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

NCT Number: NCT03521934

Document Date: SAP Version 1.0: 09 August 2020

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] Statistician

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 Evaluate the Effects of SOtagLiflozin on Clinical Outcomes in HemOdynamIcally STable Patients with Type 2 Diabetes POST Worsening Heart Failure

EFC15156

TABLE OF CONTENTS

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

SOLOIST is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group, stratified study of sotagliflozin for the treatment of patients with worsening heart failure.

After screening, patients who met all eligibility criteria were centrally randomized via in a 1:1 ratio to sotagliflozin or placebo at randomization visit. Randomization was stratified by baseline left ventricular ejection fraction (LVEF) (LVEF<50% and LVEF≥50%) and region (North America, Latin America, Western Europe, Eastern Europe, and rest of the world).

The original plan was to randomize approximately 4000 patients. However, SOLOIST enrollment was closed in March 2020 before meeting this objective.

A recent publication in the Journal of the American College of Cardiology discussed how clinical trials and programs have been disrupted by the COVID-19 pandemic.[1] It provided 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 SOLOIST. 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 enrollment and follow-up of SOLOIST 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, as recognized and treated by the medical community, is very frequent and has 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 SOLOIST is a measure of high clinical relevance, and consequently is appropriate to summarize the effects of sotagliflozin in SOLOIST.

While larger studies have been performed on SGLT inhibition in heart failure, they have not been performed in an acute setting of worsening heart failure. In contrast, sotagliflozin has been initiated at a time when patients urgently need additional treatment, and this raises important

questions about safety and efficacy of SGLT inhibitor when initiated in the hospital or immediately after discharge. Furthermore, sotagliflozin inhibits both SGLT1 and SGLT2, in contrast to approved SGLT inhibitors that only affect SGLT2. 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] The efficacy of sotagliflozin may be therefore associated with efficacy and safety profiles that differ from those of approved SGLT2 inhibitors.

1.2 OBJECTIVES

1.2.1 Primary objective

The primary objective of this analysis is to compare the effect of sotagliflozin to placebo on the total occurrences of cardiovascular (CV) death, hospitalization for heart failure (HHF), and urgent visit for heart failure (HF) in hemodynamically stable patients after admission for worsening heart failure (WHF).

1.2.2 Secondary objectives

The secondary objectives of the study are to compare the effects of sotagliflozin to placebo on:

- The total occurrences of HHF and urgent visit for HF
- The occurrence of CV death
- The occurrence of all-cause mortality
- The total occurrences of CV death, HHF, urgent visit for HF, non-fatal myocardial infarction (MI), and non-fatal stroke
- Change in KCCQ-12 score
- Change in estimated glomerular filtration rate (eGFR)

