STATISTICAL ANALYSIS PLAN	
Study Code	D9480C00023
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An Open-Label, Randomised, Phase 4 Study of Continuing Sodium Zirconium Cyclosilicate (SZC) after Discharge in Participants with Chronic Kidney Disease treated for Hyperkalaemia

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LIST OF ABBREVIATIONS

Abbreviation or Specialised Term	Definition
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under curve
AZ	AstraZeneca
BMI	Body Mass Index
CI	Confidence Interval
CKD	chronic kidney disease
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CSP	Clinical Study Protocol
CTC	Common Terminology Criteria
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ED	Emergency Department
EDC	Electronic data capture
eGFR	estimated glomerular filtration rate
EMPOWER	Excellence in Medical Partnership for Outsourced Worldwide Evidence Research
EOT	End of treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
HK	Hyperkalaemia
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
IPW	Inverse Probability Weighting
IRB/IEC	Institutional Review Board/Independent Ethics Committee
LOS	Length of Stay
K+ or K	Potassium
MCC	Mean Cumulative Count
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Specialised Term	Definition
MMRM	Mixed Model for Repeated Measures
NK	Normokalemia or normokalemic
PPS	Per Protocol Set
PT	Preferred Term
QTc	QT interval corrected
QTcF	QT interval corrected by the Fridericia method
RAASi	Renin-angiotensin-aldosterone system inhibitor
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SMQ	Standardised MedDRA Query or Queries
SOC	System Organ Class
SoC	Standard of Care
SSO	Safety Set Open
SSR	Safety Set Randomised
SZC	Sodium zirconium cyclosilicate
TEAE	Treatment Emergent Adverse Events
TFLs	Tables, Figures and Listings
WHO	World Health Organisation

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
Primary or secondary endpoints	15-Jan-2025	Additional sensitivity analysis from primary endpoint to analyse all K+ measurements recorded in Electronic Data Capture (EDC) at visit 10 while on SZC irrespective of visit windowing.	No	To explore the sensitivity of the results to the use of visit windowing.
Primary or secondary endpoints	15-Jan-2025	ECG results from site 7001 are excluded from analysis.	No	A serious breach was identified at this site with the recording of ECG measurements. To avoid bias these measurements are excluded.
Analysis Populations	15-Jan-2025	The per protocol set definition was updated to exclude important protocol deviations considered to have a major effect on efficacy.	No	Previous definition was too broad and did not reflect the purpose of the analysis population, which is to be used for sensitivity analyses of efficacy endpoints.

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Primary or secondary endpoints	27-Nov-2023	In the definition of the first secondary objective and endpoint, “time to first occurrence of hospital admissions or ED visits with HK as a contributing factor”. In relation to this change, a sensitivity analysis with hospital admission with HK as a contributing factor has been added as well as 2 secondary objectives and endpoints.	Yes, version 4.	To expand the definition of the main secondary endpoint to encompass a wider range of hospital admissions to facilitate a larger, clinically meaningful effect size for detection in order to reduce sample size.
Other: Sample size	27-Nov-2023	The sample size was re-calculated based on the new definition of the secondary endpoint.	Yes, version 4.	To align with changes in the main secondary endpoint.
Other: Interim analysis	27-Nov-2023	The planned interim analysis has been cancelled.	Yes, version 4.	Due to the decreased sample size, running an interim analysis is not justified.

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D9480C00023 supporting the clinical study report. The reader is referred to the Clinical Study Protocol (CSP) and the Case Report Form (CRF) for the details of study conduct and data collection.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

The definition of the Per Protocol Set has been updated to exclude important protocol deviations considered to have a major effect on efficacy. Summaries of ECG results will exclude measurements from site 7001 where a serious breach was identified.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

A final analysis will be conducted when all randomised participants have completed Visit 11 of the follow-up phase, data cleaning has been completed and the database has been locked for analysis.

3.2 Analysis Populations

This study will include the following analysis populations:

- Screened Set
- Full Analysis Set
- Per Protocol Set
- Safety Set Open
- Safety Set Randomised

Screened Set

The screened set will include all participants who were screened for inclusion in the inpatient period of the study. This analysis set will be used to describe the demographics of participants considered for inclusion in the study. The assignment of participants to a treatment group for analysis is not applicable.

Full Analysis Set

The Full Analysis Set (FAS) will include all randomised participants. Participants will be analysed according to their randomised treatment. The FAS will be the analysis population used for the primary, secondary and exploratory efficacy analyses.

Per Protocol Set

The Per Protocol Set (PPS) will include all FAS participants who do not have any important protocol deviations considered to have a major effect on efficacy. All important protocol deviations will be classified according to the protocol deviation management plan. Participants will be analysed according to their randomised treatment. The PPS will be the analysis population used for sensitivity analysis of primary and secondary efficacy analyses.

Safety Set Open

The Safety Set Open (SSO) will include all participants who receive at least one dose of sodium zirconium cyclosilicate (SZC) during the study, up until discharge from hospital/randomisation. Participants will be analysed as a single group. The SSO will be the analysis population used for presentations of safety information during the inpatient period.

Safety Set Randomised

The Safety Set Randomised (SSR) will include all randomised participants receiving at least one dose of SZC after the date and time of randomisation in Arm A (SZC), and all randomised participants in Arm B (Standard of Care (SOC) according to local practice). The date and time of randomisation will be as recorded in the IRT system. Participants will be analysed according to treatment actually received. The SSR will be the analysis population used for presentations of safety information during the outpatient period.

3.3 General Considerations

The principal analyses outlined in this SAP will be conducted by Fortrea, in accordance with the contract with AstraZeneca (AZ) AB and following the Excellence in Medical Partnership for Outsourced Worldwide Evidence Research (EMPOWER) description of services.

The general principles below will be followed for analyses:

Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation (SD), median, Q1, Q3, minimum and maximum. For log-transformed data, it is more appropriate to present geometric mean, coefficient of variation (CV), median, minimum and maximum.

Categorical variables will be summarised by frequency counts and percentages for each category.

For qualitative variables, the number (n) and percentage (%) of subjects with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Number of subjects in the analysis population will be used as denominator for percentages calculation, unless stated otherwise in TFLs mock shell(s).

For continuous data, the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.

For categorical data, percentages will be rounded to 1 decimal place.

SAS® version 9.3 or higher will be used for all analyses

It is acceptable to present large numerical values in more appropriate units. For example, an Area Under Curve (AUC) value of 123,000 ng h/mL may be reported as 123 µg h/mL instead. It is however, important to keep the units consistent within the report and the precision consistent with that prior to conversion.

3.3.1 General Study Level Definitions

During the in-hospital phase, all assessment days will be related to the first day of first dose of study intervention SZC. Day 1 of the in-hospital phase is defined as first dose of study intervention SZC. During the outpatient phase, all assessment days will be related to the date of randomisation. Day 1 of the outpatient phase is defined as the date of randomisation. During the follow-up phase, all assessment days will be related to the last dose of SZC. Day 1 of the follow-up phase is defined as the last dose of SZC + 1.

The date of the first dose of SZC for each subject will be taken from the Drug Accountability (Inpatient) eCRF page. If the date in this eCRF page is missing, alternatively the date of first dose dispensed will be used.

The date and time of randomisation will be as recorded in the IRT system. Relative days after day 1 are calculated as (assessment date – day 1 date) + 1. Relative days prior to day 1 are calculated as (assessment date – day 1 date). The day prior to day 1 is day -1. Day 0 is not defined.

3.3.1.1 Screening / Baseline Period

For all subjects, the screening period is defined as the period from informed consent to the first dose of SZC. For some variables, data from more than one assessment within the screening period may be collected prior to the first dose of SZC.

The baseline value for a variable is therefore defined as the last non-missing observation before the first dose of study treatment (SZC) in the inpatient period. For assessments on the day of first dose, where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose. Any observation made after the first dose of study treatment will be considered post-baseline.

Assessments on the day of the first dose when neither time nor a nominal pre-dose indicator are captured will be considered prior to the first dose if such procedures are required by the protocol to be conducted before first dose.

In all quantitative summaries from baseline, absolute changes from baseline will be calculated as the post-baseline value minus the value at baseline. The percentage change from baseline will be calculated as [(post-baseline value – baseline value) / baseline value] x 100.

3.3.1.2 Analysis Periods

Treatment Period

Data collected at Day 1 will be assigned to the Treatment Period unless the time (HH[:MM]) of data collection and time (HH[:MM]) of first dose of SZC are both recorded and the data collection time is before the time of first dose of SZC. In this case, the assessment will be assigned to the screening period. If the time (HH:MM) of data collection is not recorded but the protocol and / or eCRF includes an instruction to the effect that all Day 1 assessments are to be performed prior to the first dose of SZC, the data collected at Day 1 will be assigned to the screening period. However, adverse events and medications starting on Day 1 will be assigned to the Treatment Period.

The Treatment Period is defined as the period from the date / time of the first dose of SZC (start of inpatient period) up to the earliest date of last assessment during the outpatient period, withdrawal of consent, last contact with the participant or death (inclusive) (end of outpatient period).

Inpatient Period

The inpatient period refers to the period from the date of first study intervention dispensation of SZC until the date of randomisation at discharge (exclusive) or until 21 days after the first dose of SZC for participants who have not been randomised.

Outpatient Period

The outpatient period refers to the period from the date of randomisation until the earliest date of end of treatment, withdrawal of consent, last contact with the participant or death (inclusive).

3.3.1.3 Handling of missing dates

Incomplete dates (partial or missing dates where a full date is permissible) will be presented in the data listings as recorded on the eCRF. Missing hospital admission, emergency department and death dates will not be imputed. Every effort will be made to ensure complete information for these dates are available. However, for adverse event start and stop date and for prior and concomitant medication start and stop date, missing dates will be estimated as follows:

3.3.1.3.1 Partial start dates

If the year is unknown, then:

- The date will not be imputed, and will be assigned a missing value

If the month is unknown, then:

- If the year matches the year of the first dose date in the inpatient period, then impute the month and day of the first dose date.
- Otherwise, assign the month as July

If the day is unknown, then:

- If the month and year match the month and year of the first dose date in the inpatient period, then impute the day of the first dose date.
- Otherwise, assign the day as mid-month (14th for February, 15th for all other months).

3.3.1.3.2 Partial end dates

If the year is unknown, then the date will not be imputed and will be assigned a missing value.

If the month is unknown, then assign July.

If the day is unknown, then assign the day as mid-month (14th for February, 15th for all other months).

If the above rules for end dates result in illogical date (i.e. end date < start date or end date > participant's date of completion/discontinuation) with regards to the dates the participant was in the study, then the end date will be replaced with the participant's date of completion/discontinuation.

3.3.1.4 Handling of Missing Data

3.3.1.4.1 Handling of Missing Efficacy Data

Participants with missing data for the primary efficacy endpoint of occurrence (yes/no) of normokalaemia (NK) (K^+ between 3.5 and 5.0 mmol/L, inclusive) at 180 days post-discharge will be treated as non-responders for the main analysis. Additionally, participants who receive rescue medication for HK during the outpatient period will also be deemed as non-responders, regardless of any subsequent measurement for K^+.

K+ measurements up to 180 days post-discharge will be analysed using mixed-effects models repeated measures, which assumes that missing outcomes are missing at random (MAR). Details of this analysis are provided in section 4.2.13.

3.3.1.4.2 Handling of Missing Safety Data

In general, missing clinical laboratory data, vital signs and ECG data will not be imputed. Adverse event imputations for missing intensity or relationship are given in section 4.6.2.1. Unknown or partial medication and AE date imputations are given in section 3.3.1.3 and are to be used only for the assessment of prior / concomitant status for medications and treatment-emergent status for AEs.

3.3.2 Visit Window

For all populations, assessments will be assigned to visits and analysis periods for categorical summaries as follows:

- Assessments with missing data and assessments marked “Not Done” will be considered as providing a missing response and are not permitted to be assigned to a visit window.
- The worst value (e.g. out of reference range preferred to within range; abnormal preferred to normal) will be used in each window. If multiple assessments fall within the same window with equal value, then the first non-missing value will be used for the summary.
- In the AZ Standard TFL shells, “Time Point” is used interchangeably with “Visit” as, in this study; multiple observations are not made at the same visit.

Target day and protocol/analysis visit windows in Table 2 and Table 3 are with respect to the date of randomisation. Visit windowing related to the date of hospital admissions and ED visits will use Table 2. All other assessments will use visit windowing provided by Table 3. Alternative windowing is required because outpatient phase visits 5, 6, 8 and 9 are conducted by phone and collect information on concomitant medication, adverse events, hospital admission and ED visits only. Target day and protocol analysis visit windows in Table 4 are with respect to the date of last dose of SZC (EOT).

Table 1 Definition of visit windows during the inpatient period

Visit	Target Day of Visit	Visit Window
Visit 1	Date of Informed Consent	NA[a]
Visit 2	Date of first dose of SZC	NA

[a] For potassium measurements only, the visit windowing will allow any potassium measurement recorded prior to the date of informed consent

Table 2: Definition of visit windows during the outpatient period for hospital admissions and ED visits

Visit	Study Day[a]	Target Day of Visit[b]	Protocol Visit Window[b]	Analysis Visit Window[b]
Visit 3	2 to 21	Date of randomisation	NA	NA
Visit 4	9 to 28	7	6 to 8	2 to 19
Visit 5	32 to 51	30	24 to 36	20 to 45
Visit 6	62 to 81	60	54 to 66	46 to 75
Visit 7	92 to 111	90	84 to 96	76 to 105
Visit 8	122 to 141	120	114 to 126	106 to 135
Visit 9	152 to 171	150	144 to 156	136 to 165
Visit 10	182 to 201	180	174 to 186	166 to 186

[a] Relative to the date of first study intervention dispensation of SZC during the inpatient phase
[b] Relative to the date of randomisation

Table 3: Definition of visit windows during the outpatient period for all other assessments

Visit	Study Day[a]	Target Day of Visit[b]	Protocol Visit Window[b]	Analysis Visit Window[b]
Visit 3	2 to 21	Date of randomisation	NA	NA
Visit 4	9 to 28	7	6 to 8	2 to 45
Visit 7	92 to 111	90	84 to 96	46 to 135
Visit 10	182 to 201	180	174 to 186	136 to 186

[a] Relative to the date of first study intervention dispensation of SZC during the inpatient phase
[b] Relative to the date of randomisation

Table 4: Definition of visit windows during the follow-up period

Visit	Target Day of Visit	Protocol Visit Window	Analysis Visit Window
Visit 11	EOT+7	EOT+4 to EOT+10	EOT+1 to EOT+10

3.3.3 Handling of Unscheduled Visits

Unscheduled visits will be considered for by-visit presentations and listings according to the rules outlined in Section 3.3.2. All unscheduled visits will be included in listings.

3.3.4 Multiplicity/Multiple Comparisons

To control for type I error, a hierarchical testing procedure will be followed when formally testing the primary and secondary efficacy analysis endpoints. The hierarchical testing procedure will follow a stepwise algorithm where each endpoint is only formally tested if the preceding null hypothesis is rejected (two-sided p-value < 0.05). If the preceding null hypothesis is not rejected, then the evaluation of the endpoint will be reduced to that of an exploratory endpoint. The testing order for the primary and secondary efficacy analysis endpoints is displayed in Table 5:

Table 5: Testing order for primary and secondary efficacy endpoints

Order	Efficacy Endpoint	Section
1	Occurrence (yes/no) of normokalaemia (NK) (K^+ between 3.5 and 5.0 mmol/L, inclusive) at 180 days post-discharge	4.2.2
2	Time to first occurrence of all-cause hospital admission or ED visit with HK as a contributing factor, or all-cause death, or use of rescue therapy for HK at any time post-discharge up to 180 days inclusive.	4.2.3
3	Time to first occurrence of all-cause hospital admission or ED visit with HK as a contributing factor at any time post-discharge up to 180 days inclusive.	4.2.4
4	Number of all-cause hospital admission or ED visits with HK as a contributing factor, at any time post-discharge up to 180 days.	4.2.5
5	Time to first occurrence of RAASi down-titration (or discontinuation) at any time post-discharge up to 180 days.	4.2.6
6	Time to first occurrence of hospital admission or ED visit, both with HK as a contributing factor at any time post-discharge up to 180 days.	4.2.7
7	Number of hospital admission or ED visits, both with HK as a contributing factor, at any time post-discharge up to 180 days.	4.2.8

3.3.5 Handling of Protocol Deviations in Study Analysis

Protocol deviations are defined as any change, divergence, or departure from the study design of procedures defined in the clinical study protocol (CSP).

Important protocol deviations will be defined by AZ before database lock following the process described in the protocol deviation management plan and the project specific protocol deviations list. Important protocol deviations are a subset of protocol deviations, which may significantly impact the correctness, accuracy, and / or reliability of the study data or that may significantly affect a subject's rights, safety or well-being. The following criteria may be considered as important protocol deviations which may have a major effect on efficacy or that could potentially affect the interpretability of the study results.

1. Informed Consent, such as Informed Consent Form (ICF) not signed before project specific assessments or procedures.

2. Study Conduct/Procedures, such as failure to complete or comply with inclusion/exclusion criteria, including discrepancy within source documentation and / or raw data, non-compliance with protocol / CIP requirements (Note: this does not include ICF issues), use of prohibited medication or prohibited treatment therapy or a subject's first dose date prior to baseline evaluations.

