cancer	Renal cell carcinoma stage I
Renal cell cancer	Renal cell carcinoma stage II
Renal cell cancer	Renal cell carcinoma stage III
Renal cell cancer	Renal cell carcinoma stage IV
Renal cell cancer	Renal neoplasm
Pancreatic cancer	Acinar cell carcinoma of pancreas
Pancreatic cancer	Adenocarcinoma pancreas
Pancreatic cancer	Cystadenocarcinoma pancreas
Pancreatic cancer	Carcinoid tumour of the pancreas
Pancreatic cancer	Ductal adenocarcinoma of pancreas
Pancreatic cancer	Gastrinoma malignant
Pancreatic cancer	Glucagonoma
Pancreatic cancer	Insulinoma
Pancreatic cancer	Intraductal papillary-mucinous carcinoma of pancreas
Pancreatic cancer	Malignant neoplasm of islets of Langerhans
Pancreatic cancer	Mucinous cystadenocarcinoma of pancreas
Pancreatic cancer	Neurotensinoma
Pancreatic cancer	Pancreatic carcinoma
Pancreatic cancer	Pancreatic carcinoma metastatic
Pancreatic cancer	Pancreatic carcinoma recurrent
Pancreatic cancer	Pancreatic carcinoma stage 0
Pancreatic cancer	Pancreatic carcinoma stage I
Pancreatic cancer	Pancreatic carcinoma stage II
Pancreatic cancer	Pancreatic carcinoma stage III
Pancreatic cancer	Pancreatic carcinoma stage IV
Pancreatic cancer	Pancreatic neoplasm
Pancreatic cancer	Pancreatic neuroendocrine tumour
Pancreatic cancer	Pancreatic neuroendocrine tumour metastatic
Pancreatic cancer	Pancreatic sarcoma
Pancreatic cancer	Pancreatoblastoma
Pancreatic cancer	Serous cystadenocarcinoma of pancreas
Pancreatic cancer	Solid pseudopapillary tumor of the pancreas
Pancreatic cancer	Somatostatinoma
Pancreatic cancer	Vipoma
Bladder cancer	Bladder adenocarcinoma recurrent
Bladder cancer	Bladder adenocarcinoma stage 0
Bladder cancer	Bladder adenocarcinoma stage I
Bladder cancer	Bladder adenocarcinoma stage II
Bladder cancer	Bladder adenocarcinoma stage III
Bladder cancer	Bladder adenocarcinoma stage IV
Bladder cancer	Bladder adenocarcinoma stage unspecified
Bladder cancer	Bladder cancer
Bladder cancer	Bladder cancer recurrent
Bladder cancer	Bladder cancer stage 0, with cancer in situ
Bladder cancer	Bladder cancer stage 0, without cancer in situ
Bladder cancer	Bladder cancer stage I, with cancer in situ

Bladder cancer	Bladder cancer stage I, without cancer in situ
Bladder cancer	Bladder cancer stage II
Bladder cancer	Bladder cancer stage III
Bladder cancer	Bladder cancer stage IV
Bladder cancer	Bladder neoplasm
Bladder cancer	Bladder squamous cell carcinoma recurrent
Bladder cancer	Bladder squamous cell carcinoma stage 0
Bladder cancer	Bladder squamous cell carcinoma stage I
Bladder cancer	Bladder squamous cell carcinoma stage II
Bladder cancer	Bladder squamous cell carcinoma stage III
Bladder cancer	Bladder squamous cell carcinoma stage IV
Bladder cancer	Bladder squamous cell carcinoma stage unspecified
Bladder cancer	Bladder transitional cell carcinoma
Bladder cancer	Bladder transitional cell carcinoma metastatic
Bladder cancer	Bladder transitional cell carcinoma recurrent
Bladder cancer	Bladder transitional cell carcinoma stage 0
Bladder cancer	Bladder transitional cell carcinoma stage I
Bladder cancer	Bladder transitional cell carcinoma stage II
Bladder cancer	Bladder transitional cell carcinoma stage III
Bladder cancer	Bladder transitional cell carcinoma stage IV
Bladder cancer	Metastatic carcinoma of the bladder
Bladder cancer	Neuroendocrine carcinoma of the bladder
Bladder cancer	Urinary bladder sarcoma

Appendix C Key Changes to Original Planned Analysis and Protocol

Change	Rationale
Primary endpoint analyzes total occurrences (first and potentially subsequent) rather than first occurrence	Total occurrences are expected to be a more sensitive indicator of treatment benefit, are clinically relevant in a population at high risk for heart failure, and have been sensitive to change in several cardiovascular outcome trials
Primary endpoint adds urgent HF visit to original planned endpoint of CV mortality and HHF	Urgent HF visits are clinically relevant and can be reduced by effective treatment
All event endpoints based on investigator reporting rather than adjudication	Adjudication was not completed, and investigator-reported events are clinically relevant
Only one primary objective is applied to the overall population: initially there were co-primary objectives, one relating to MACE non-inferiority (nonfatal MI, nonfatal stroke, and CV death), the other relating to HHF and CV death	Focus on the most relevant and consistent endpoint that has established the benefit of SGLT inhibition across studies, at a time when FDA guidance has eliminated the formal requirement for MACE non-inferiority testing for registration of products for the treatment of type 2 diabetes
List of secondary endpoints ordered to emphasize first HHF and urgent HF visit, then CV mortality, followed by broad cardiovascular composite endpoints, then the composite renal endpoint, all-cause mortality, and finally narrow 3-point MACE	HF risk in SCORED indicates the endpoint of total occurrences of HHF and urgent HF visit can be very well powered, CV mortality is very important, and the high overall CV risk of the SCORED population indicates that broad CV composite endpoints are highly relevant to this population, and all-cause mortality is more important than 3-point MACE
Addition of ARR, DAOH and PDAOH as other endpoints	ARR provides a perspective of treatment benefit, and DAOH and PDAOH capture clinical relevance of decreased hospitalizations
Hypoglycemia safety moved to efficacy endpoint	Reductions in hypoglycemia have been seen with sotagliflozin in both type 1 diabetes and T2D, indicating the value of statistical analyses of hypoglycemia results
Added versions of the composite renal endpoint	Declines of 40% or 30% in eGFR may be more

looking at different cut-offs of eGFR decline, added endpoint of eGFR decline after Week 4, and added UACR endpoint	common than declines of 50%, and may better characterize differences between treatment groups, overall eGFR change after Week 4 may be a more sensitive measure of renal disease progression than the composite renal endpoint, and UACR change may provide a relevant perspective on renal effects of sotagliflozin