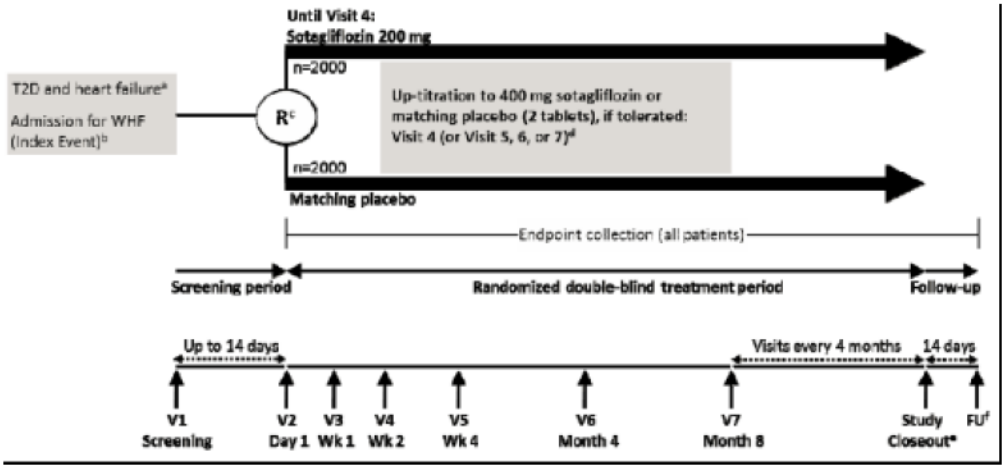
1.3 DETERMINATION OF SAMPLE SIZE

The originally assumed sample size of 4,000 patients was based on a hazard ratio of 0.81 and the desire to examine effects in both the overall population and those with LVEF>50%. Given the early termination of SOLOIST, the study is not powered for these assumptions. However, an examination of efficacy is relevant because hazard ratios less than 0.81 have been reported with SGLT inhibition in stable heart failure, the potential for efficacy may differ in the setting of acute worsening of heart failure (where efficacy has not been examined to date), and the profile of sotagliflozin (with gastrointestinal SGLT1 inhibition in addition to SGLT2 inhibition) may differ from that of selective SGLT2 inhibitors.[4] These analyses are conducted without any new sample size calculations.

1.4 STUDY PLAN

The following figure presents graphically the study design. Of note, the population of SOLOIST is described as one with T2D. While an amendment to SOLOIST allowed the enrollment of

patients without T2D who had reduced ejection fraction, few such patients were enrolled. The primary endpoint will be examined for all patients regardless of diagnosis of T2D:



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.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

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 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 of specific interest includes:

- Diabetes history information
- Type 2 diabetes (yes/no)
- Heart failure history:
    - Principle cause of heart failure (ischemic, nonischemic, unknown)
    - Patient admitted for HF at least one time prior to the index event (yes/no)
    - Patient's NYHA class prior to index event (approximately 1 months prior to index event) (Class I, II, III, IV, and undetermined)
- Atrial fibrillation

Disease characteristics at baseline

- LVEF (%)
- LVEF category (<50%, ≥50%)
- eGFR (mL/min/1.7m^2)
- % of patients with eGFR category <60 mL/min/1.7m^2
- HbA1c (%)

Other characteristics at baseline

- Body mass index (BMI) (kg/m^2)
- Systolic blood pressure (SBP) (mmHg)
- Heart rate (beats/min)
- NT-proBNP (pg/ml)

2.1.2 Baseline medications and devices

- 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 and devices of special interest will be summarized:

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

Heart failure device

Implementation status (yes/no) of ICD/CRT

2.1.3 Efficacy endpoints

Efficacy endpoint events with onset date prior to randomization will not be included in efficacy analysis and instead will be treated as pre-treatment adverse events.

In the analyses of time-to-event efficacy endpoints:

- 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; and
- In the case where the exact date of occurrence of an event is not known (the day, month, and/or year are missing), the date will be imputed as described in Appendix .

2.1.3.1 Primary efficacy endpoint

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

2.1.3.2 Secondary efficacy endpoints

- Total occurrences (first and potentially subsequent) of HHF and urgent HF visits
- Time from randomization to occurrence of CV death
- Total occurrences (first and potentially subsequent) of CV death, HHF, non-fatal myocardial infarction, and non-fatal stroke
- Total occurrences (first and potentially subsequent) of HHF, urgent HF visit, CV death, and HF while hospitalized
- Time from randomization to all-cause mortality
- Change in KCCQ-12 scores from baseline to Month 4
- Rate of decline in eGFR after Week 4 (mL/min/1.73m2/year) to the end of the study

2.1.3.3 Other efficacy endpoints

- First occurrence of CV death, HHF, or urgent visit for HF
- First occurrence of CV death or HHF
- Total occurrences (first and potentially subsequent) of HHF after randomization
- Total occurrences (first and potentially subsequent) of urgent HF visits after randomization
- First occurrence of CV death, HHF, urgent visit for HF, non-fatal myocardial infarction, and non-fatal stroke
- First occurrence of fatal and non-fatal MI
- First occurrence of fatal and non-fatal stroke
- First occurrence of new onset of atrial fibrillation or atrial flutter (adverse events (AEs) with a preferred terms (PTs) of atrial fibrillation or atrial flutter)
- First occurrence of a composite renal endpoint, consisting of events 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)
- 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
- Days alive and out of hospital (DAOH) and percent DAOH (PDAOH)

- Changes from baseline in NT-proBNP, hematocrit, HbA1c, body weight, and SBP

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

Cardiovascular death includes death of undetermined cause.

The first occurrence of the composite renal endpoint is defined as follows:

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	Dialysis lasted for ≥90 days (e.g. end date – start date+ 1 ≥90) as recorded in eCRF "Renal Event – Dialysis", or answered Yes to the question "Does the subject meet the criteria for ESRD".
Renal transplant**Error! Reference source not found.**	"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.