3. Investigational Product, such as inadequate supply of materials/IMP (includes issues with regard to expiration date e.g. subject takes IMP which has expired).

4. Safety, such as non-recording of AEs and SAEs by PIs (e.g. recording on time, etc.).

In addition, protocol deviations will be defined by AZ before database lock as coronavirus disease (COVID)-19 pandemic related or not by judging the root cause of the protocol deviation, in line with US Food and Drug Administration (FDA) guidance (FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency; March 2020). These will be identified as protocol deviations, which start with the prefix "COVID19". The following criteria may be considered indicative of a protocol deviation related to the COVID-19 pandemic.

- Missed in-person visit due to COVID-19 illness and/or COVID-19 public health control measures

- Study visit out of window due to COVID-19 illness and/or COVID-19 public health control measures

- Missed doses due to COVID-19 illness and/or COVID-19 public health control measures

- Missed central laboratory K+ measurements due to COVID-19 illness and/or COVID-19 public health control measures

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivations and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers participant disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical history, prior and concomitant medication and study intervention compliance.

4.1.1 Participant Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Participants are defined as entering the inpatient period if they received one or more doses of SZC.

4.1.1.2 Presentation

Participant disposition will be listed and summarised by treatment group and overall. The number and percentages of participants in the following categories will be summarised for participants in the screened set:

- Participants enrolled;
- Participants entered inpatient period
- Participants randomised;
- Participants who were not randomised and associated reasons;
- Randomised participants who received treatment;
- Randomised participants who did not receive treatment and associated reasons;
- Randomised participants who completed treatment;
- Randomised participants who discontinued treatment and associated reasons
- Randomised participants who completed the study;
- Randomised participants withdrawn from the study and associated reasons;

The denominator used for percentages will be calculated as follows. The denominator for participants who are screened or who did not enter the inpatient period (and associated reasons) will be calculated using the number of screened participants. The denominator for participants who entered the inpatient period and received treatment, who entered the inpatient period and did not receive treatment (and associated reasons), randomised and not randomised (and associated reasons) will be calculated using the number of participants who entered the inpatient period. The remaining participant disposition categories will use the number of participants who were randomised for the denominator.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

The definition for analysis sets is described in section 3.2.

4.1.2.2 Presentation

The number of participants in each of the analysis sets and the reasons for exclusion from each will be summarised for all screened participants by treatment group and overall.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Important protocol deviations will be defined according to section 3.3.5, and determined in prior to database lock as outlined in the protocol management plan.

4.1.3.2 Presentation

All important protocol deviations will be listed and summarised by treatment group and overall for the FAS. Important protocol deviations will be further classified as either pandemic-related or excluding pandemic related important protocol deviations.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

The demographic and baseline characteristics include the following:

- Age (years);
- Age groups (18-64, 65-84 and 85 years and over);
- Sex (male, female);
- Race category (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaskan Native, Other, Not reported);
- Ethnic group (Hispanic or Latino, Not Hispanic or Latino);
- Participant recruitment country;

4.1.4.2 Presentation

The demographic characteristics defined in Section 4.1.4.1 will be listed and summarised in total for the SSO and by treatment group and total for the SSR and FAS.

No formal tests of statistical significance will be performed on the demographic and baseline data.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline body mass index (BMI; kg/m^2) will be calculated as baseline weight/baseline $height^2$ where weight is in kg and height is in m.

4.1.5.2 Presentation

A separate table will summarize the participant baseline characteristics and will be listed and summarised in total for the SSO and by treatment group and total for the SSR and FAS. They will include:

- Baseline height (cm);
- Baseline weight (kg);
- BMI (kg/m^2);

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

The following disease characteristics will be defined:

- Presence of heart failure (Yes/No, identified per Medical History using an SMQ of "Cardiac failure" with a narrow scope; SMQ Code: 20000004 which includes preferred terms of: Acute left ventricular failure, Acute pulmonary oedema, Acute right ventricular failure, Cardiac asthma, Cardiac failure, Cardiac failure acute, Cardiac failure chronic, Cardiac failure congestive, Cardiac failure high output, Cardiogenic shock, Cardiohepatic syndrome, Cardiopulmonary failure, Cardiorenal syndrome, Chronic left ventricular failure, Chronic right ventricular failure, Congestive hepatopathy, Cor pulmonale, Cor pulmonale acute, Cor pulmonale chronic, Ejection fraction decreased, Hepatojugular reflux, Left ventricular failure, Low cardiac output syndrome, Neonatal cardiac failure, Obstructive shock, Pulmonary oedema, Pulmonary oedema neonatal, Radiation associated cardiac failure, Right ventricular ejection fraction decreased, Right ventricular failure, Ventricular failure.

- Diabetes (Yes/No, identified per Medical History eCRF using an SMQ of "Hyperglycaemia/new onset diabetes mellitus" with a narrow scope; SMQ Code: 20000041 which includes preferred terms of: Acquired generalised lipodystrophy, Blood 1,5-anhydroglucitol decreased, Blood glucose increased, Diabetes complicating pregnancy, Diabetes mellitus, Diabetes mellitus inadequate control, Diabetes with hyperosmolarity, Diabetic arteritis, Diabetic coma, Diabetic coronary microangiopathy, Diabetic hepatopathy, Diabetic hyperglycaemic coma, Diabetic hyperosmolar coma, Diabetic ketoacidosis, Diabetic ketoacidotic hyperglycaemic coma, Diabetic ketosis, Diabetic metabolic decompensation, Diabetic wound, Euglycaemic diabetic ketoacidosis, Fructosamine increased, Fulminant type 1 diabetes mellitus, Gestational diabetes, Glucose tolerance impaired, Glucose tolerance impaired in pregnancy, Glucose urine present, Glycated albumin increased, Glycated serum protein increased, Glycosuria, Glycosuria during pregnancy, Glycosylated haemoglobin abnormal, Glycosylated haemoglobin increased, Hepatogenous diabetes, Hyperglycaemia, Hyperglycaemic crisis, Hyperglycaemic hyperosmolar nonketotic syndrome, Hyperglycaemic seizure, Hyperglycaemic unconsciousness, Impaired fasting glucose, Insulin resistance, Insulin resistant diabetes, Insulin-requiring type 2 diabetes mellitus, Ketoacidosis, Ketonuria, Ketosis, Ketosis-prone diabetes mellitus, Latent autoimmune diabetes in adults, Maternally inherited diabetes and deafness, Monogenic diabetes, Neonatal diabetes mellitus, Neonatal hyperglycaemia, New onset diabetes after transplantation, Pancreatogenous diabetes, Pseudodiabetes, Steroid diabetes, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Type 3 diabetes mellitus, Urine ketone body present)

- Renin-angiotensin-aldosterone system inhibitors (RAASi) use at screening (Yes/No, identified per Concomitant Medication eCRF as CMCLASCD in ('C09AA', 'C09BA', 'C09BB', 'C09BX', 'C09CA', 'C09DA', 'C09DB', 'C09DX', 'C09XA') where Start Date is prior to admission date for in-patient phase of hospital visit)

- CKD diagnosis (identified per Medical History eCRF using a LLT containing "Chronic kidney disease"

- CKD stage (derived based on eGFR value), calculated as:

    - Grade 1 (eGFR $\geq$ 90)

    - Grade 2 (60 $\leq$ eGFR <90)

    - Grade 3a (45 $\leq$ eGFR $\leq$ 59)

    - Grade 3b (30 $\leq$ eGFR $\leq$ 44)

- Grade 4 ($15 \leq eGFR \leq 29$)
- Grade 5 ($eGFR < 15$)

- Baseline K^+ ($5.0 < K^+ \leq 5.5$ versus $5.5 < K^+ \leq 6.5$ mmol/L)
- Duration of index hospitalisation (<7 days versus ≥7 days)

4.1.6.2 Presentation

Disease characteristics will be summarised by treatment group and in total for the FAS.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 24.1 (or a later version if updated during the study)].

4.1.7.2 Presentation

The number and percentage of participants with any medical history will be summarised for the SSO and by treatment group and in total for the SSR. The number and percentage of participants with at least one medical history record within each primary SOC and PT will be presented. The summary will be sorted alphabetically by SOC and PT. A participant can have one or more PTs reported under a given SOC but will be reported once per PT and SOC.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Medications received prior to or concomitantly with study treatment will be coded using the WHO Drug Dictionary [Version March 2021 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

Prior medications are those taken with a stop date prior to the first dose date of study treatment during the inpatient period.

Concomitant medications during the inpatient period are those with a stop date prior to the first dose of study treatment during the outpatient period and either a start date on or after the first dose date of study treatment during the inpatient period, or those with a start date before, and either a stop date on or after the first dose date of study treatment during the inpatient period or those which are ongoing.

Concomitant medications during the outpatient period are those with a start date on or after the first dose date of study treatment during the outpatient period, or those with a start date before, and either a stop date on or after the first dose date of study treatment during the outpatient period or those which are ongoing.

If a medication cannot be classified as "prior" or "concomitant during the inpatient period" or "concomitant during the outpatient period" after applying imputation rules for missing/incomplete dates, it will be classified as concomitant during the outpatient period.

4.1.8.2 Presentation

Prior medications, concomitant medications during the inpatient period and concomitant medications during the outpatient period will be listed separately. Prior medications will be summarised overall using the SSO. Concomitant medications during the inpatient period will be summarised overall using the SSO. Concomitant medications during the outpatient period will be summarised by treatment group and overall using the SSR.

The number and percentages of participants using each medication will be displayed together with the number and percentage of participants using at least one medication within each therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term. The summaries will be sorted using numerical counts by descending order of therapeutic class, then descending order of chemical subgroup, then descending order of generic term in the total column. Where groups or terms tie these will be sorted alphabetically.

4.1.9 Study Intervention Compliance

4.1.9.1 Definitions and Derivations

The percentage compliance for SZC will be calculated overall in the inpatient period and in arm A in the outpatient period only and is calculated as:

$$\text{Compliance (\%)} = \frac{\text{(Number of sachets dispensed in inpatient/outpatient period - Number of sachets returned in inpatient/outpatient period)}}{\text{Number of days on treatment in inpatient/outpatient period} \times \text{Number of sachets prescribed per day}}$$

Number of days on treatment will be calculated as follows:

(last dose of SZC in inpatient/outpatient period – first dose of SZC in inpatient/outpatient period)+1.

The percentage compliance for SZC will be calculated separately for the inpatient and outpatient periods and will be summarised descriptively overall using the SSO and in Arm A using the SSR respectively.

4.1.9.2 Presentation

Compliance will be summarised separately for the inpatient and outpatient periods using the SSO and SSR respectively using descriptive statistics (n; Mean; SD; Minimum; 1st quartile; Median; 3rd quartile, Maximum) with the number and proportion of participants in the following compliance categories:

- <50%
- ≥50% to <80%
- ≥80% to <120%
- ≥120%

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses. The primary and secondary endpoints use the classification of all-cause hospital admissions and emergency department (ED) visits as either having or not having HK as a contributing factor. Rescue therapy is also defined as being related to HK. Final classification of these for analysis will be made by an independent blinded adjudication committee and is covered in a separate charter.

4.2.1 Overview

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 1: To evaluate the efficacy of continuing SZC as part of the discharge medications, compared to SoC, in maintaining NK					
Primary	Occurrence (yes/no) of NK (K+ between 3.5 and 5.0 mmol/L, inclusive) at 180 days post-discharge	FAS	Participants who discontinue treatment with a K+ measurement at 180 days post-discharge will have this value used irrespective of treatment discontinuation (treatment policy strategy). Use of rescue therapy for HK will be	Logistic regression analysis with response (occurrence) as the dependent variable and randomised treatment group as the independent variable. The odds ratio along with	4.2.2

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
			considered to be non-response (composite variable strategy). The RAASi down-titration (including discontinuation) will be considered to be non-response (composite variable strategy). Participants who die of any cause prior to 180 days post-discharge or who are lost to follow-up for any reason will be considered to be non-response (composite variable strategy).	the two-sided 95% confidence intervals and two-sided p-value (significance declared <0.05) will be displayed.	
Objective 2: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of the composite outcome of all-cause hospital admissions, or ED visits with HK as a contributing factor, or all-cause death, or use of rescue-therapy for HK					
Secondary	Time to first occurrence of all-cause hospital admission, or ED visit with HK as a contributing factor, or all-cause death, or use of rescue therapy for HK, at any time post-discharge up to 180 days	FAS	Participants who discontinue treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Rescue therapy for HK will be considered an event (composite variable strategy). Participants who require ED visits without HK as a contributing factor will continue to be followed-up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause will be considered an event	Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value. Cox proportional hazards ratio for estimation with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and	4.2.3

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
			(composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).	two-sided 95% confidence interval will be presented.	
Objective 3: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of all-cause hospital admissions or ED visit with HK as a contributing factor					
Secondary	Time to first occurrence of all-cause hospital admission, or ED visit with HK as a contributing factor at any time post-discharge up to 180 days	FAS	Participants who discontinue treatment or who have ED visit without HK as a contributing factor will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause, use rescue therapy for HK or are lost to follow-up will be censored at the date of death, use of rescue therapy or loss to follow-up respectively. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite	Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value. Cox proportional hazards ratio for estimation with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence	4.2.4

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
			endpoint (treatment policy strategy).	interval will be presented.	
Objective 4: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the number of all-cause hospital admission or ED visits with HK as a contributing factor.					
Secondary	Number of all-cause hospital admission or ED visit with HK as a contributing factor, at any time post-discharge up to 180 days.	FAS	Participants who discontinue treatment, use rescue therapy for HK or who have an ED visit without HK as a contributing factor, will continue to be followed up for the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause or are lost to follow-up will be censored at the date of death or loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy)	Mean number of all-cause hospital admissions or ED visits, with HK as a contributing factor by randomised treatment group. Negative binomial regression model with randomised treatment group as the independent variable and including duration of time in study as an offset. The incidence rate (SZC/SoC), along with 95% confidence intervals and two-sided p-values will be displayed.	4.2.5
Objective 5: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, on reducing the risk of RAASi down-titration (or discontinuation).					
Secondary	Time to first occurrence of RAASi down-titration (or discontinuation) at any time post-discharge up to 180 days.	FAS	Participants who discontinue treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause or are lost to follow-up will	Log-rank test for testing, Cox proportional hazards ratio for estimation with randomised treatment group as the independent variable.	4.2.6

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
			be censored at their date of death or loss to follow-up respectively.		
Objective 6: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of hospital admissions or ED visits with HK as a contributing factor					
Secondary	Time to first occurrence of hospital admission or ED visit, both with HK as a contributing factor at any time post-discharge up to 180 days.	FAS	Participants who discontinue treatment or who have hospital admission or ED visit without HK as a contributing factor will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause, use rescue therapy for HK or are lost to follow-up will be censored at the date of death, use of rescue therapy or loss to follow-up respectively.	Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value. Cox proportional hazards ratio for estimation with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.	4.2.7
Objective 7: evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the number of hospital admissions or ED visits with HK as a contributing factor					
Secondary	Number of hospital admission or ED visits with HK as a contributing factor, at any	FAS	Participants who discontinue treatment, use rescue therapy for HK or who have a hospital admission, or an ED visit without HK as a contributing factor, will	Mean number of hospital admissions or ED visits, with HK as a contributing factor by randomised	4.2.8

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
	time post-discharge up to 180 days.		continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause or are lost to follow-up will be censored at the date of death or loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).	treatment group. Negative binomial regression model with randomised treatment group as the independent variable and including duration of time in study as an offset. The incidence rate (SZC/SoC), along with 95% confidence intervals and two-sided p-values will be displayed.	
Objective 8: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of the composite outcome of hospital admissions or ED visits with HK as a contributing factor or all-cause death.					
Exploratory	Time to first occurrence of any component of hospital admission or ED visit, both with HK as a contributing factor, or all-cause death at any time post-discharge up to 180 days.	FAS	Participants who discontinue treatment, use rescue therapy for HK, or require hospital admissions or ED visits without HK as a contributing factor will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who are lost to follow-up will be censored at their date of loss to follow-up. Participants who die of any cause will be considered an event (composite variable strategy). Participants who have RAASi down-titration (including discontinuation) will	Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value. Cox proportional hazards ratio for estimation with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be	4.2.9

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
			continue to be followed up to the first component of the composite endpoint (treatment policy strategy).	presented. The risk difference and two-sided 95% confidence interval will be presented.	
Objective 8: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of hospital admissions with HK as a contributing factor or all-cause death.					
Exploratory	Time to first occurrence of either hospital admission with HK as a contributing factor or all-cause death at any time post-discharge up to 180 days.	FAS	Participants who discontinue treatment, have an ED visit without hospital admission with HK as a contributing factor, hospital admission or ED visits without HK as a contributing factor or use rescue therapy for HK will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who die of any cause will be considered an event (composite variable strategy). Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).	Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.	4.2.10
Objective 9: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of ED visits with HK as a contributing factor or all-cause death					
Exploratory	Time to first occurrence of either ED visit with HK as a contributing	FAS	Participants who discontinue treatment will continue to be followed up to the first component of the	Kaplan-Meier plots of the survival function for the SZC and SoC treatment	4.2.11

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
	factor or all-cause death at any time post-discharge up to 180 days		composite endpoint (treatment policy strategy). Participants who require any hospital admission or ED visits without HK as a contributing factor or who use rescue therapy will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause will be considered an event (composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).	groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value. Cox proportional hazards ratio for estimation with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.	
Objective 10: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of the composite outcome of all-cause hospitalisations, ED visits, all-cause death or use of rescue therapy for HK					
Exploratory	Time to first occurrence of any component of all-cause hospitalisations, ED visits, use of rescue therapy for HK or all-	FAS	Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Rescue therapy for HK will be considered an event	Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a	4.2.12

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
	cause death in each arm at any time post-discharge up to 180 days		(composite variable strategy). Participants who require any hospital admission or ED visit will be considered an event (composite variable strategy). Participants who die of any cause will be considered an event (composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).	two-sided p-value. Cox proportional hazards ratio for estimation with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.	
Objective 11: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, on mean K+ levels					
Exploratory	K+ level up to 180 days post-discharge	FAS	K+ levels from participants after discontinuation of treatment, hospital admissions or ED visits for any reason will be included in the analysis (treatment policy strategy). Participants who use rescue therapy for HK will have K+ levels prior to rescue therapy for HK used in the analysis (while on treatment strategy). Participants who have RAASi down-titration	Mixed model repeated measures analysis with randomised treatment group as an independent variable. The coefficient estimates, standard error, 95% confidence intervals for coefficient estimate, and p-values will be reported.	4.2.13

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
			(including discontinuation) will have K+ levels prior to the RAASi down-titration used in the analysis (while on treatment strategy). Participants who die of any cause or who are lost to follow-up prior to 180 days post-discharge will have all available K+ included in the analysis (treatment policy strategy).		
Objective 12: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the number of hospital admissions with HK as a contributing factor					
Exploratory	Number of hospital admissions with HK as a contributing factor, at any time post-discharge up to 180 days.	FAS	Participants who discontinue treatment, use rescue therapy for HK, have RAASi down-titration (including discontinuation), experience all-cause death or loss to follow-up prior to 180 days post-discharge will have all available hospital admission data used irrespective of the intercurrent event (treatment policy strategy).	Mean number of hospital admissions with HK as a contributing factor, by randomised treatment group. Negative binomial regression model with randomised treatment group as a main effect and including duration of time in study as an offset. The incidence rate ratio (SZC/SoC), along with 95% confidence intervals and two-sided p-values will be displayed.	4.2.14

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 13: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SOC, in reducing the total LOS in hospitalisations with HK as a contributing factor.					
Exploratory	Total LOS for hospitalisations (including multiple hospitalisations) with HK as a contributing factor in each arm at any time post-discharge up to 180 days.	FAS	Participants who discontinue treatment, use rescue therapy for HK, experience all-cause death, or loss to follow-up prior to 180 days post-discharge will have all available hospital admission data used irrespective of the intercurrent event (treatment policy strategy).	Continuous variable summary (mean and median) of total LOS with HK as a contributing factor, by randomised treatment group. A Wilcoxon rank-sum test by randomised treatment group will be used to calculate a two-sided p-value.	4.2.15
Objective 14: To evaluate the effect of continuing SZC, as part of the discharge medications, compared to SoC, in reducing the total LOS in all-cause hospitalisations					
Exploratory	Total LOS for all-cause hospitalisations (including multiple hospitalisations) in each arm at any time post-discharge up to 180 days.	FAS	Participants who discontinue treatment, use rescue therapy for HK, experience all-cause death, or loss to follow-up prior to 180 days post-discharge will have all available hospital admission data used irrespective of the intercurrent event (treatment policy strategy).	Continuous variable summary (mean and median) of total LOS of all-cause hospitalisation, by randomised treatment group. A Wilcoxon rank-sum test by randomised treatment group will be used to calculate a two-sided p-value.	4.2.16
Objective 15: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of K-binder use.					
Exploratory	Time to first use of K-binder to treat	FAS	Participants who discontinue treatment will continue to be	Kaplan-Meier plots of the survival function	4.2.17

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
	HK any time post-discharge up to 180 days.		followed up to the first use of K-binder to treat HK (treatment policy strategy). Participants who require any hospital admission or ED visits will continue to be followed up to the first use of K-binder to treat HK (treatment policy strategy). Participants who die of any cause will be censored at the date of death. Participants who are lost to follow-up will be censored at the date of loss to follow-up.	for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.	
Objective 16: To evaluate the effect of continuing SZC, as part of discharge medications, compared to SoC in reducing the frequency of K-binder use					
Exploratory	Frequency of the use of K-binder to treat HK as any time post-discharge up to 180 days in each arm.	FAS	Participants who discontinue treatment, use rescue therapy for HK, experience all-cause death, or loss to follow-up prior to 180 days post-discharge will have all K-binder use used irrespective of the intercurrent event (treatment policy strategy).	Mean number of uses of K-binder, by randomised treatment group. Negative binomial regression model with randomised treatment group as a main effect and including duration of time in study as an offset. The incidence rate ratio (SZC/SoC), along with 95% confidence intervals and two-	4.2.18

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
				sided p-values will be displayed.	
Objective 17: To evaluate the effect of continuing SZC, as part of the discharge medications, compared to SoC in reducing the duration of K-binder use.					
Exploratory	Time to discontinuation of K-binders from initiation in the first instance of K-binder use post-discharge up to 180 days in each arm.	Subset of FAS who require use of K-binders	Participants who discontinue treatment will continue to be followed up till discontinuation of K-binder (treatment policy strategy). Participants who require any hospital admission or ED visits will continue to be followed up to discontinuation of K-binder (treatment policy strategy). Participants who die of any cause will be considered to have ended K-binder use. Participants who are lost to follow-up will be will be considered to have ended K-binder use.	Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.	4.2.19
Objective 18: To evaluate the effect of continuing SZC, as part of the discharge medications, compared to SoC, in reducing the incidence of rescue therapy for HK use.					
Exploratory	Time to first occurrence of rescue therapy use in each arm any time post-discharge	FAS	Participants who discontinue treatment will continue to be followed up to the first use of rescue therapy to treat HK (treatment policy strategy). Participants who require	Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for	4.2.20

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
	up to 180 days.		any hospital admission or ED visits will continue to be followed up to the first use rescue therapy to treat HK (treatment policy strategy). Participants who die of any cause will be censored at the date of death. Participants who are lost to follow-up will be censored at the date of loss to follow-up.	testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.	
Objective 19: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of the composite outcome of all-cause hospitalisations, ED visits or outpatient visits.					
Exploratory	Time to first occurrence of all-cause hospitalisations, ED visits or outpatient visits in each arm at any time post-discharge up to 180 days.	FAS	Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who require rescue therapy for HK will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who require any hospital admission or ED visit will be considered an event (composite variable strategy). Participants	Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be	4.2.21

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
			who die of any cause will be censored at the date of death. Participants who are lost to follow-up will be censored at the date of loss to follow-up.	presented. The risk difference and two-sided 95% confidence interval will be presented.	
Objective 20: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in the change in eGFR.					
Exploratory	Rate of change in (slope) eGFR from inpatient phase to 90 and 180 days post-discharge respectively, in each arm.	FAS	Participants who discontinue of treatment will have all available eGFR measurements included (treatment policy strategy). Participants who require rescue therapy for HK will have all available eGFR measurements included (treatment policy strategy). Participants who require any hospital admission or ED visit will have all available eGFR measurements included (treatment policy strategy). Participants who die of any cause or are lost to follow-up will have all measurements up to death or loss to follow-up included (hypothetical strategy).	Change in eGFR will be analysed with a MMRM approach where the dependent variable is post randomisation eGFR and with fixed terms for randomised treatment group, eGFR at randomisation, participant recruitment country, time from randomisation (days), and the interaction of treatment group by time from randomisation with random effects for participant, intercept and slope. The covariance structure will be unstructured. The coefficient estimates, standard error, 95% CI for coefficient estimates, and p-	4.2.20

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
				values will be reported.	
Objective 21: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in the incidence of dialysis initiation.					
Exploratory	Time to first occurrence of dialysis initiation in each arm at any time post-discharge up to 180 days.	FAS	Participants who discontinue of treatment will continue to be followed up to the first use of dialysis post-discharge (treatment policy strategy). Participants who require rescue therapy for HK will continue to be followed up to the first use of dialysis post-discharge (treatment policy strategy). Participants who require any hospital admission or ED visit will continue to be followed up to the first use of dialysis post-discharge (treatment policy strategy). Participants who die of any cause will be censored at the date of death. Participants who are lost to follow-up will be censored at the date of loss to follow-up.	Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.	4.2.21
Objective 22: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of ICU admissions.					
Exploratory	Time to first occurrence of ICU admission in each arm at any time post-	FAS	Participants who discontinue of treatment will continue to be followed up to the first ICU admission post-discharge (treatment policy strategy).	Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-	4.2.24

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
	discharge up to 180 days.		Participants who require rescue therapy for HK will continue to be followed up to the first ICU admission post-discharge (treatment policy strategy). Participants who require any hospital admission or ED visit will continue to be followed up to the first ICU admission post-discharge (treatment policy strategy). Participants who die of any cause will be censored at the date of death. Participants who are lost to follow-up will be censored at the date of loss to follow-up.	rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.	
Objective 23: To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, on the ability to continue RAASi.					
Exploratory	Descriptive summary of use of, and changes in use of, RAASi at up to 90 and 180 days post-discharge, respectively, in each arm.	FAS	Participants who discontinue treatment, use rescue therapy for HK or require either hospitalisation or ED visits will have all available RAASi use data used irrespective of the intercurrent event (treatment policy strategy). Participants who experience all-cause death, or loss to follow-up prior to days 90 and 180 respectively will be excluded from the numerator and denominator of the	Number and proportion of participants requiring RAASi at visit 7 and visit 10 by treatment arm	4.2.25

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
			analysis (while on treatment strategy).		

4.2.2 Primary Endpoint (Normokalemia)

Occurrence (yes/no) of normokalaemia (NK) (K^+ between 3.5 and 5.0 mmol/L, inclusive) at 180 days post-discharge

4.2.2.1 Definition

Primary estimand definition:

- Population: Full analysis set
- Endpoint: Occurrence (yes/no) of NK at 180 days post-discharge
- Intercurrent event strategy: Participants who discontinue treatment with a K^+ measurement at 180 days post-discharge will have this value used irrespective of treatment discontinuation (treatment policy strategy). Use of rescue therapy for HK will be considered to be non-response (composite variable strategy). RAASi down-titration (including discontinuation) will be considered to be non-response (composite variable strategy). Participants who die of any cause prior to 180 days post-discharge, or who are lost to follow-up for any reason will be considered to be non-response (composite variable strategy).
- Population level summary (analysis): Logistic regression analysis with response (occurrence) as the dependent variable and randomised treatment group (reference level SoC) and participant recruitment country as the independent variables. The odds ratio along with the two-sided 95% confidence intervals and two-sided p-value (significance declared < 0.05) will be displayed.

4.2.2.2 Derivations

NK will be a binary variable, derived as a K^+ value between 3.5 and 5.0 mmol/L, inclusive classified as yes and K^+ value<3.5 or K^+ value>5.0 mmol/L classified as no.

4.2.2.3 Handling of Dropouts and Missing Data

Participants who die prior to 180 days post-discharge, who are missing an assessment at visit 10 or who are lost to follow-up for any reason will be considered to be non-response for the primary analysis.

4.2.2.4 Primary Analysis of Primary Endpoint

Occurrence (yes/no) will be compared between treatment groups in the FAS using a logistic regression model including response as the dependent variable and randomised treatment (reference level SoC) and participant recruitment country as an independent variable, and

will be tested using a two-sided alpha = 0.05. For participants who are assigned a non-response value, a sub table will be provided to summarize the intercurrent events, which led to this assignment, by treatment group. The common odds ratio will be derived together with the two-sided 95% confidence interval.

4.2.2.5 Sensitivity Analyses of the Primary Endpoint

The analyses of the primary endpoint will be repeated as per section 4.2.2.4 but with alternative modelling:

- Population level summary (analysis): Providing there are sufficient participants within each covariate to support the analysis, the logistic regression model will include randomised treatment group and the following baseline variables: age (as a cubic spline), sex (male/female), participant recruitment country, presence of heart failure (yes/no), diabetes (yes/no), RAASi use (yes/no), CKD stage and baseline K^+ ($5.0 < K^+ \leq 5.5$ versus $5.5 < K^+ \leq 6.5$ mmol/L) as independent variables. Sufficient participants for a covariate to be included will be considered if there are more than 10 participants with an event in each level of the covariate.

The analyses of the primary endpoint will be repeated as per section 4.2.2.4 but the estimand will be varied:

- Intercurrent event strategy: As primary estimand, but participants needing rescue therapy for HK will follow the treatment policy strategy (i.e., regardless of the intercurrent event).
- Intercurrent event strategy: As primary estimand, participants with RAASi down-titration (including discontinuation) will follow the treatment policy strategy (e.g. regardless of the intercurrent event).
- Intercurrent event strategy: As primary estimand, but participants who die or are lost to follow-up prior to 180 days post-discharge will not be evaluated (completers analysis only).
- Hypothetical strategy: As primary estimand, but participants who are lost to follow-up after 90 days (visit 7) or who are missing K^+ status at 180 days will have their K^+ status at 90 days, if available, carried forward to 180 days and included in the analysis using the principle of last observation carried forward.
- COVID-19 supplementary analysis: Intercurrent events not related to COVID-19 will be treated as per section 4.2.2.4. Participants who discontinue treatment due to COVID-19 will be treated as missing (hypothetical strategy). Use of rescue therapy for HK due to COVID-19 will be considered to be non-response (composite variable strategy). RAASi down-titration due to COVID-19 (including discontinuation) will be considered to be non-response (composite variable strategy). Participants who die due to COVID-19 will be treated as missing (hypothetical strategy).

- Alternative population: As primary estimand, but the per protocol set (PPS) will be used as the population for analysis. Payer relevant sensitivity analysis: An alternative definition of normokalaemia will be applied where NK will be a binary variable, derived as a K^+ value between 3.5 and 5.5 mmol/L, inclusive classified as yes and K^+ value<3.5 or K^+ value>5.5 mmol/L classified as no. Analysis will be conducted as per section 4.2.2.4.
- No visit windowing: As primary estimand but all K+ measurements recorded in EDC as a visit 10 study visit while the participant remains on SZC will be used in analysis. No visit windowing (Section 3.3.2) will be applied.

4.2.2.6 Subgroup Analyses

Subgroup analyses will be performed using separate logistic regression models, as per section 4.2.2.4, by age (18-64, 65-84 and ≥85 years), sex (female, male), recruitment country (France, Italy, Spain, UK, Belgium and Netherlands), presence of heart failure (Yes/No, identified per Medical History using an SMQ of "Cardiac Failure"; SMQ Code: 20000004), diabetes (Yes/No, identified per Medical History eCRF using a PT of "Type 2 diabetes mellitus"), RAASi use at screening (Yes/No, identified per Concomitant Medication eCRF as CMCLASCD in ('C09AA', 'C09BA', 'C09BB', 'C09BX', 'C09CA', 'C09DA', 'C09DB', 'C09DX', 'C09XA') where Start Date is prior to date of informed consent), CKD stage, without diagnosis of CKD (but eGFR <90 ml/min/1.73m^2), baseline K^+ ($5.0 < K^+ \leq 5.5$ versus $5.5 < K^+ \leq 6.5$ mmol/L) at baseline, an alternative baseline K^+ categorisation ($5.0 < K+ \leq 5.5$, $5.5 < K+ \leq 6.0$, and $6.0 < K+ \leq 6.5$ mmol/L) and by duration of index hospitalisation (<7 days versus ≥7 days). Subgroup analyses will only be conducted providing there are 10 or more events per subgroup category.

4.2.3 Secondary Endpoint #1 (All-cause hospital admission, ED visit with HK, all-cause death, rescue therapy for HK)

Time to first occurrence of any component of all-cause hospital admission or ED visits with HK as a contributing factor, or all-cause death, or use of rescue therapy for HK at any time post-discharge up to 180 days.

4.2.3.1 Definition

- Population: Full analysis set
- Endpoint: Time to first occurrence of either component of the composite outcome at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Rescue therapy for HK will be considered an event (composite variable strategy). Participants who require ED visits without HK as a contributing factor will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause will be considered an event

(composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).

- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group (reference level SoC) as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The Risk Difference (RD) and two-sided 95% confidence interval will be presented at 180 days post-discharge.

4.2.3.2 Derivations

Time to first occurrence will be defined as the earliest date of (all-cause hospital admission, ED visits with HK as a contributing factor, all-cause death, use of rescue therapy for HK, date of loss to follow-up, date of 180 days post-discharge) – date of randomization + 1.

Risk Difference (RD) is calculated using the Austin method (Austin et al; 2010). First, the predicted probability of survival for each participant at 180 days post-discharge is calculated assuming that all participants do not receive SZC (Cmean). Second, the predicted probability of survival for each participant at 180 days post-discharge is calculated assuming that all participants receive SZC (Tmean). The RD is calculated as Tmean-Cmean. The 95% confidence interval will be calculated by taking the 2.5^{th} and 97.5^{th} percentiles of RDs across 1000 bootstrap samples where each bootstrap sample is drawn randomly with replacement from the original sample, such that the new sample is of the same size as the original sample.