2.1.4 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 injection to the last dose of double-blind IMP dose +10 days.
- Post-treatment period: defined as the time starting the day after the end of the TEAE period.

2.1.4.1 Adverse events variables

Occurrence 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 study.

All AEs will be coded to a Lowest Level Term (LLT), PT, High Level Term (HLT), High Level Group Term (HLGT), and associated primary System Organ Class (SOC)"using the version of MedDRA currently in effect at 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
- Severe hypoglycemia
- Fournier's gangrene

EOSI will be identified based on criteria in the table below. 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.

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 D
Pancreatitis	Identified by using MedDRA preferred terms listed in Appendix D
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 D Thyroid cancer: PTs in Appendix D Renal cell cancer: PTs in Appendix D Pancreatic cancer: PTs in Appendix D Bladder cancer: PTs in Appendix D
Genital mycotic infections	Identified by using MedDRA preferred terms listed in Appendix D
Urinary tract infection	Identified by using MedDRA preferred terms listed in Appendix D
Diarrhea	Narrow search on "Noninfectious diarrhoea (SMQ)" [20000218] plus the following PTs (MedDRA v21.1): Gastroenteritis (10017888), Antidiarrhoeal supportive care (10055660), Enteritis (10014866), Enteritis leukopenic (10014877), Enterocolitis (10014893), Enterocolitis haemorrhagic (10014896)
Volume depletion	Identified by using MedDRA preferred terms listed in Appendix D
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 D

*Search terms will be updated using the MedDRA version currently in effect at Sanofi 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.

2.1.5 Quality-of-life endpoints (KCCQ-12)

A 12-item version of KCCQ-12 questionnaire was used in SOLOIST, capturing symptom frequency (4 items), physical (4 items) and social limitations (3 items), and quality of life impairment (2 items) as a result of having congestive HF (Appendix B Kansas City Cardiomyopathy Questionnaire). 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 was to be completed by all patients as described in the study flow chart of protocol. In case of premature permanent IMP discontinuation, the KCCQ-12 was to be completed by patients at the visit planned for the last dosing day with IMP and afterwards as normally planned.

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 prior to study discontinuation. A patient will be considered as having discontinued the study for CV death, HHF, or urgent HF visit if the date of the last information on this endpoint (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 date of death or last known alive – randomization date + 1 day. The study duration will be summarized according to median, 25th percentile, 75th percentile, and range for each treatment group and for the overall population.

Additionally, the following populations will be summarized by treatment group:

- Randomized 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 population

The efficacy analysis population will be the ITT population, consisting of all randomized patients.

Patients in the ITT population will be analyzed according to the treatment group allocated by randomization.

2.3.3 Safety population

The safety analysis population is defined as the randomized patients 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 described above (Section 2.1.1 Demographic and baseline characteristics) will be summarized 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 population 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 who were up-titrated to 400 mg by Visit 7 (Month 8) 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 LVEF (<50%, ≥50%). This primary comparison will be a 2-sided test at the 0.05 type 1 error level for the following hypothesis:

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 ever event time is unique.

To determine whether the treatment effect on the primary endpoint is different before and after 240 days (the end of the window for up-titration of dose), a marginal proportional hazards model that allows the treatment HR to vary before and after 240 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 for the primary endpoint. Bars for sotagliflozin and placebo will be provided for the numbers of first events, second events, and a category of "third 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:

- LVEF in two categories (<50%, ≥50%)
- LVEF in three categories (<40%, ≥40% <50%, ≥50%)
- Region in three categories (The Americas, Europe, Rest of the world)
- Age (<65, ≥65)
- Gender (male, female)
- Race/ethnicity (white, black, Hispanic, Asian, other)
- Baseline eGFR (<60 mL/min/1.73m^2, ≥60 mL/min/1.73m^2)
- Baseline BMI (<30, ≥30 kg/m^2)
- NYHA Class (II, III, IV)
- NT-proBNP (≤Median, >Median)
- MRA at Baseline
- GLP-1 receptor agonist at Baseline
- Sacubitril-valsartan at Baseline
- 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)
- Start of first IMP dose prior to vs. after hospital discharge (or urgent care facility where appropriate)

For each factor, a marginal Cox proportional hazard model stratified by region and LVEF (note that when region is the subject of the analysis stratification will only be by LVEF; similarly when LVEF 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 HR 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-I error rate when testing the secondary efficacy endpoints are described in Section *2.4.4.3 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.