4.2.3.3 Handling of Dropouts and Missing Data

Participants who are lost to follow-up will be censored at the date of discontinuation as recorded on the participant's disposition form.

4.2.3.4 Primary Analysis of Secondary Endpoint #1

The primary analysis for the main secondary endpoint will be conducted using a log-rank test by treatment group in the FAS to calculate a two-sided p-value. A Cox proportional hazards model will be used in the FAS for estimation with randomised treatment group (reference level SoC) and subject recruitment country as the independent variables. Kaplan-Meier survival curves (product-limit estimates) of time to first event will be presented by treatment group, together with a summary of associated statistics (median time to failure and 95% CI). The proportion of participants event free at 90 day intervals (90, 180) will be summarised by treatment group. The summary at 90 days will be descriptive as the primary analysis is focused on 180 days. The median (range) duration of follow-up in censored participants will also be calculated.

To assess for the proportionality of hazards the log(-log(estimated survival function)) will be plotted compared to log(days) for each randomised treatment group and visually inspected to determine if the curves are approximately parallel. To assess for the impact of censoring, and the duration of follow-up, a reverse Kaplan-Meier figure will be produced where the status indicators are reversed such that the censor becomes the event and the composite event of interest as the censor. These will be presented by randomised treatment group, together with a summary of associated statistics (median time and associated 95% Cis).

4.2.3.5 Sensitivity Analyses of the Secondary Endpoint #1

Providing there are sufficient events within each covariate (> 10 events) to support the analysis, the analyses of time-to-event secondary endpoints will be repeated in the FAS using an alternative population level summary where the Cox proportional hazards model will include randomised treatment group and the following baseline variables: age (as a cubic spline), sex (female, male), participant recruitment country, presence of heart failure (yes/no), diabetes (yes/no), RAASi use (yes/no), CKD stage and baseline K^+ ($5.0 < K^+ \leq 5.5$ versus $5.5 < K^+ \leq 6.5$ mmol/L) as independent variables.

Additionally, the analysis will be repeated with the PPS analysis population.

Furthermore, a supplementary analysis will be conducted where participants who down-titrate (or discontinue) RAASi will be censored at the date of down-titration.

An additional sensitivity analysis will be conducted where participants who are lost to follow-up will be accounted for using an inverse probability weighting (IPW) approach where similar participants who were not lost to follow-up will be re-weighted (hypothetical strategy). First, a logistic regression model will be performed where the dependent variable is a binary indicator variable where 1 indicates not lost to follow-up and 0 indicates lost to follow-up. Randomised treatment group and the following baseline variables: age (as a cubic spline), sex, participant recruitment country, presence of heart failure, diabetes, RAASi use, CKD stage and baseline K^+ ($5.0 < K^+ \leq 5.5$ versus $5.5 < K^+ \leq 6.5$ mmol/L) will be included as independent variables. The predicted values from this model will be calculated and the reciprocal of these will be the IPW. The Cox proportional hazards model will then be conducted on participants not lost to follow-up, following the intercurrent event strategy in section 4.2.3.1, where participants will be reweighted using the IPW.

4.2.3.6 Supplementary Analyses of the Secondary Endpoint #1

Not Applicable.

4.2.3.7 Subgroup Analyses

Subgroup analyses will be performed using separate Cox models, as per section 4.2.3.4, by age (18-64, 65-84 and over 85 years), sex (female, male), recruitment country (France,

Italy, Spain, UK, Belgium and Netherlands), presence of heart failure (Yes/No, identified per Medical History using an SMQ of "Cardiac Failure"; SMQ Code: 20000004), diabetes (Yes/No, identified per Medical History eCRF using a PT of "Type 2 diabetes mellitus"), RAASi use at screening (Yes/No, identified per Concomitant Medication eCRF as CMCLASCD in ('C09AA', 'C09BA', 'C09BB', 'C09BX', 'C09CA', 'C09DA', 'C09DB', 'C09DX', 'C09XA') where Start Date is prior to date of informed consent), CKD stage, without diagnosis of CKD (but eGFR <90 ml/min/1.73m^2), baseline K^+ ($5.0 < K^+ \leq 5.5$ versus $5.5 < K^+ \leq 6.5$ mmol/L), an alternative baseline K^+ categorisation ($5.0 < K+ \leq 5.5$, $5.5 < K+ \leq 6.0$, and $6.0 < K+ \leq 6.5$ mmol/L) and by duration of index hospitalisation (<7 days versus ≥7 days hospitalisation during the inpatient phase). Subgroup analyses will only be conducted providing there are 10 or more events per subgroup category.

4.2.4 Secondary Endpoint #2 (All-cause Hospital admission or ED visit with HK)

Time to first occurrence of any component of all-cause hospital admission or ED visit with HK as a contributing factor at any time post-discharge up to 180 days.

4.2.4.1 Definition

- Population: Full analysis set
- Endpoint: Time to first occurrence of either component of the composite outcome at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue treatment or who have ED visit without HK as a contributing factor will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause, use rescue therapy for HK or are lost to follow-up will be censored at the date of death, use of rescue therapy or loss to follow-up respectively. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who do not have an event by 180 days post-discharge will be administratively censored at the date of 180 days post-discharge.
- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group (reference level SoC) as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented (as per section 4.2.3.2) at 180 days post-discharge.

4.2.4.2 Derivations

Time to first occurrence will be defined as the earliest date of (all-cause hospital admission, ED visits with HK as a contributing factor, all-cause death, use of rescue therapy for HK, date of loss to follow-up, date of 180 days post-discharge) – date of randomization + 1.

4.2.4.3 Handling of Dropouts and Missing Data

Participants who are lost to follow-up will be censored at the date of discontinuation as recorded on the participant's disposition form.

4.2.4.4 Primary Analysis of Secondary Endpoint #2

The primary analysis of this secondary endpoint will be performed as per section 4.2.3.4.

4.2.4.5 Sensitivity Analyses of the Secondary Endpoint #2

Sensitivity analyses of this secondary endpoint will be performed as per section 4.2.3.5.

4.2.4.6 Supplementary Analyses of the Secondary Endpoint #2

Not Applicable.

4.2.4.7 Subgroup Analyses

Subgroup analyses will be performed using separate Cox models, as per section 4.2.3.4, by presence of heart failure (Yes/No, identified per Medical History using an SMQ of "Cardiac Failure"; SMQ Code: 20000004), RAASi use at screening (Yes/No, identified per Concomitant Medication eCRF as CMCLASCD in ('C09AA', 'C09BA', 'C09BB', 'C09BX', 'C09CA', 'C09DA', 'C09DB', 'C09DX', 'C09XA') where Start Date is prior to date of informed consent), CKD stage, without diagnosis of CKD (but eGFR <90), baseline K^+ ($5.0 < K^+ \leq 5.5$ versus $5.5 < K^+ \leq 6.5$ mmol/L) and an alternative baseline K^+ categorisation ($5.0 < K+ \leq 5.5$, $5.5 < K+ \leq 6.0$, and $6.0 < K+ \leq 6.5$ mmol/L) at baseline. Subgroup analyses will only be conducted providing there are 10 or more events per subgroup category.

4.2.5 Secondary Endpoint #3 (Number of all-cause hospital admissions or ED visits with HK)

Number of all-cause hospital admissions or ED visits with HK as a contributing factor, at any time post-discharge up to 180 days.

4.2.5.1 Definition

- Population: Full analysis set
- Endpoint: Number of all-cause hospital admissions or ED visits with HK as a contributing factor at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue treatment, use rescue therapy for HK or who have an ED visit without HK as a contributing factor, will continue to be followed up to the first component of the composite endpoint (treatment policy

strategy). Participants who die of any cause or are lost to follow-up will be censored at the date of death or loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).

- Population level summary (analysis): Mean number of all-cause hospital admissions or ED visits, with HK as a contributing factor by randomised treatment group. Negative binomial regression model with randomised treatment group as the independent variable and including duration of time in study as an offset. The incidence rate (SZC/SoC), along with 95% confidence intervals and two-sided p-values will be displayed.

4.2.5.2 Derivations

For each participant the total number of separate all-cause hospital admissions or ED visits with HK as a contributing factor up to 180 days will be calculated. Hospital admissions and ED visits will be calculated as separate admissions if start and stop dates of admission do not overlap. If hospital admissions or ED visits are missing a start, stop date or both then they will be calculated as separate admissions. Hospital admissions or ED visits started after 180 days will not be counted.

4.2.5.3 Handling of Dropouts and Missing Data

All available data on hospital admissions and ED visits are to be used irrespective of intercurrent events. For the primary analysis, no adjustment is made for dropout but the sensitivity of the results to this approach are investigated using a sensitivity analysis in section 4.2.5.5.

4.2.5.4 Primary Analysis of Secondary Endpoint #3

A descriptive summary (Mean, SD, Median, Range) of the number of all-cause hospital admissions or ED visits with HK as a contributing factor will be presented by randomised treatment group in the FAS. A negative binomial regression model will be conducted with the number of all-cause hospital admissions or ED visits with HK as a contributing factor as the dependent variable and randomised treatment group (reference level SoC) as the independent variable. The duration of time per participant in study is calculated until the earliest of loss to follow-up or 180 days post-discharge and will be included in the model as an offset term. The incidence rate ratio (SZC/SoC), along with 95% CIs and two-sided p-values will be displayed.

4.2.5.5 Sensitivity Analyses of the Secondary Endpoint #3

Three sensitivity analyses will be conducted for this secondary endpoint:

- Providing there are sufficient participants within each covariate to support the analysis, an alternative population level summary using the FAS population where the negative binomial regression model will include randomised treatment group, duration of time in study as an offset and the following baseline variables: age (as a cubic spline), sex, participant recruitment country, presence of heart failure, diabetes, RAASi use, CKD

stage, and baseline K^+ ($5.0 < K^+ \leq 5.5$ versus $5.5 < K^+ \leq 6.5$ mmol/L) as independent variables. Baseline variables will be defined as described in section 4.2.2.6.

- A sensitivity analysis will be conducted using the mean cumulative count method (MCC) (Austin et al, 2010) if a greater than 10% difference by treatment arm in the proportion who are lost to follow-up is observed. The MCC method reflects a summarisation of all events that occur in a population by a given time. The recurring event in this analysis will be hospital admission with HK as a contributing factor. The MCC will be performed by randomised treatment group in the FAS and an estimate (95% CI) of the MCC at 90 and 180 days post discharge will be presented. A figure of the MCC by randomised treatment group with 95% CI will also be displayed. SAS Code to conduct an MCC analysis is described in sections 7.1 and 7.2.
- Alternative population: As primary estimand, but the per protocol set (PPS) will be used as the population for analysis.

4.2.5.6 Supplementary Analyses of the Secondary Endpoint #3

Not Applicable.

4.2.5.7 Subgroup Analyses

Subgroup analyses will be performed using separate negative binomial regression models, as per section 4.2.5.4, by presence of heart failure (Yes/No, identified per Medical History using an SMQ of "Cardiac Failure"; SMQ Code: 20000004), RAASi use at screening (Yes/No, identified per Concomitant Medication eCRF as CMCLASCD in ('C09AA', 'C09BA', 'C09BB', 'C09BX', 'C09CA', 'C09DA', 'C09DB', 'C09DX', 'C09XA') where Start Date is prior to date of informed consent), CKD stage, without diagnosis of CKD (but eGFR <90 ml/min/1.73m^2), baseline K^+ ($5.0 < K^+ \leq 5.5$ versus $5.5 < K^+ \leq 6.5$ mmol/L) at baseline and an alternative baseline K^+ categorisation ($5.0 < K+ \leq 5.5$, $5.5 < K+ \leq 6.0$, and $6.0 < K+ \leq 6.5$ mmol/L) at baseline. Subgroup analyses will only be conducted providing there are 10 or more events per subgroup category.

4.2.6 Secondary Endpoint #4 (RAASi down-titration)

Time to first occurrence of RAASi down-titration (or discontinuation) at any time post-discharge up to 180 days

4.2.6.1 Definition

- Population: Full analysis set
- Endpoint: Time to first occurrence of RAASi down-titration (or discontinuation) at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause or are lost to follow-up will be censored at their date of death or loss to follow-up respectively. Participants who do not have an

event by 180 days post-discharge will be administratively censored at the date of 180 days post-discharge.

- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group (reference level SoC) as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented (as per section 4.2.3.2) at 180 days post-discharge.

4.2.6.2 Derivations

Time to first occurrence will be defined as the earliest date of (date of RAASi down-titration (or discontinuation), all-cause death, date of loss to follow-up, date of 180 days post-discharge) – date of randomization + 1.

4.2.6.3 Handling of Dropouts and Missing Data

Participants who are lost to follow-up will be censored at the date of discontinuation as recorded on the participant's disposition form.

4.2.6.4 Primary Analysis of Secondary Endpoint #4

The primary analysis of this secondary endpoint will be performed as per section 4.2.3.4.

4.2.6.5 Sensitivity Analyses of the Secondary Endpoint #4

Sensitivity analyses of this secondary endpoint will be performed as per section 4.2.3.5 excluding the sensitivity analysis for RAASi down-titration.

4.2.6.6 Supplementary Analyses of the Secondary Endpoint #4

Not Applicable.

4.2.6.7 Subgroup Analyses

Subgroup analyses will be performed using separate Cox models, as per section 4.2.3.4, by presence of heart failure (Yes/No, identified per Medical History using an SMQ of "Cardiac Failure"; SMQ Code: 20000004), RAASi use at screening (Yes/No, identified per Concomitant Medication eCRF as CMCLASCD in ('C09AA', 'C09BA', 'C09BB', 'C09BX', 'C09CA', 'C09DA', 'C09DB', 'C09DX', 'C09XA') where Start Date is prior to date of informed consent), CKD stage, without diagnosis of CKD (but eGFR <90 ml/min/1.73m^2), baseline K^+ ($5.0 < K^+ \leq 5.5$ versus $5.5 < K^+ \leq 6.5$ mmol/L) at baseline and an alternative baseline K^+ categorisation ($5.0 < K+ \leq 5.5$, $5.5 < K+ \leq 6.0$, and $6.0 < K+ \leq 6.5$ mmol/L) at baseline. Subgroup analyses will only be conducted providing there are 10 or more events per subgroup category.

4.2.7 Secondary Endpoint #5 (Hospital admission or ED visit with HK)

Time to first occurrence of any component of all-cause hospital admission or ED visit with HK as a contributing factor at any time post-discharge up to 180 days.

4.2.7.1 Definition

- Population: Full analysis set
- Endpoint: Time to first occurrence of either component of the composite outcome at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue treatment or who have hospital admission or ED visit without HK as a contributing factor will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause, use rescue therapy for HK or are lost to follow-up will be censored at the date of death, use of rescue therapy or loss to follow-up respectively. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who do not have an event by 180 days post-discharge will be administratively censored at the date of 180 days post-discharge.
- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group (reference level SoC) as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented (as per section 4.2.3.2) at 180 days post-discharge.

4.2.7.2 Derivations

Time to first occurrence will be defined as the earliest date of (all-cause hospital admission or ED visit with HK as a contributing factor, all-cause death, use of rescue therapy for HK, date of loss to follow-up, date of 180 days post-discharge) – date of randomization + 1.

4.2.7.3 Handling of Dropouts and Missing Data

Participants who are lost to follow-up will be censored at the date of discontinuation as recorded on the participant's disposition form.

4.2.7.4 Primary Analysis of Secondary Endpoint #5

The primary analysis of this secondary endpoint will be performed as per section 4.2.3.4.

4.2.7.5 Sensitivity Analyses of the Secondary Endpoint #5

Sensitivity analyses of this secondary endpoint will be performed as per section 4.2.3.5.

4.2.7.6 Supplementary Analyses of the Secondary Endpoint #5

Not Applicable.

4.2.7.7 Subgroup Analyses

Subgroup analyses will be performed using separate Cox models, as per section 4.2.3.4, by presence of heart failure (Yes/No, identified per Medical History using an SMQ of "Cardiac Failure"; SMQ Code: 20000004), RAASi use at screening (Yes/No, identified per Concomitant Medication eCRF as CMCLASCD in ('C09AA', 'C09BA', 'C09BB', 'C09BX', 'C09CA', 'C09DA', 'C09DB', 'C09DX', 'C09XA') where Start Date is prior to date of informed consent), CKD stage, without diagnosis of CKD (but eGFR <90 ml/min/1.73m^2), baseline K+ ($5.0 < K+ \leq 5.5$ versus $5.5 < K+ \leq 6.5$ mmol/L) and an alternative baseline K+ categorisation ($5.0 < K+ \leq 5.5$, $5.5 < K+ \leq 6.0$, and $6.0 < K+ \leq 6.5$ mmol/L) at baseline. Subgroup analyses will only be conducted providing there are 10 or more events per subgroup category.

4.2.8 Secondary Endpoint #6 (Number of hospital admissions or ED visits with HK)

Number of hospital admissions or ED visits with HK as a contributing factor, at any time post-discharge up to 180 days.

4.2.8.1 Definition

- Population: Full analysis set
- Endpoint: Number of hospital admissions or ED visits with HK as a contributing factor at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue treatment, use rescue therapy for HK or who have a hospital admission or an ED visit without HK as a contributing factor, will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause or are lost to follow-up will be censored at the date of death or loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).
- Population level summary (analysis): Mean number of hospital admissions or ED visits, with HK as a contributing factor by randomised treatment group. Negative binomial regression model with randomised treatment group as the independent variable and including duration of time in study as an offset. The incidence rate (SZC/SoC), along with 95% confidence intervals and two-sided p-values will be displayed.

4.2.8.2 Derivations

For each participant the total number of separate hospital admissions or ED visits with HK as a contributing factor up to 180 days will be calculated. Hospital admissions and ED visits will be calculated as separate admissions if start and stop dates of admission do not overlap. If hospital admissions or ED visits are missing a start, stop date or both then they

will be calculated as separate admissions. Hospital admissions or ED visits started after 180 days will not be counted.

4.2.8.3 Handling of Dropouts and Missing Data

All available data on hospital admissions and ED visits are to be used irrespective of intercurrent events. For the primary analysis, no adjustment is made for dropout but the sensitivity of the results to this approach are investigated using a sensitivity analysis in section 4.2.5.5.

4.2.8.4 Primary Analysis of Secondary Endpoint #6

The primary analysis of this secondary endpoint will be performed as per section 4.2.5.4.

4.2.8.5 Sensitivity Analyses of the Secondary Endpoint #6

Sensitivity analyses of this secondary endpoint will be performed as per section 4.2.5.5.

4.2.8.6 Supplementary Analyses of the Secondary Endpoint #6

Not Applicable.

4.2.8.7 Subgroup Analyses

Subgroup analyses will be performed using separate negative binomial regression models, as per section 4.2.5.4, by presence of heart failure (Yes/No, identified per Medical History using an SMQ of "Cardiac Failure"; SMQ Code: 20000004), RAASi use at screening (Yes/No, identified per Concomitant Medication eCRF as CMCLASCD in ('C09AA', 'C09BA', 'C09BB', 'C09BX', 'C09CA', 'C09DA', 'C09DB', 'C09DX', 'C09XA') where Start Date is prior to date of informed consent), CKD stage, without diagnosis of CKD (but eGFR <90 ml/min/1.73m^2), baseline K^+ ($5.0 < K^+ \leq 5.5$ versus $5.5 < K^+ \leq 6.5$ mmol/L) at baseline and an alternative baseline K^+ categorisation ($5.0 < K+ \leq 5.5$, $5.5 < K+ \leq 6.0$, and $6.0 < K+ \leq 6.5$ mmol/L) at baseline. Subgroup analyses will only be conducted providing there are 10 or more events per subgroup category.

4.2.9 Exploratory Endpoint #1 (Hospital admission/ED visit with HK, all-cause death)

Time to first occurrence of any component of hospital admission or ED visit, both with HK as a contributing factor, or all-cause death at any time post-discharge up to 180 days inclusive.

4.2.9.1 Definition

- Population: Full analysis set
- Endpoint: Time to first occurrence of either component of the composite outcome at any time post-discharge up to 180 days inclusive.
- Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy

strategy). Participants who require hospital admission or ED visits without HK as a contributing factor or use rescue therapy will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause will be considered an event (composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint. Participants who do not have an event by 180 days post-discharge will be administratively censored at the date of 180 days post-discharge.

- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group (reference level SoC) as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented (as per section 4.2.3.2) at 180 days post-discharge.

4.2.9.2 Derivations

Time to first occurrence will be defined as the earliest date of (hospital admission or ED visits with HK as a contributing factor, all-cause death, date of loss to follow-up, date of 180 days post-discharge) – date of randomization + 1.

4.2.9.3 Handling of Dropouts and Missing Data

Participants who are lost to follow-up will be censored at the date of discontinuation as recorded on the participant's disposition form.

4.2.9.4 Primary Analysis of Exploratory Endpoint #1

The primary analysis of this exploratory endpoint will be performed as per section 4.2.3.4.

4.2.9.5 Sensitivity Analyses of Exploratory Endpoint #1

Sensitivity analyses of this exploratory endpoint will be performed as per section 4.2.3.5.

4.2.9.6 Supplementary Analyses of Exploratory Endpoint #1

Not Applicable.

4.2.9.7 Subgroup Analyses

Not Applicable.

4.2.10 Exploratory Endpoint #2 (Hospital admission with HK, all-cause death)

Time to first occurrence of either hospital admission with HK as a contributing factor or all-cause death at any time post-discharge up to 180 days inclusive.

4.2.10.1 Definition

- Population: Full analysis set
- Endpoint: Time to first occurrence of either component of the composite outcome at any time post-discharge up to 180 days inclusive.
- Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who require hospital admission without HK as a contributing factor or any ED visits or who use rescue therapy will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause will be considered an event (composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who do not have an event by 180 days post-discharge will be administratively censored at the date of 180 days post-discharge.
- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group (reference level SoC) as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented (as per section 4.2.3.2) at 180 days post-discharge.
- Sensitivity analyses will be conducted as per secondary endpoint #1.

4.2.10.2 Derivations

Time to first occurrence will be defined as the earliest date of (hospital admission with HK as a contributing factor, all-cause death, date of loss to follow-up, date of 180 days post-discharge) – date of randomization + 1.

4.2.10.3 Handling of Dropouts and Missing Data

Participants who are lost to follow-up will be censored at the date of discontinuation as recorded on the participant's disposition form.

4.2.10.4 Primary Analysis of Exploratory Endpoint #2

The primary analysis of this other endpoint will be performed as per section 4.2.3.4.

4.2.10.5 Sensitivity Analyses of Exploratory Endpoint #2

Sensitivity analyses of this exploratory endpoint will be performed as per section 4.2.3.5.

4.2.10.6 Supplementary Analyses of Exploratory Endpoint #2

Not Applicable.

4.2.10.7 Subgroup Analyses

Not Applicable.

4.2.11 Exploratory Endpoint #3 (ED visit with HK, all-cause death)

Time to first occurrence of either ED visit with HK as a contributing factor or all-cause death at any time post-discharge up to 180 days inclusive.

4.2.11.1 Definition

- Population: Full analysis set
- Endpoint: Time to first occurrence of either component of the composite outcome at any time post-discharge up to 180 days inclusive.
- Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who require any hospital admission or ED visits without HK as a contributing factor or who use rescue therapy will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause will be considered an event (composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who do not have an event by 180 days post-discharge will be administratively censored at the date of 180 days post-discharge.
- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group (reference level SoC) as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented (as per section 4.2.3.2) at 180 days post-discharge.

4.2.11.2 Derivations

Time to first occurrence will be defined as the earliest date of (ED visit with HK, all-cause death, date of loss to follow-up, date of 180 days post-discharge) – date of randomization + 1.

4.2.11.3 Handling of Dropouts and Missing Data

Participants who are lost to follow-up will be censored at the date of discontinuation as recorded on the participant's disposition form.

4.2.11.4 Primary Analysis of Exploratory Endpoint #3

The primary analysis of this other endpoint will be performed as per section 4.2.3.4.

4.2.11.5 Sensitivity Analyses of the Exploratory Endpoint #3

Sensitivity analyses of this exploratory endpoint will be performed as per section 4.2.3.5.

4.2.11.6 Supplementary Analyses of the Exploratory Endpoint #3

Not Applicable.

4.2.11.7 Subgroup Analyses

Not Applicable.

4.2.12 Exploratory Endpoint #4 (All-cause hospitalisations, ED visits, use of rescue therapy for HK, all-cause death)

Time to first occurrence of any component of all-cause hospitalisations, ED visits, use of rescue therapy for HK or all-cause death in each arm at any time post-discharge up to 180 days.

4.2.12.1 Definition

- Population: Full analysis set
- Endpoint: Time to first occurrence of any component of all-cause hospitalisations, ED visits, use of rescue therapy for HK or all-cause death in each arm at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Rescue therapy for HK will be considered an event (composite variable strategy). Participants who require any hospital admission or ED visit will be considered an event (composite variable strategy). Participants who die of any cause will be considered an event (composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who do not have an event by 180 days post-discharge will be administratively censored at the date of 180 days post-discharge.
- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group (reference level SoC) as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented (as per section 4.2.3.2) at 180 days post-discharge.

4.2.12.2 Derivations

Time to first occurrence will be defined as the earliest date of (all-cause hospital admission, all-cause ED visit, all-cause death, use of rescue therapy for HK, date of loss to follow-up, date of 180 days post-discharge) – date of randomization + 1.

4.2.12.3 Handling of Dropouts and Missing Data

Participants who are lost to follow-up will be censored at the date of discontinuation as recorded on the participant's disposition form.

4.2.12.4 Primary Analysis of Exploratory Endpoint #3

The primary analysis of this exploratory endpoint will be performed as per section 4.2.3.4.

4.2.12.5 Sensitivity Analyses of the Exploratory Endpoint #3

Sensitivity analyses of this exploratory endpoint will be performed as per section 4.2.3.5.

4.2.12.6 Supplementary Analyses of the Exploratory Endpoint #3

Not Applicable.

4.2.12.7 Subgroup Analyses

Not Applicable.

4.2.13 Exploratory Endpoint #5 (K^+ up to 180 days post-discharge)

Potassium level up to 180 days post-discharge.

4.2.13.1 Definition

- Population: Full analysis set
- Endpoint: Potassium levels up to 180 days post-discharge.
- Intercurrent event strategy: Potassium levels from participants after discontinuation of treatment, hospital admissions, or ED visits for any reason will be included in the analysis (treatment policy strategy). Participants who use rescue therapy for HK will have K^+ levels prior to rescue therapy for HK used in the analysis (while on treatment strategy). Participants who have RAASi down-titration (including discontinuation) will have K^+ levels prior to the RAASi down-titration used in the analysis (while on treatment strategy). Participants who die of any cause or who are lost to follow-up prior to 180 days post-discharge will have all available K^+ included in the analysis (treatment policy strategy).
- Population level summary (analysis): A mixed model repeated measures (MMRM) analysis, described in section 4.2.13.4, will be used. The population level summary will be the coefficient estimates, standard error, 95% CI for coefficient estimate, and p-values for the randomised treatment group term.

4.2.13.2 Derivations

Time from randomisation will be calculated as date of K^+ - date of randomisation + 1.

4.2.13.3 Handling of Dropouts and Missing Data

All available K^+ measurements up to the date of rescue therapy for HK will be used in the MMRM. Measurements after rescue therapy starts are assumed to be missing at random and that K^+ measurements would behave similarly to other participants in the same treatment group with similar covariate values.

4.2.13.4 Primary Analysis of Exploratory Endpoint #5

A MMRM will be fitted in the FAS with K^+ measurements as the dependent variable and randomised treatment group (reference level SoC), time from randomisation, country and the interaction of treatment group by time from randomisation with random effects for participant, intercept and slope. The covariance structure will be unstructured. The coefficient estimates, standard error, 95% CI for coefficient estimates, and p-values will be reported. The model assumptions will be assessed by plotting a histogram of the model residuals and a scatter plot of the model residuals versus predicted values.

4.2.13.5 Sensitivity Analyses of the Exploratory Endpoint #5

Providing there are sufficient participants within each covariate to support the analysis, an alternative population level summary using the FAS population where the MMRM analysis will include randomised treatment group and the following baseline variables: age (as a cubic spline), sex, presence of heart failure, diabetes, RAASi use, CKD stage and baseline K^+ (mild HK defined by $5.0 < K^+ \leq 5.5$ and moderate/severe HK defined by $5.5 < K^+ \leq 6.5$ mmol/L) as independent variables. Baseline variables will be defined as described in section 4.1.6.1.

4.2.13.6 Supplementary Analyses of the Exploratory Endpoint #5

Not Applicable.

4.2.13.7 Subgroup Analyses

Not Applicable.

4.2.14 Exploratory Endpoint #6 (Number of hospital admissions with HK)

Number of hospital admissions with HK as a contributing factor at any time post-discharge up to 180 days.

4.2.14.1 Definition

- Population: Full analysis set
- Endpoint: Number of hospital admissions with HK as a contributing factor, at any time post-discharge up to 180 days.

- Intercurrent event strategy: Participants who discontinue treatment, use rescue therapy for HK, have RAASi down-titration (including discontinuation), experience all-cause death or loss to follow-up prior to 180 days post-discharge will have all available hospital admission and ED visit data used irrespective of the intercurrent event (treatment policy strategy).
- Population level summary: Mean number of hospital admissions with HK as a contributing factor, by randomised treatment group will be summarised. Negative binomial regression model with randomised treatment group as a main effect and including duration of time in study as an offset. The incidence rate ratio (SZC/SoC), along with 95% confidence intervals and two-sided p-values will be displayed.

4.2.14.2 Derivations

For each participants the total number of separate hospital admissions with HK as a contributing factor up to 180 days will be calculated. Hospital admissions will be calculated as separate admissions if start and stop dates of admission do not overlap. If hospital admissions are missing a start, stop date or both then they will be calculated as separate admissions. Hospital admissions after 180 days will not be counted.

4.2.14.3 Handling of Dropouts and Missing Data

All available data on hospital admissions are to be used irrespective of intercurrent events. For the primary analysis, no adjustment is made for dropout but the sensitivity of the results to this approach are investigated using a sensitivity analysis in section 4.2.14.5.

4.2.14.4 Primary Analysis of Exploratory Endpoint #6

A descriptive summary (Mean, SD, Median, Range) of the number of hospital admissions with HK as a contributing factor will be presented by randomised treatment group in the FAS. A negative binomial regression model will be conducted with the number of hospital admissions with HK as a contributing factor as the dependent variable and randomised treatment group (reference level SoC) as the independent variable. The duration of time per participant in study is calculated until the earliest of loss to follow-up or 180 days post-discharge and will be included in the model as an offset term. The incidence rate ratio (SZC/SoC), along with 95% CIs and two-sided p-values will be displayed. To check the model assumptions, that the conditional means are not equal to the conditional variance, the dispersion parameter will be checked by fitting a Poisson model and by performing a chi-squared test with 1 degree of freedom with a test statistic of twice the difference in log likelihoods.

4.2.14.5 Sensitivity Analyses of the Exploratory Endpoint #6

Two sensitivity analyses will be conducted for this exploratory endpoint:

- Providing there are sufficient participants within each covariate to support the analysis, an alternative population level summary using the FAS population where the negative

binomial regression model will include randomised treatment group, duration of time in study as an offset and the following baseline variables: age (as a cubic spline), sex, participant recruitment country, presence of heart failure, diabetes, RAASi use, CKD stage, and baseline K^+ (mild HK defined by $5.0 < K^+ \leq 5.5$ and moderate/severe HK defined by $5.5 < K^+ \leq 6.5$ mmol/L) as independent variables. Baseline variables will be defined as described in section 4.2.2.6.

- A sensitivity analysis will be conducted using the mean cumulative count method (MCC) (Dong et al, 2015) if a greater than 10% difference by treatment arm in the proportion who are lost to follow-up is observed. The MCC method reflects a summarisation of all events that occur in a population by a given time. The recurring event in this analysis will be hospital admission with HK as a contributing factor. The MCC will be performed by randomised treatment group in the FAS and an estimate (95% CI) of the MCC at 90 and 180 days post discharge will be presented. A figure of the MCC by randomised treatment group with 95% CI will also be displayed. SAS Code to conduct an MCC analysis is described in sections 7.1 and 7.2.

4.2.14.6 Supplementary Analyses of the Exploratory Endpoint #6

Not Applicable.

4.2.14.7 Subgroup Analyses

Not Applicable.

4.2.15 Exploratory Endpoint #7 (LOS for hospitalisation with HK)

Total length of stay (LOS) for hospitalisations (including multiple hospitalisations) with HK as a contributing factor in each arm at any time post-discharge up to 180 days.

4.2.15.1 Definition

- Population: Full analysis set
- Endpoint: Total LOS for hospitalisations (including multiple hospitalisations) with HK as a contributing factor in each arm at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue treatment, use rescue therapy for HK, experience all-cause death, have RAASi down-titration (including discontinuation) or loss to follow-up prior to 180 days post-discharge will have all available hospital admission data used irrespective of the intercurrent event (treatment policy strategy). Hospital admissions which extend beyond 180 days post-discharge will be truncated at 180 days post-discharge.
- Population level summary: Continuous variable summary (mean and median) of total LOS with HK as a contributing factor, by randomised treatment group. A Wilcoxon rank-sum test by randomised treatment group will be used to calculate a two-sided p-value.

4.2.15.2 Derivations

LOS will be calculated using the hospital admission details eCRF with the adjudication committee determination of whether HK was a contributing factor. Each hospital duration will be calculated as the number of days: (Min(Stop date of admission, Randomisation date + 180) – Start date of admission + 1) and the total duration per participant will be calculated as the sum of all relevant hospital admissions.

4.2.15.3 Handling of Dropouts and Missing Data

All available data on hospital admissions are to be used irrespective of intercurrent events, no adjustment is made for dropout.

4.2.15.4 Primary Analysis of Exploratory Endpoint #7

The total duration of LOS with HK as a contributing factor will be summarised as a continuous variable (mean, SD, median, range) by randomised treatment group in the FAS. A Wilcoxon rank-sum test by randomised treatment group will be used to calculate a two-sided p-value.

4.2.15.5 Additional Analyses of the Exploratory Endpoint #7

Not Applicable.

4.2.15.6 Subgroup Analyses

Not Applicable.