As with the primary endpoint, the absolute risk reduction (ARR) of time-to-event secondary endpoints will be estimated by the difference between treatment groups in the number of events per 100 patient-years of follow-up. For those secondary endpoints which are a composite of events, results will be provided for both the overall composite and its individual components.

Absolute change in KCCQ-12 scores from baseline to Month 4 will be analyzed by analysis of covariance (ANCOVA) with treatment group as factor and baseline KCCQ-12 score and randomization stratification factors as covariates. The last available post-baseline score will be

carried forward to Month 4 if the patient is alive at Month 4 but the Month 4 value is missing. For patients who die, a worst score (0) will be imputed for the clinical summary score at all subsequent scheduled visits after the date of death where the clinical summary score would have been assessed.

The rate of decline in eGFR observed over time will be analyzed by repeated-measures mixed-effects models with absolute change in eGFR from baseline as the outcome, a random effect for intercept, and fixed effects for treatment, baseline value, and time. An additional model will be developed with an interaction between treatment and time. The variance-covariance matrix will be specified to be unstructured.

2.4.4.3 Multiplicity issues

In order to handle multiple main secondary endpoints, the overall type-I 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 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 Secondary efficacy endpoints*. This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the required 0.05 2-sided level.

2.4.4.4 Additional efficacy analysis(es)

Time-to-event other efficacy endpoints 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 given 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 as of 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 mode 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 (ie, PDAOH =100%), 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, 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.

General common rules

All safety analyses will be performed on the safety population as defined in Section 0, 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.
- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Section 2.1.4.

2.4.5.1 Analyses of adverse events

Generalities

Analysis of treatment-emergent 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 and preferred term
- All TEAEs related to IMP by primary SOC and preferred term

Analysis of treatment-emergent serious adverse events

- All treatment-emergent SAEs by primary SOC and preferred term
- All treatment-emergent SAEs related to IMP by primary SOC and preferred term

Analysis of treatment-emergent adverse events leading to permanent discontinuation

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

2.4.5.2 Analyses of laboratory variables

Summary statistics of all laboratory variables (number, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum) will be calculated for each visit or study assessment by treatment group during the treatment period.

2.4.5.3 Analyses of vital signs variables

Summary statistics of all laboratory variables (number, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum) will be calculated for each visit or study assessment by treatment group during the treatment period.

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 imputations are detailed in Appendix A Assignment of dates to events.

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 does 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, KCCQ-12) 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 1	8	5 to 11
Week 2	15	12 to 18
Week 4	29	22 to 36
Week 16 (Month 4)	113	85 to 141
Beyond Week 16	Number of weeks of the planned visit x 7	Targeted study day ±28 days

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 Assignment of dates to events

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.

The time to death will be used for CV death and all-cause mortality rather than the time to onset of the associated event causing the death. For example, if a patient has a fatal stroke that leads to death several days later, the date of death (a later date) will be used rather than the date of stroke onset.

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 proceeding/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 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 fulfil 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 will be the latest of all imputed event dates and patient's last trial contact date.

Appendix B Kansas City Cardiomyopathy Questionnaire

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

Scoring the KCCQ-12

Four domain scores and one summary score are generated from the KCCQ-12:

Physical Limitation Score	(KCCQ12-PL)
Symptom Frequency Score	(KCCQ12-SF)
Quality of Life Score	(KCCQ12-QL)
Social Limitation Score	(KCCQ12-SL)
Summary Score	(KCCQ12)

Scores are scaled 0-100, where 0 denotes the lowest reportable health status and 100 the highest.