4.2.16 Exploratory Endpoint #8 (LOS for all-cause hospitalisation)

Total LOS for all-cause hospitalisations (including multiple hospitalisations) in each arm at any time post-discharge up to 180 days.

4.2.16.1 Definition

- Population: Full analysis set
- Endpoint: Total LOS for all-cause hospitalisations (including multiple hospitalisations) in each arm at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue treatment, use rescue therapy for HK, experience all-cause death, or loss to follow-up prior to 180 days post-discharge will have all available hospital admission data used irrespective of the intercurrent event (treatment policy strategy). Hospital admissions which extend beyond 180 days post-discharge will be truncated at 180 days post-discharge.
- Population level summary: Continuous variable summary (mean and median) of total LOS of all-cause hospitalisation, by randomised treatment group. A Wilcoxon rank-sum test by randomised treatment group will be used to calculate a two-sided p-value.

4.2.16.2 Derivations

LOS will be calculated using the hospital admission details eCRF. Each hospital duration will be calculated as (Min(Stop date of admission, Randomisation date + 180) – Start date of admission + 1) and the total duration per participant will be calculated as the sum of all hospital admissions.

4.2.16.3 Handling of Dropouts and Missing Data

All available data on hospital admissions are to be used irrespective of intercurrent events, no adjustment is made for dropout.

4.2.16.4 Primary Analysis of Exploratory Endpoint #8

The total duration of LOS will be summarised as a continuous variable (mean, SD, median, range) by randomised treatment group in the FAS. A Wilcoxon rank-sum test by randomised treatment group will be used to calculate a two-sided p-value.

4.2.16.5 Additional Analyses of the Exploratory Endpoint #8

Not Applicable.

4.2.16.6 Subgroup Analyses

Not Applicable.

4.2.17 Exploratory Endpoint #9 (Frequency of K-binder use)

Frequency of the use of K-binders to treat HK at any time post-discharge up to 180 days in each arm.

4.2.17.1 Definition

- Population: Full analysis set
- Endpoint: Number of participants requiring K-binders to treat HK at any time post-discharge up to 180 days in each treatment group. Number of uses of K-binders to treat HK at any time post-discharge up to 180 days
- Intercurrent event strategy: Participants who discontinue treatment, use rescue therapy for HK, experience all-cause death, have RAASi down-titration (or discontinuation), or loss to follow-up prior to 180 days post-discharge will have all K-binder use used irrespective of the intercurrent event (treatment policy strategy).
- Population level summary: Number of participants requiring K-binder use to treat HK by randomised treatment group. Mean number of uses of K-binder, by randomised treatment group. Negative binomial regression model with randomised treatment group (reference level SoC) as a main effect and including duration of time in study as an offset. The incidence rate ratio (SZC/SoC), along with 95% confidence intervals and two-sided p-values will be displayed.

4.2.17.2 Derivations

Not Applicable.

4.2.17.3 Handling of Dropouts and Missing Data

All available data on K-binder use up to 180 days post-discharge are to be used irrespective of intercurrent events, no adjustment is made for dropout. K-binders required after 180 days post-discharge will be excluded from analysis.

4.2.17.4 Primary Analysis of Exploratory Endpoint #9

A descriptive summary (Mean, SD, Median, Range) of the number of instances of K-binder use will be presented by randomised treatment group in the FAS. A negative binomial regression model will be conducted with the number of uses of K-binder as the dependent variable and randomised treatment group (reference level SoC) as the independent variable. The duration of time per participant in study is calculated until the earliest of loss to follow-up or 180 days post-discharge and will be included in the model as an offset term.. The incidence rate ratio (SZC/SoC), along with 95% CIs and two-sided p-values will be displayed.

4.2.17.5 Additional Analyses of the Exploratory Endpoint #9

Not Applicable.

4.2.17.6 Subgroup Analyses

Not Applicable.

4.2.18 Exploratory Endpoint #10 (K-binder use)

Time to first occurrence of K-binder use to treat HK post-discharge at any time post-discharge up to 180 days in each arm.

4.2.18.1 Definition

- Population: Full analysis set
- Endpoint: Time to first use of K-binder to treat HK any time post-discharge up to 180 days inclusive.
- Intercurrent event strategy: Participants who discontinue treatment will continue to be followed up to the first use of K-binder to treat HK (treatment policy strategy). Participants who require any hospital admission or ED visits or who have RAASi down-titration (including discontinuation) will continue to be followed up to the first use of K-binder to treat HK (treatment policy strategy). Participants who die of any cause will be censored at the date of death. Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who do not have an event by 180 days post-discharge will be administratively censored at the date of 180 days post-discharge.

- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group (reference level SoC) as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented (as per section 4.2.2.2) at 180 days post-discharge.

4.2.18.2 Derivations

Time to first occurrence will be defined as the earliest date of (K-binder use to treat HK, date of death, loss to follow-up, date of 180 days post-discharge) – date of randomization + 1.

4.2.18.3 Handling of Dropouts and Missing Data

Participants who are lost to follow-up will be censored at the date of discontinuation as recorded on the participant's disposition form.

4.2.18.4 Primary Analysis of Exploratory Endpoint #10

The primary analysis for this exploratory endpoint will be conducted using a log-rank test by treatment group in the FAS to calculate a two-sided p-value. A Cox proportional hazards model will be used in the FAS for estimation with randomised treatment group (reference level SoC) and subject recruitment country as the independent variables.

To assess for the proportionality of hazards the log(-log(estimated survival function)) will be plotted compared to log(days) for each randomised treatment group and visually inspected to determine if the curves are approximately parallel. To assess for the impact of censoring, and the duration of follow-up, a reverse Kaplan-Meier figure will be produced where the status indicators are reversed such that the censor becomes the event and the composite event of interest as the censor. These will be presented by randomised treatment group, together with a summary of associated statistics (median time and associated 95% CIs).

4.2.18.5 Additional Analyses of the Exploratory Endpoint #10

The analysis will be repeated in the FAS using an alternative population level summary where the Cox proportional hazards model will include randomised treatment group and the following baseline variables: age (as a cubic spline), sex (female, male), participant recruitment country, presence of heart failure (yes/no), diabetes (yes/no), RAASi use (yes/no), CKD stage and baseline K^+ (mild HK defined by $5.0 < K^+ \leq 5.5$ and moderate/severe HK defined by $5.5 < K^+ \leq 6.5$ mmol/L) as independent variables.

4.2.18.6 Subgroup Analyses

Not Applicable.

4.2.19 Exploratory Endpoint #11 (Duration of K-binder use)

Duration of time on K-binders from initiation in the first instance of K-binder use post-discharge up to 180 days in each arm.

4.2.19.1 Definition

- Population: Subset of full analysis set who require use of K-binders
- Endpoint: Time to discontinuation of K-binders from initiation in the first instance of K-binder use post-discharge up to 180 days in each arm.
- Intercurrent event strategy: Participants who discontinue treatment will continue to be followed up until discontinuation of K-binder (treatment policy strategy). Participants who require any hospital admission or ED visits will continue to be followed up to discontinuation of K-binder (treatment policy strategy). Participants who die of any cause will be considered to have ended K-binder use. Participants who are lost to follow-up will be considered to have ended K-binder use.
- Population level summary (analysis): Continuous summary statistics of the duration of K-binder use will be presented by randomised treatment group. A Wilcoxon rank-sum test by randomised treatment group will be used to calculate a two-sided p-value.

4.2.19.2 Derivations

Duration of K-binder use will be defined as the date of first K-binder discontinuation – date of first K-binder initiation + 1. If first K-binder discontinuation or after 180 days post-discharge then the date of first K-binder discontinuation will be administratively censored at 180 days post-discharge (date of randomisation + 180).

4.2.19.3 Handling of Dropouts and Missing Data

Not Applicable

4.2.19.4 Primary Analysis of Exploratory Endpoint #11

The primary analysis for this exploratory endpoint will be conducted as per section 4.2.15.4.

4.2.19.5 Additional Analyses of the Exploratory Endpoint #11

Not Applicable.

4.2.19.6 Subgroup Analyses

Not Applicable.

4.2.20 Exploratory Endpoint #12 (Rescue therapy for HK)

Time to first occurrence of rescue therapy use to treat HK at any time post-discharge up to 180 days in each arm.

4.2.20.1 Definition

- Population: Full analysis set
- Endpoint: Time to first use of rescue therapy to treat HK any time post-discharge up to 180 days inclusive.
- Intercurrent event strategy: Participants who discontinue treatment will continue to be followed up to the first use of rescue therapy to treat HK (treatment policy strategy). Participants who require any hospital admission or ED visits or have RAASi down-titration (including discontinuation) will continue to be followed up to the first use rescue therapy to treat HK (treatment policy strategy). Participants who die of any cause will be censored at the date of death. Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who do not have an event by 180 days post-discharge will be administratively censored at the date of 180 days post-discharge.t
- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group (reference level SoC) as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented (as per section 4.2.2.2) at 180 days post-discharge.

4.2.20.2 Derivations

Time to first occurrence will be defined as the earliest date of (rescue therapy to treat HK, date of death, loss to follow-up, date of 180 days post-discharge) – date of randomization + 1.

4.2.20.3 Handling of Dropouts and Missing Data

Participants who are lost to follow-up will be censored at the date of discontinuation as recorded on the participant's disposition form.

4.2.20.4 Primary Analysis of Exploratory Endpoint #12

The primary analysis for this exploratory endpoint will be conducted as per section 4.2.18.4.

4.2.20.5 Additional Analyses of the Exploratory Endpoint #12

The analysis will be repeated in the FAS using an alternative population level summary where the Cox proportional hazards model will include randomised treatment group and the following baseline variables: age (as a cubic spline), sex (female, male), participant recruitment country, presence of heart failure (yes/no), diabetes (yes/no), RAASi use (yes/no), CKD stage and baseline K^+ (mild HK defined by $5.0 < K^+ \leq 5.5$ and moderate/severe HK defined by $5.5 < K^+ \leq 6.5$ mmol/L) as independent variables.

4.2.20.6 Subgroup Analyses

Not Applicable.

4.2.21 Exploratory Endpoint #13 (All-cause hospitalisations, ED or outpatient visits)

Time to first occurrence of all-cause hospitalisations, ED visits or outpatient visits at any time post-discharge up to 180 days in each arm.

4.2.21.1 Definition

- Population: Full analysis set
- Endpoint: Time to first occurrence of any component of the composite outcome at any time post-discharge up to 180 days inclusive.
- Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who require rescue therapy for HK or have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who require any hospital admission, ED visit, or outpatient visit will be considered an event (composite variable strategy). Participants who die of any cause will be censored at the date of death. Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who do not have an event by 180 days post-discharge will be administratively censored at the date of 180 days post-discharge.
- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group (reference level SoC) as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented (as per section 4.2.2.2) at 180 days post-discharge.

4.2.21.2 Derivations

Time to first occurrence will be defined as the earliest date of (all-cause hospitalisation, all-cause ED visits, outpatient visit, date of death, loss to follow-up, date of 180 days post-discharge) – date of randomization + 1.

4.2.21.3 Handling of Dropouts and Missing Data

Participants who are lost to follow-up will be censored at the date of discontinuation as recorded on the participant's disposition form.

4.2.21.4 Primary Analysis of Exploratory Endpoint #13

The primary analysis for this exploratory endpoint will be conducted as per section 4.2.18.4.

4.2.21.5 Additional Analyses of the Exploratory Endpoint #13

The analysis will be repeated in the FAS using an alternative population level summary where the Cox proportional hazards model will include randomised treatment group and the following baseline variables: age (as a cubic spline), sex (female, male), participant recruitment country, presence of heart failure (yes/no), diabetes (yes/no), RAASi use (yes/no), CKD stage and baseline K^+ (mild HK defined by $5.0 < K^+ \leq 5.5$ and moderate/severe HK defined by $5.5 < K^+ \leq 6.5$ mmol/L) as independent variables.

4.2.21.6 Subgroup Analyses

Not Applicable.

4.2.22 Exploratory Endpoint #14 (eGFR slope)

Rate of change in (slope) eGFR between treatment arms.

4.2.22.1 Definition

- Population: Full analysis set
- Endpoint: Change in eGFR between treatment arms
- Intercurrent event strategy: Participants who discontinue of treatment will have all available eGFR measurements included (treatment policy strategy). Participants who require rescue therapy for HK or have RAASi down-titration (including discontinuation) will have all available eGFR measurements included (treatment policy strategy). Participants who require any hospital admission or ED visit will have all available eGFR measurements included (treatment policy strategy). Participants who die of any cause or are lost to follow-up will have all measurements up to death or loss to follow-up included (hypothetical strategy).
- Population level summary (analysis): Change in eGFR will be analysed with a MMRM approach where the dependent variable is post randomisation eGFR and with fixed terms for randomised treatment group (reference level SoC), eGFR at randomisation, participant recruitment country, time from randomisation (days), and the interaction of treatment group (reference level SoC) by time from randomisation with random effects for participant, intercept and slope. The covariance structure will be unstructured. The coefficient estimates, standard error, 95% CI for coefficient estimates, and p-values will be reported.

4.2.22.2 Derivations

Time from randomisation will be calculated a date of eGFR measurement – date of randomisation + 1.

4.2.22.3 Handling of Dropouts and Missing Data

Participants who die or are lost to follow-up are assumed to be missing at random and that eGFR measurements would behave similarly to other participants in the same treatment group with similar covariate values.

4.2.22.4 Primary Analysis of Exploratory Endpoint #14

A MMRM will be fitted in the FAS with eGFR measurements as the dependent variable and randomised treatment group (reference level SoC), time from randomisation, country and the interaction of treatment group (reference level SoC) by time from randomisation with random effects for participant, intercept and slope. The covariance structure will be unstructured. The coefficient estimates, standard error, 95% CI for coefficient estimates, and p-values will be reported. The interaction term of treatment group by time from randomisation will provide the evidence of any difference in slope of eGFR by randomised treatment group. An interaction term>0 will demonstrate an increase in eGFR in the SZC arm compared to SoC.

4.2.22.5 Additional Analyses of the Exploratory Endpoint #14

Not Applicable

4.2.22.6 Subgroup Analyses

Not Applicable

4.2.23 Exploratory Endpoint #15 (Dialysis initiation)

Time to first occurrence of dialysis initiation at any time post-discharge up to 180 days in each arm.

4.2.23.1 Definition

- Population: Full analysis set
- Endpoint: Time to first occurrence of dialysis initiation at any time post-discharge up to 180 days inclusive.
- Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first use of dialysis post-discharge (treatment policy strategy). Participants who require rescue therapy for HK or have RAASi down-titration (including discontinuation) will continue to be followed up to the first use of dialysis post-discharge (treatment policy strategy). Participants who require any hospital admission or ED visit will continue to be followed up to the first use of dialysis post-discharge (treatment policy strategy). Participants who die of any cause will be censored at the date of death. Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who do not have an event by 180 days post-discharge will be administratively censored at the date of 180 days post-discharge.

- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented (as per section 4.2.4.2) at 180 days post-discharge.

4.2.23.2 Derivations

Time to first occurrence will be defined as the earliest date of (dialysis initiation, date of death, loss to follow-up, date of 180 days post-discharge) – date of randomization + 1.

4.2.23.3 Handling of Dropouts and Missing Data

Participants who are lost to follow-up will be censored at the date of discontinuation as recorded on the participant's disposition form.

4.2.23.4 Primary Analysis of Exploratory Endpoint #15

The primary analysis for this exploratory endpoint will be conducted as per section 4.2.18.4.

4.2.23.5 Additional Analyses of the Exploratory Endpoint #15

The analysis will be repeated in the FAS using an alternative population level summary where the Cox proportional hazards model will include randomised treatment group and the following baseline variables: age (as a cubic spline), sex (female, male), participant recruitment country, presence of heart failure (yes/no), diabetes (yes/no), RAASi use (yes/no), CKD stage and baseline K^+ (mild HK defined by $5.0 < K^+ \leq 5.5$ and moderate/severe HK defined by $5.5 < K^+ \leq 6.5$ mmol/L) as independent variables.

4.2.23.6 Subgroup Analyses

Not Applicable

4.2.24 Exploratory Endpoint #16 (ICU admission)

Time to first occurrence of ICU admissions at any time post-discharge up to 180 days in each arm.

4.2.24.1 Definition

- Population: Full analysis set
- Endpoint: Time to first occurrence of ICU admission at any time post-discharge up to 180 days inclusive.
- Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first ICU admission post-discharge (treatment policy strategy). Participants who require rescue therapy for HK or who have RAASi down-titration

(including discontinuation) will continue to be followed up to the first ICU admission post-discharge (treatment policy strategy). Participants who require any hospital admission or ED visit will continue to be followed up to the first ICU admission post-discharge (treatment policy strategy). Participants who die of any cause will be censored at the date of death. Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who do not have an event by 180 days post-discharge will be administratively censored at the date of 180 days post-discharge.

- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group (reference level SoC) as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.

4.2.24.2 Derivations

Time to first occurrence will be defined as the earliest date of (ICU admission, date of death, loss to follow-up, date of 180 days post-discharge) – date of randomization + 1.

4.2.24.3 Handling of Dropouts and Missing Data

Participants who are lost to follow-up will be censored at the date of discontinuation as recorded on the participant's disposition form.

4.2.24.4 Primary Analysis of Exploratory Endpoint #16

The primary analysis for this exploratory endpoint will be conducted as per section 4.2.18.4.