Physical Limitation Score

The Physical Limitation score corresponds to Questions 1a, 1b and 1c. Responses are coded as follows:

Extremely limited	1
Quite a bit limited	2
Moderately limited	3
Slightly limited	4
Not at all limited	5
Limited for other reasons or did not do the activity	6

A response of 6 is treated as a missing value for the purposes of scoring. If responses to two or more questions are missing, no score is computed. Otherwise, the score is then calculated by taking the average of the non-missing responses and rescaling to 0-100, as follows:

KCCQ12-PL = 100*[(average of Questions 1a, 1b and 1c) – 1]/4

Symptom Frequency Score

The Symptom Frequency score corresponds to Questions 2, 3, 4 and 5. Responses are coded as follows:

Question 2 Response

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

Questions 3 and 4 Response

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

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

If responses to three or more questions are missing, no score is computed. Otherwise, the score is then calculated by first rescaling each non-missing response to 0-100, then taking the average of the rescaled non-missing responses, as follows:

Q2 rescaled = 100 × (Q2 response – 1) ÷ 4
Q3 rescaled = 100 × (Q3 response – 1) ÷ 6
Q4 rescaled = 100 × (Q4 response – 1) ÷ 6
Q5 rescaled = 100 × (Q5 response – 1) ÷ 4
KCCQ12-SF = average of rescaled responses

Quality of Life Score

The Quality of Life score corresponds to Questions 6 and 7. Responses are coded as follows:

Question 6 Response
It has extremely limited my enjoyment of life 1
It has limited my enjoyment of life quite a bit 2
It has moderately limited my enjoyment of life 3
It has slightly limited my enjoyment of life 4
It has not limited my enjoyment of life at all 5

Question 7 Response
Not at all satisfied.....1
Mostly dissatisfied.....2
Somewhat satisfied.....3
Mostly satisfied.....4
Completely satisfied 5

If responses to both questions are missing, no score is computed. Otherwise, the score is calculated by taking the average of the non-missing responses and rescaling to 0-100, as follows:

KCCQ12-QL = 100*[(average of Questions 6 and 7) – 1]/4

Social Limitation Score

The Social Limitation score corresponds to Questions 8a, 8b and 8c. Responses are coded as follows:

Severely limited.....1
Limited quite a bit.....2
Moderately limited 3
Slightly limited 4
Did not limit at all.....5
Does not apply or did not do for other reasons.....6

A response of 6 is treated as a missing value for the purposes of scoring. If responses to two or more questions are missing, no score is computed. Otherwise, the score is then calculated by taking the average of the non-missing responses and rescaling to 0-100, as follows:

KCCQ12-SL = 100*[(average of Questions 8a, 8b and 8c) – 1]/4

Summary Score

The Summary score represents an integration of the patient's physical limitation, symptom frequency, quality of life and social limitation. If all four domain scores are missing, no summary score is computed. Otherwise, the score is calculated as the average of the non-missing domain scores:

KCCQ12 = average of KCCQ12-PL, KCCQ12-SF, KCCQ12-QL and KCCQ12-SL

APPENDIX C 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 D 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 to patients with heart failure, and have been sensitive to change in several cardiovascular outcomes 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 to demonstrate reductions in CV morbidity and mortality in those with LVEF<50%, and one to demonstrate reductions in CV morbidity and mortality in the overall population	Primary focus is on overall population rather than subgroups
Composite renal endpoint was moved from a secondary objective to other objective; change in eGFR over time was added as a secondary benefit	Given the current follow-up in SOLOIST, change in eGFR over time is a more sensitive measure of renal benefit than the composite renal endpoint
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
CV death and HHF in patients with LVEF <50%, with and without T2D (a secondary endpoint in Amendment 2) is not included in current analysis plan	Limited enrollment after Amendment 2 means subgroup analysis of those without T2D is not adequately powered for a secondary endpoint
All-cause mortality was a secondary endpoint in the original protocol, moved to "other	Original move to "other endpoint" was based on FDA feedback that it would not be included

endpoint" in Protocol Amendment 2, and returned to a secondary endpoint in this analysis plan	in labeling, but it was returned to secondary endpoint because of its high clinical relevance
Amendment 2 of SOLOIST allowed recruitment of patients without T2D	DAPA-HF results indicated that SGLT inhibition benefits a broader patient population, although enrollment after amendment 2 was very limited
Amendment 2 of SOLOIST allowed enrollment on the first day of hospitalization	Confidence in safety of SGLT inhibition indicated this could benefit patients
Amendment 2 of SOLOIST expanded randomization window to 7 days after hospitalization	Investigators reported that seven days after discharge was often the first time the patient was seen at the end of an episode of worsening heart failure