4.2.24.5 Additional Analyses of the Exploratory Endpoint #16

The analysis will be repeated in the FAS using an alternative population level summary where the Cox proportional hazards model will include randomised treatment group and the following baseline variables: age (as a cubic spline), sex (female, male), participant recruitment country, presence of heart failure (yes/no), diabetes (yes/no), RAASi use (yes/no), CKD stage and baseline K^+ (mild HK defined by $5.0 < K^+ \leq 5.5$ and moderate/severe HK defined by $5.5 < K^+ \leq 6.5$ mmol/L) as independent variables.

4.2.24.6 Subgroup Analyses

Not Applicable.

4.2.25 Exploratory Endpoint #17 (RAASi use)

Use of RAASi at 90 and 180 days post-discharge by treatment arm.

4.2.25.1 Definition

- Population: Full analysis set

- Endpoint: Number and proportion of participants on RAASi at discharge who remained on RAASi at days 90 and 180 post-discharge, respectively, by treatment arm. The number and proportion of participants on RAASi at discharge who have increased RAASi dose by 90 and 180 days post-discharge, respectively, by treatment arm. The number and proportion of participants on RAASi at discharge who have decreased RAASi dose by 90 and 180 days post-discharge, respectively, by treatment arm. The number and proportion of participants who have initiated RAASi by 90 and 180 days post-discharge respectively.
- Intercurrent event strategy: Participants who discontinue treatment, use rescue therapy for HK or require either hospitalisation or ED visits will have all available RAASi use data used irrespective of the intercurrent event (treatment policy strategy). Participants who experience all-cause death, or loss to follow-up prior to days 90 and 180 respectively will be excluded from the numerator and denominator of the analysis (while on treatment strategy).
- Population level summary: Number and proportion of participants on RAASi at discharge who remained on RAASi at 90 and 180 days post-discharge by treatment arm. Number and proportion of participants on RAASi at discharge who have increased RAASi dose by 90 and 180 days post-discharge by treatment arm. Number and proportion of participants on RAASi at discharge who have decreased RAASi dose by 90 and 180 days post-discharge by treatment arm. Number and proportion of participants who initiated RAASi by 90 and 180 days post-discharge by treatment arm.

4.2.25.2 Derivations

RAASi use at discharge is derived using the concomitant medication rescue medications eCRF as where one or more CMCLASCD in (‘C09AA’, ‘C09BA’, ‘C09BB’, ‘C09BX’, ‘C09CA’, ‘C09DA’, ‘C09DB’, ‘C09DX’, ‘C09XA’) where Start Date is prior to the date of randomisation and End Date is ongoing or after the date of randomisation. RAASi use at day 90 post-discharge is derived using the concomitant medication rescue medications eCRF as above where Start Date is prior to day 90 post-discharge and End Date is ongoing or after day 90 post-discharge. RAASi use at day 180 post-discharge is derived using the concomitant medication rescue medications eCRF as above where Start Date is prior to day 180 post-discharge and End Date is ongoing or after day 180 post-discharge. A RAASi dose increase at 90 and 180 days post-discharge is defined where the CMDECOD at discharge is different at 90 or 180 days or where CMDECOD at 90 or 180 matches that at discharge but the CMDOSTXT is greater than at discharge. A RAASi dose decrease at 90 and 180 days post-discharge is defined, where CMDECOD at 90 or 180 days matches that at discharge but the CMDOSTXT is less than at discharge.

4.2.25.3 Handling of Dropouts and Missing Data

Participants who experience all-cause death, or loss to follow-up prior to days 90 and 180 respectively will be excluded from the numerator and denominator of the analysis.

4.2.25.4 Primary Analysis of Exploratory Endpoint #17

The number and proportion of participants requiring RAASi at days 90 and 180 by treatment arm will be summarised.

4.2.25.5 Additional Analyses of the Exploratory Endpoint #17

Not Applicable.

4.2.25.6 Subgroup Analyses

Not Applicable.

4.3 Pharmacodynamic Endpoint(s) (if not already covered as endpoint variables)

4.3.1 Analysis

Not Applicable.

4.3.2 Definitions and Derivations

Not Applicable.

4.3.3 Presentation

Not Applicable.

4.4 Pharmacokinetics (if not already covered as endpoint variables)

Not Applicable.

4.5 Immunogenicity (if applicable and if not already covered as endpoint variables)

Not Applicable.

4.6 Safety Analyses (if not already covered as endpoint variables)

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, and ECG.

Tables are provided for the SSO and the SSR, listings are provided for All participants or the safety set depending on the availability of data.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Exposure (i.e. duration of treatment) will be defined as follows:

Total (or intended) exposure of study treatment

- Total (or intended) exposure = min (last dose date where dose > 0g, date of death, date of discontinuation) – first dose date + 1

The dosage (g/day) will be calculated for the inpatient period and outpatient period respectively:

The total cumulative dose received (g)/Number of days receiving study drug (i.e. excluding dose interruptions)

4.6.1.2 Presentation

Actual and total exposure (days) will be summarised in total for the SSO and by treatment group for the SSR by the following: mean, standard deviation, minimum, maximum, median and number of observations.

SZC (g/day) will be summarised in total for the SSO and by treatment group for the SSR by the following: range of dose for any participant, mean dose, range of mean doses, median dose, interquartile range of dose. Total cumulative dose received (g) will be summarised by mean and range. The range of the maximum dose received (g/day) will be summarised. For each study visit period (e.g. from visit 1 to visit 2, visit 2 to visit 3) the total number (%) of participants who received dose will be presented and the prescribed daily dose.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

All Adverse events, (non-serious and serious adverse events (SAEs) will be collected from time of signature of the informed consent form, throughout the treatment period including during the follow-up period. A treatment emergent AE (TEAE) will be defined as an AE with the start date on or after the first dose date during the inpatient period up to (and including) 7 days after the last dose date, and events with start date prior to the date of first dose of study treatment whose severity worsens on or after the date of first dose during the inpatient period.

TEAEs will be further categorised as either (i) occurring during the inpatient period, if the start date is on or after the first dose date during the inpatient period and prior to the date of randomization, (ii) occurring during the outpatient period if the start date is on or after the date of randomization and prior to the date of study treatment discontinuation+7.

MedDRA [Version 24.1 (or a later version if updated during the study)] will be used to classify AEs system organ class (SOC) and preferred term (PT).

Every effort should be made to collect the maximum intensity and relationship to treatment for all AEs. However, if the maximum intensity is missing for a TEAE then it will be considered as severe only in the overall category in the summary tables. If the relationship to treatment is missing, then the AE will be considered as possibly related to treatment.

Deaths

All adverse events leading to death, including those not related to an AE, will be collected until the end of the study.

4.6.2.2 Presentation

AE Summary

An overall summary table of the number of participants experiencing each category of AEs will be produced using the SSO and SSR. Analyses using the SSO will be restricted to AEs which occurred during the inpatient period and will be presented overall. Analyses using the SSR will include all AEs and will be presented by treatment group received during the outpatient period and overall.

Any AE occurring within 7 days of the discontinuation of investigational product will be included in the AE summaries. Treatment emergent adverse events (TEAEs) occurring prior to first dose of investigational product (i.e. before study day 1) which subsequently worsen in severity following dosing will be presented in the summary tables. All other AEs occurring prior to first dose of investigational product (i.e. before study day 1) or more than 7 days after the discontinuation of investigational product will be listed separately, but not included in the summaries.

An overview table will summarize the number and percentage of participants with at least one of the following AEs, where participants with more than one AE in a particular category are counted only once in that category, as well as the absolute counts of number of AEs. In the overall summary table for the SSO, no event rate will be displayed. In the overall summary table for the SSR, the event rate, per 100 patient years, will be displayed. This will be calculated as the number of participants with at least one AE (in either inpatient or outpatient phase) divided by the total time as risk (i.e. time from first dose of SZC during the inpatient phase to date of study discontinuation) across all participants in given group, multiplied by 365.25 multiplied by 100.

- Any AEs
- Any AEs with outcome of death
- Any SAEs (including events with outcome of death)

- Any AEs leading to treatment discontinuation

Number of participants with AEs

The number and percentage of participants reporting each AE and the absolute count of AEs will be summarised by system organ class (SOC) and preferred term (PT). Tables will be sorted by international order for SOC and PTs will be sorted alphabetically. The following summaries will be produced using the SSO and SSR:

- AEs;
- Most common AEs (>5% in any treatment group);
- AEs by relationship to treatment;
- AEs by maximum intensity;
- AEs leading to treatment discontinuation;
- SAEs;
- SAEs related to treatment;
- AEs leading to death;

All AE data will be listed appropriately for all participants including information on AE duration, intensity, seriousness, action taken, outcome, relationship as assessed by investigator, timing of onset of AE in relation to the first dose of study treatment in the inpatient period, study treatment at the time of event.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

Absolute change from baseline in haematology and clinical chemistry variables will be calculated for each post-dose visit.

4.6.3.2 Presentations

Laboratory data (clinical chemistry and haematology) will be summarised and listed. Laboratory data outside the reference ranges will be indicated in the listings. If a participant has multiple results for a particular test at a particular time point, the rules of section 3.3.2 will be followed. System international (SI) units will be reported for all analytes.

Laboratory data absolute and change from baseline values for continuous chemistry and haematology parameters will be summarised at each scheduled assessment time. Separate tables will be provided for the SSO, restricted to visits during the inpatient period and presented overall and for the SSR, which will include all visits and be presented by treatment received during the outpatient period.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

The following urinalysis parameters will be presented: U-hb/Erthrocytes/Blood, U-protein/Albumin, U-Glucose.

4.6.4.2 Presentations

Shift tables will be presented where shift from baseline to the maximum value will be summarised. These will be provided separately for the SSO, which will be limited to visits during the inpatient period, and the SSR, which will summarize the worst overall value across all visits.

4.6.5 Other Laboratory Evaluations

4.6.5.1 Definitions and Derivations

Not Applicable.

4.6.5.2 Presentations

Not Applicable.

4.6.6 Vital Signs

4.6.6.1 Definitions and Derivations

Vital signs will be evaluated and assessed at screening, the start of the inpatient period, at randomization and all further study visits according to the SoA, Tables 1 of the CSP. Vital signs include height (cm, visit 1 only), weight (kg), pulse rate (beats per minute), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg). Absolute change from baseline will be calculated for each post-dose visit.

4.6.6.2 Presentations

Vital sign values will be summarised and listed. Vital sign data absolute and change from baseline will be summarised at each scheduled timepoint. The continuous vital sign parameters will be summarised with descriptive statistics. If a participant has multiple results for a particular test at a particular time point, the result selected by the rules in section 3.3.2 will be used for the summary. These will be provided for the SSO, limited to visits during the inpatient period and presented overall, and the SSR, which will include all visits with scheduled vital sign assessment and be presented by treatment received during the outpatient period.

4.6.7 Electrocardiogram

4.6.7.1 Definitions and Derivations

Electrocardiogram (ECG) assessments will be performed at screening, randomization, visit 4, visit 7, EOT, and follow-up (as specified in the SoA), and according to clinical

judgement in connection with severe hypokalaemia ($K^+ < 3.0$ mmol/L), severe hyperkalaemia ($K^+ > 6.0$ mmol/L) or any symptoms or clinical events suggesting cardiac arrhythmia. ECG parameters will include heart rate (beats/min), PR interval (msec), RR interval (msec), QRS duration (msec), QT interval (msec) and QTcF interval (msec). The absolute change from baseline will be calculated for each post-dose visit.

4.6.7.2 Presentations

ECG data will be summarised and listed. Absolute and change from baseline in ECG parameters will be summarised at each scheduled timepoint. The continuous ECG parameters will be summarised with descriptive statistics. If a participant has multiple results for a particular test at a particular time point, the result selected per rules in section 3.3.2 will be used for the summary. These will be provided for the SSO, limited to visits during the inpatient period and presented overall, and the SSR, which will include all visits with ECG assessments and be presented by treatment received during outpatient period.

All summaries of ECG data will exclude observations from site 7001 where a serious breach in the collection of ECG results was identified.

The number and percentage of participants with QTcF results exceeding ICH boundaries (>450ms, >480ms, >500ms), with increases from baseline >30ms, >60ms, >90ms, decreases from baseline >30ms, >60ms, >90ms and for each combination of post-baseline values (>450ms, >480ms, >500ms) and increases (>30ms, >60ms, >90ms) will be presented for the SSO, limited to visits during the inpatient period and presented overall, and the SSR which will include all visits with scheduled ECG assessment and be presented by treatment received during the outpatient period. Participants are included based on maximum QTcF value and are counted in all cumulative categories (e.g., a participant with a QTcF value of 510ms would be included in 450ms, 480ms and 500ms rows).

4.6.8 Other Safety Assessments

4.6.8.1 Definitions and Derivations

Not Applicable.

4.6.8.2 Presentations

Not Applicable.

5 INTERIM ANALYSIS

No interim analysis is planned for this study.

6 REFERENCES

Austin et al, 2010
Austin, P.C., 2010. Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes. Journal of clinical epidemiology, 63(1), pp.46-55.

Dong et al, 2015
Dong H, Robison LL, Leisenring WM, Martin LJ, Armstrong GT, Yasui Y. Estimating the burden of recurrent events in the presence of competing risks: the method of mean cumulative count. American journal of epidemiology. 2015 Apr 1;181(7):532-40.

7 APPENDIX

7.1 cuminc.sas

```
/************************************************************************/
/*****    Algorithms for actual and actuarial Analysis                  */
/************************************************************************/

/************************************************************************/
/*   Usage                                                              */
/*                                                                      */
/*   %Greenwod(inset =, outset =, timevar =, eventvar= , lastevnt=)     */
/*      A value must be given for each of the five macro parameters     */
/************************************************************************/

/************************************************************************/
/*                                                                      */
/* Computes actual incidence of events, together with standard errors   */
/* from the matrix form of Greenwood's formula.                         */
/*                                                                      */
/*   Coded into SAS by PPD , September 1999                             */
/*  The code uses macro assignments instead of array multplicatiok      */
/************************************************************************/

/************************************************************************/
/*  Input data set:  SAS dataset or view  Unchanged by the algorithm    */
/*                                                                      */
/*  Output data set: New SAS data set, whose name is a macro parameter */
/*                                                                      */
/*  Other interactions:  Creates data sets temp and tempset.            */
These are not needed at end of execution of the macro.                  */
/*                                                                      */
/*  Input data set variables used                                       */
/*                                                                      */
/*      The variable names are passed as parameters to the macro; the   */
/*      values of the variables are as further stated  below.           */
/*                                                                      */
/*  &timevar    The numeric variable containing outcome times.          */
/*              There will be exactly one outcome for each time;        */
/*              multiple outcomes are handled by multiple records,      */
/*              with the same value of the outcome time.                */
/*                                                                      */
/*  &eventvar   the numeric variable containing event info.  Values:    */
/*                   1 --- &lastevnt   transitions to a new state       */
/*                   others            censored, for this              */
/*                                     use of the macro                 */
/*              THE CODE ASSUMES THAT EVENTVAR CONTAINS INTEGERS ONLY,  */
/*              AND DOES NOT CHECK FOR THIS CONDITION.  IF              */
/*              THE CONDITION IS VIOLATED, THE RESULTS ARE UNDEFINED.   */
/*                                                                      */
```

```
/*  &lastevnt   The highest event value that will be analyzed.         */
/*              This must be an integer >= 1. The SAS statements in    */
/*              the code will in principle allow values of ,           */
/*              &lastevnt <= 99but the number of variables will become */
/*              so large as to cause poor execution long before that   */
/*              time.  (Interpretation of large values of &lastevnt is */
/*              questionable, so this limitation is one of form,       */
/*              rather than substance.)                                */
/*                                                                     */
/*              In a typical use of the macro, event 1 will be an      */
/*              event of primary interest, such as structural          */
/*              valve failure, event 2 will be death, and other values */
/*              will represent different forms of censoring.           */
/*              Using the macro with &lastevnt = 1 will produce        */
/*              the ordinary Kaplan-Meier analysis with death being    */
/*              just one form of censoring; using the macro with       */
/*              &lastevnt = 2 will produce the actual incidence of     */
/*              the event of interest, as well as the                  */
/*              actual incidence of death.                             */
/*                                                                     */
/*      Output   Variable names are fixed in the macro, and some       */
/*               labels are supplied.                                  */
/*                                                                     */
/*   &timevar   The same name as in the input data set. There is one   */
/*              output record for each distinct value in the           */
/*              input data set, as long as there is at least one event */
/*              occurring at that time; other times are ignored.       */
/*                                                                     */
/*    atrisk    The number of patients at risk at the time             */
/*                                                                     */
/*    event1 - event&lastevnt                                          */
/*              The number of events of that type at that time.        */
/*                                                                     */
/*    censored  The number of censored observations.                   */
/*                                                                     */
/*                                                                     */
/*    incid0    The estimated probability of remaining in state 0.     */
/*              This is the ordinary Kaplan-Meier estimate of          */
/*              freedom from all events.                               */
/*                                                                     */
/*    incid1 - incid&lastevnt                                          */
/*              The incidence of that event, up to and including the   */
/*              time; freedom from event is 1 - incidence.             */
/*                                                                     */
/*    error0 - error&lastevnt                                          */
/*              The standard errors of each incidence estimate.        */
/*              These are the square roots of the corresponding        */
/*              entries of the variance matrix;  the user may capture  */
/*              the entire variance matrix for other use.              */
/*                                                                     */
/***********************************************************************/

%macro Greenwod(inset =, outset =, timevar =, eventvar =, lastevnt =);

data tempset (keep = &timevar &eventvar); set &inset;
/* Kill undefined times, and reclassify events */
 if &timevar >= 0;
 if &eventvar < 1 | &eventvar > &lastevnt then &eventvar = 0;
/* Censor these events */
 run;

/* Count total at risk */
/* Add dummy observations to ensure that all designated events are     */
/* reflected by variables in the output data set */
/* These will have missing time, and will be killed in a couple of steps */
data tempset; set tempset nobs = numpats end = last;
 output;
 if last then do; &timevar = .; do &eventvar = 1 to &lastevnt; output; end; end;
 call symput('numpats', put(numpats, 10.));
 run;
```

```
proc sort data = tempset;
 by &timevar;
 run;

proc freq noprint data = tempset;
 by &timevar;
 tables &eventvar/out = temp;
 run;

proc transpose data = temp out = &outset;
 by &timevar;
 id &eventvar;
 var count;
 run;

data &outset; set &outset; if &timevar ^= .; run;
/* kill the dummy observations */

/* Now add an at risk column and put missing counts to zero */
/* Also make the variable names as promised */
data &outset; set &outset;
 rename _0 = censored;
 %do event = 1 %to &lastevnt; rename _&event = event&event; %end;
 attrib atrisk label = 'Patients at Risk';
 retain atrisk newrisk &numpats;
 drop newrisk;
 atrisk = newrisk;
  if _0 = . then _0 = 0; newrisk = atrisk - _0;
  %do event = 1 %to &lastevnt;
   if _&event = . then _&event = 0;
   newrisk = newrisk - _&event;
   %end;
 run;

/* Now do the actual computations */
data &outset; set &outset;

 /* Some labels for variables coming in */
 attrib
  censored label = 'Censored Observations'
  %do event = 1 %to &lastevnt; event&event label = "Incidents of Event &event" %end;
  ;

 /* Components of present incidence vector */
 /* (In the general model, this is the first row of the transition matrix) */
 /* Only the first row is variable */
 attrib
  pk0_0 label = 'Freedom from all events'
  %do event = 1 %to &lastevnt;
   pk0_&event label = "Incidence of event &event"
   %end;;

  /* Components of previous incidence vector */
 attrib
  pkb0_0 label = 'Previous freedom from all events'
  %do event = 1 %to &lastevnt;
   pkb0_&event label = "Previous incidence of event &event"
   %end;;

  /* Components of present covariance matrix */
 attrib
  %do row = 0 %to &lastevnt; %do col = 0 %to &lastevnt;
    ck&row._&col label = "Variance component (&row, &col)"
    %end; %end;;

  /* Components of previous covariance matrix */
 attrib
  %do row = 0 %to &lastevnt; %do col = 0 %to &lastevnt;
    ckb&row._&col label = "Previous variance component (&row, &col)"
    %end; %end;;
```

```
  /* Standard Errors */
 attrib error0 label = 'Standard Error of Freedom from All Events'
  %do event = 1 %to &lastevnt; error&event label = "Standard Error of Incidence of Event
&event" %end;;

  /* Components of variance addition due to new terms */
  /* These are from the multinomial distribution */
 attrib
  %do row = 0 %to &lastevnt; %do col = 0 %to &lastevnt;
    va&row._&col label = "Additional variance component (&row, &col)"
    %end; %end;;

 /* Components of differential transition Matrix */
 /* All but the first row are constant, but are made explicit for clarity of code */
 attrib
  %do row = 0 %to &lastevnt; %do col = 0 %to &lastevnt;
    da&row._&col label = "Differential transition (&row, &col)"
   %end; %end;;

 /* retain variables needed for the recursion */
 /* also initialize, for use the first time around */
 retain
  pkb0_0 1 %do event = 1 %to &lastevnt; pkb0_&event 0 %end;
  %do row = 0 %to &lastevnt; %do col = 0 %to &lastevnt;
    ckb&row._&col 0
    %end; %end;;


 /* Now to the general case */
 /* Compute terms needed for the update */
 /* Differential transition matrix */
 da0_0 = 1;
 %do event = 1 %to &lastevnt;
  da0_&event = event&event/atrisk;
  da0_0 = da0_0 - da0_&event;
  %end;
 /* The rest of this section is logically redundant, */
/* and kept in to clarify the matrix multiplication */
 %do row = 1 %to &lastevnt; %do col = 0 %to &lastevnt;
   %if &row = &col %then %do; da&row._&col = 1; %end;
   %else %do; da&row._&col = 0; %end;
   %end; %end;

 /* Additional variance component */
 /* The matrix is symmetric; for clarity all terms are explicitly created */
 %do row = 0 %to &lastevnt; %do col = 0 %to &lastevnt;
   %if &row = &col %then %do; va&row._&col = da0_&row*(1 - da0_&row)/atrisk; %end;
   %else %do; va&row._&col = -da0_&row*da0_&col/atrisk; %end;
   %end; %end;

 /* Updating the incidence vector is one matrix multiplication */
 %do col = 0 %to &lastevnt;
   pk0_&col = 0;
   %do event = 0 %to &lastevnt;
     pk0_&col = pk0_&col + pkb0_&event*da&event._&col;
     %end; %end;

 /* Updating the Variance matrix is more complicated */
 /* There is the sum of two products of three matrices each */
 /* The first part of the first product has the temporary name t1 */
 %do row = 0 %to &lastevnt; %do col = 0 %to &lastevnt;
   t1&row._&col = 0;
   %do event = 0 %to &lastevnt;
    t1&row._&col = t1&row._&col + da&event._&row*ckb&event._&col;
    %end; %end; %end;

 /* Finishing the first product */
 %do row = 0 %to &lastevnt; %do col = 0 %to &lastevnt;
   ck&row._&col = 0;
   %do event = 0 %to &lastevnt;
    ck&row._&col = ck&row._&col + t1&row._&event*da&event._&col;
```

```
    %end; %end; %end;

 /* Now add in the second term */
 %do row = 0 %to &lastevnt; %do col = 0 %to &lastevnt;
   ck&row._&col = ck&row._&col + va&row._&col*pkb0_0**2;
   %end; %end;

 /* Finally fix up the terms to be retained for next time around */
 %do event = 0 %to &lastevnt; pkb0_&event = pk0_&event; %end;
 %do row = 0 %to &lastevnt; %do col = 0 %to &lastevnt;
   ckb&row._&col = ck&row._&col;
   %end; %end;

 /* And the output standard errors */
 %do event = 0 %to &lastevnt; error&event = sqrt(ck&event._&event); %end;
 run;

data &outset /* keep only those variables likely to be of interest */
 (keep = &timevar atrisk censored
         %do event = 1 %to &lastevnt; event&event %end;
         %do event = 0 %to &lastevnt; pk0_&event %end;
         %do event = 0 %to &lastevnt; error&event %end;);
 set &outset;
 run;
```

7.2 MCC.SAS

```
/*##########################################################################################*/
/*##########################################################################################*/
/*December 2014, Qi Liu
This macro calculates the Mean Cumulative Count (MCC).
Reference: Dong H, Robison LL, Leisenring WM, Martin LJ, Armstrong GT, Yasui Y. American
Journal of Epidemiology.
             Estimating the burden of recurrent events in the presence of competing risks:
The method of mean cumulative count.
Dependence: It depends on the macro of cumulative incidence: cuminc.sas

The input data should have at least the following variables. For those who had no events
(events of interest or competing risk events),
one line per participant. For those with events, there is on line for each individual event.
So if one had event 1,2 then there are 2 lines for
this participant.

Macro paramters:
     input:            The input dataset
     id:               The id of participants
     d_event:      Date of occurrence of events/competing risk, if censor then the date of
censoring
     event:            The event of interest that the MCC will be calculated, 1 for the
event Yes and 0 for No
     event_outcome:    The outcome variable, with 0 for censoring, 1 for the event of
interest, 2,3,4... for competing risk outcomes etc.
     d_last:       The end of follow up date. --This is the same as d_event for those who
censored.
                       For those with at non-0 in event_outcome, this is on or after the
latest non-0 event date.
     d_dx:             The start time, In CCSS example, it is the cancer diagnosis date.
     timeQQ:       The time to event, calculated from (d_event) and the start date of each
person.
     output:           The output dataset */
/*##########################################################################################*/

%macro MCC(input=,id=,d_event=,event=,event_outcome=,d_last=,d_dx=d_dx,timeQQ=,output=);

proc sort data=&input; by &id &d_event; run;
/*Multiple SMNs.*/
data alldata;
     set &input;
     by &id;
     if first.&id then first=1;
```

```
    else first+1;
run;
/*output the last record for each person so we know how many events each person has*/
data last(keep=&id first);
    set alldata;
    by &id;
    if last.&id;
run;
data alldata;
    merge alldata last(rename=(first=maxN));
    by &id;
run;
/*For cumulative incidence (not MCC), only use the first event. This is the data for first
event analysis.*/
data data_1;
    set alldata(where=(first=1));
run;

proc freq data=alldata; table &event &event_outcome; run;  /*This has multiple records*/
proc freq data=data_1; table &event &event_outcome; run; /*This has only the first record*/

/*In order to calculate the MCC, in the ith event, assuming there is no event before the ith
event,
and need the data for this event of each person (for those less than
the number of event, take the maximum event record). So in each data set, one person appears
only once.*/
proc SQL; select max(maxN) into: max_number from alldata; quit;
%put the maximum number of SMNs one person had is : &max_number;

%if &max_number<2 %then %do;
    %put WARNING: The maximum number of &event events one participant had is &max_number
and hence no need to do MCC. Cumulative incidence is suggested;
    %goto mexit;
%end;

/*The maximum number is &max_number then I need &max_number datasets. -----all dataset
should contain the same number of people, i.e., everyone.
The first data for the first event is made above as data_1.*/
%macro MCCdata;
%do i=2 %to &max_number;
/*%let i=2;*/
/*For those with only 1 record:
If this only 1 record is a event, then it contributed to data_1 already and should not
contribute to furture event analysis ---change event=0 and its date.
If the d_last>&d_event then the cencor date is d_last; if d_last=&d_event then it means
there is no further FU of the &d_event date, hence take &d_event;
--- in summary, in both case, d_last can be taken.*/
data data_&i;
    set alldata(where=(first=1 and maxN=1));
    if &event=1 then do; &event=0; &d_event=&d_last; end;
run;
/*we need the last record for those with maxN<i (for these, in the ith event analysis, if
the last record is event it should be change to event=0 because it contributed already),
    and the ith record for those with maxN>= i*/
/*if i=2, we only need the ones with only 1 record and the last record for those with 2
records.*/
%if &i>=3 %then %do;
    %do j=2 %to %eval(&i-1);
    data see;
        set alldata(where=(first=&j and maxN=&j)); /**for those with 2 record, this will
get the 2nd record; for those with 3 record, this will get the 3rd record**/
        if &event=1 then do; &event=0; &d_event=&d_last; end;
    run;
    data data_&i; set data_&i see; run;
    %end;
%end;
    /*we need the ith record for those with maxN>=i*/
    data the_i; set alldata(where=(first=&i and maxN>=&i)); run;
    /*the final data for each i*/
    data data_&i; set data_&i the_i; run;
    /*make new event categories and time*/
```

```
    data data_&i;
        set data_&i;
        if &event=1 then &event_outcome=1;
        else if &event_outcome=1 and &event^=1 then &event_outcome=0;  /*in the outcome
categories, competing risk events remain the same. Those with last event of interest being
used in previous is now censored.*/
        &timeQQ=(&d_event-&d_dx)/365.25;
    run;
%end; /*end of i loop*/
%mend MCCdata;

%MCCdata;


/*In the outcome variable, 0 is censoring, what is the number of last event?
If in &event_outcome, it is 0,1,2 and hence it is 2*/
    proc SQL;
         select max(&event_outcome) into:nmax_outcome separated by "" from alldata;
    quit;
    %put The last category in the outcome variable is: &nmax_outcome;

/*Cumulative incidence for each of the events*/
%macro CI_each;
/*   %let i=1;    */
%do i=1 %to &max_number;
    %Greenwod(inset =data_&i, outset =cumout&i, timevar =&timeQQ, eventvar =&event_outcome,
lastevnt =&nmax_outcome);
/*at the first row, with time being 0 and pk0: being 0*/
data time0;
    retain &timeQQ  pk0_1-pk0_&nmax_outcome 0;
run;
    data CI&i(keep=&timeQQ CI:);
        set time0 cumout&i;
        /*calculate the change/difference*/
        array ci_outcome(*) pk0_1-pk0_&nmax_outcome;
        array new(*) CI1-CI&nmax_outcome;
        Do j=1 to dim(ci_outcome);
            new(j)=dif(ci_outcome(j));
        end;
        drop j;
    run;
%end;
%mend CI_each;
%CI_each;

/*combine all the cumulative incidence to calculate MCC, assuming the event 1 is the
recurrent event of interest (i.e, below used CI1 which was calculated from Pk0_1)*/
%macro MCC_CI;
/*
%let i=1;   ###the number of recurrent events, from 1 to &max_number
*/
%do i=1 %to &max_number;
data CI_&i;
    set CI&i(keep=&timeQQ CI1);
    which=&i;
    if CI1^=0 and CI1^=.;  /*only the time points that CI value changes ---i.e, the
difference !=0*/
run;

%if &i=1 %then %do;
    data CIall; set CI_&i; run;
    %end;
%else %if &i>=2 %then %do;  /*append all the CI data together*/
    data CIall; set CIall CI_&i; run;
    %end;

%end; /*end of all the event datasets i*/

/*order the combiend data by time*/
proc sort data=CIall; by &timeQQ which; run;
data &output;
```

```
    set CIall;
    /*Running sum*/
    MCC+CI1;
run;

%mend MCC_CI;
%MCC_CI;

%mexit:

%mend MCC;


/*----------------- Bootstrap to get 95% CI  ----------------*/
%macro
MCC_95CI(input=,id=,d_event=,event=,event_outcome=,d_last=,d_dx=d_dx,timeQQ=,output=);

/*Run MCC on the original data*/
%MCC(input=&input,id=&id,d_event=&d_event,event=&event,event_outcome=&event_outcome,d_last=&
d_last,timeQQ=&timeQQ,output=MCC_org);
data MCC_org; set MCC_org(rename=(CI1=CIorg MCC=MCC_org) drop=which); run;

    data MCC_org;
        set MCC_org;
        by &timeQQ;
        if last.&timeQQ;
    run;

/*To get 95% CI for each time point, we need 1000 values for each time point.*/
/*Randomly sample the data to make a dataset of the same size: same number of people.*/
proc SQL;
    create table all_ids as
    select distinct &id from &input;
quit;
proc SQL;
    select count(distinct &id) into:nparticipants from &input;
quit;
%do boot=1 %to 1000;
    /*  %let boot=9;  */
    proc surveyselect data=all_ids
        method=urs n=&nparticipants out=ms1 seed=%eval(1981+&boot) outhits;
    run;
    /*Now there are people appeared multiple times. Need to make them as different people
by using new ids*/
    data ms2;
        set ms1(keep=&id);
        newid=_n_;
    run;
    /*many-to-many merge to get new data. */
    proc sql;
        create table boot as
        select *
        from ms2, &input
        where ms2.&id=&input..&id;
    quit;

    %MCC(input=boot,id=newid,d_event=&d_event,event=&event,event_outcome=&event_outcome,d_l
ast=&d_last,timeQQ=&timeQQ,output=MCC_boot);

    data MCC_&boot;
        merge MCC_boot(drop=which) MCC_org(keep=&timeQQ in=aa);   /*this could be many to 1
merge as MCC_boot may conatin time with different MCC due to the above reason*/
        by &timeQQ;
        if aa;
    run;
    /*CI1 is the difference between the MCC in adjncent points. If CI1 is missing (the time
point is not in MCC_&boot), then the difference
    should be 0*/
    data MCC_&boot;
        set MCC_&boot;
        if CI1=. then CI1=0;
```

```
    run;
    data MCC_&boot;
        set MCC_&boot;
        MCC_&boot+CI1;
    run;

    data MCC_&boot;
        set MCC_&boot;
        by &timeQQ;
        if last.&timeQQ;
    run;
    %if &boot=1 %then %do;
        data MCC_all;
            merge MCC_org(keep=&timeQQ MCC_org) MCC_&boot(keep=&timeQQ MCC_&boot);
            by &timeQQ;
        run;
    %end;
    %else %do;
        data MCC_all;
            merge MCC_all MCC_&boot(keep=&timeQQ MCC_&boot);
            by &timeQQ;
        run;
    %end;
%end;

/*for each time point, get the 25th and the 975th as the lower and upper bound of the 95%
CI*/
data MCC_95CI(keep=&timeQQ MCC_org Low Up);
    set MCC_all;
    Low=smallest(25,of MCC_1-MCC_1000);
    Up=smallest(975,of MCC_1-MCC_1000);
run;

data &output;
    set MCC_95CI;
    label MCC_org="MCC"
        low="95% interval, lower"
        Up="95% interval, upper";
run;
%mend MCC_95CI;

/*   proc datasets nolist; delete MCC:; quit; */
```