STATISTICAL ANALYSIS PLAN

Study Code **D9488c00001**

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A Phase 3, International, Randomised, Double-blind, Placebo-controlled Study to Evaluate the Effect of Sodium Zirconium Cyclosilicate on Chronic Kidney Disease (CKD) Progression in Participants with CKD and Hyperkalaemia or at risk of Hyperkalaemia

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACEi	Angiotensin converting enzyme inhibitor
AE	Adverse event
AIC	Akaike information criterium
ARB	Angiotensin II receptor blocker
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CDF	Cumulative distribution function
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus disease 2019
CPS	Calcium polystyrene sulfonate
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Cardiovascular
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCDF	Empirical cumulative distribution function
CRF	Electronic Case Report Form
ED	Early discontinuation
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ESD	Early study discontinuation
ESKD	End stage kidney disease
FAS	Full analysis set
FDA	Food and Drug Administration
ICF	Informed consent form

ICH	International Council for Harmonisation
IP	Investigational product
IPD	Important Protocol Deviation
IRT	Interactive Response Technology
KDIGO	Kidney Disease: Improving Global Outcomes
MI	Multiple imputation
MRA	Mineralocorticoid receptor antagonist
MTP	Multiple testing procedure
PT	Preferred Term
QD	Once daily
QOD	Once every other day
QTcF	QT interval corrected using Fridericia's formula
RAAS	Renin-angiotensin-aldosterone system
RAASi	Renin-angiotensin-aldosterone system inhibitor
RTSM	Randomisation and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety analysis set
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard Deviation
SOC	Subject Organ Class
SZC	Sodium Zirconium Cyclosilicate
UACR	Urine Albumin to Creatine Ratio

AMENDMENT HISTORY

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
N/A	15 Dec 2021	Initial approved SAP	Yes	N/A
Section 3.3.4 Multiplicity / Multiple comparisons	01 Dec 2022	The wording around the multiple testing is changed.	Yes	To align with CSP.
Section 4.1.6 Disease Characteristics	01 Dec 2022	Addition of extra disease characteristics	Yes	As per discussion with the FDA and for ease of clinical interpretation.
Section 4.1.8 Concomitant Medications and throughout the document	01 Dec 2022	Definition of short term disallowed concomitant medications added	Yes	To align with CSP.
Section 4.1.9 Study Drug Exposure and Compliance	01 Dec 2022	Definition of total exposure has been amended to state “total prescribed time on IP (i.e., the days between the first and the last scheduled dose, inclusive) during that period”	Yes	For clarity.
Section 4.2 Endpoint Analysis	01 Dec 2022	Description of missing data handling added, including a specification that eGFR values obtained from re-tests, if the original eGFR sample is missing, may be used in the analyses.	Yes	For clarity.
Section 4.2 Endpoint Analysis	01 Dec 2022	Clarification of hypothetical intercurrent events strategy has been added	Yes	For clarity.
Section 4.2 Endpoint Analysis	01 Dec 2022	The list of covariates to be included in the models has been specified (consisting of treatment arm and the factors reflecting stratification).	Yes	For clarity and analysis optimization.

Section 4.2.1 Analysis of Primary Objective	01 Dec 2022	Choice of covariance structures (unstructured to independence)	Yes	Analysis optimization.
Section 4.2.1 Analysis of Primary Objective	01 Dec 2022	Addition of extra sensitivity analysis (two-slope SP model, repeated measures model with unstructured covariance structure, imputation of first post-ESKD eGFR value, tipping point analysis for lost to FU, replication of the main analysis using the original, age-corrected, eGFR formula)	Yes	As per discussion with the FDA, as well as a consequence of changing the eGFR formula (CSP v 2) and the change of covariance structure in the main analysis.
Section 4.2.1 Analysis of Primary Objective	01 Dec 2022	Addition of extra supplementary analysis (multiple post-ESKD eGFR values imputed)	Yes	As per discussion with the FDA, as well as ease of clinical interpretation.
Section 4.2.1 Analysis of Primary Objective	01 Dec 2022	Addition of extra subgroup analysis	Yes	As per discussion with the FDA, as well as ease of clinical interpretation.
Section 4.2.2 Analysis of the Secondary Objective 1	01 Dec 2022	The derivation of the endpoint has been clarified	Yes	For clarity.
Section 4.2.7.3 Evaluation of potential impact of acute effects	01 Dec 2022	Further details regarding the supportive analysis of change in eGFR (pre vs post treatment) have been provided	Yes	For clarity.
Section 4.5.1 Safety analyses	01 Dec 2022	The presentation of rate of occurrence of AEs has been removed, replaced with a possibility to evaluate hazard ratios.	Yes	Optimization of the analysis in accordance to the recent guidance.
Section 6 References	01 Dec 2022	Addition of a reference	Yes	N/A

Section 7 Appendix	01 Dec 2022	Creation of Appendix 7.1 The mapping of CKD aetiology class. A mapping of the CKD aetiology as collected in the eCRF to a different classification, used in analyses, has been added.	Yes	For programming purposes.
Section 7 Appendix	01 Dec 2022	Creation of Appendix 7.2 The assignment of countries to regions. A mapping of countries to regions has been added.	Yes	For programming purposes.
Section 7 Appendix	01 Dec 2022	Creation of Appendix 7.2 Sample size calculation.	Yes	The sample size calculation present in CSP has been added to the SAP for readers convenience.
Section 3.3.1.2	22 Jan 2023	Definition of phases updated	Yes	To accommodate some specific cases observed in the (blinded) data during dry run preparation.
Section 4.2	22 Jan 2024	Deletion of a large part of supplementary and sensitivity analyses.	Yes	Due to the premature termination of the study, the decision was taken to slim down the scope of the CSR. All the main analyses remain as previously defined. However, majority of supportive and supplementary analyses have been removed as superfluous in view of the limited data availability.
Section 4.2	24 Apr 2024	Simplification of the data exploration	Yes	For the same reason as above, even other simplifications have been introduced. For instance, no extensive exploration of missing data patterns will be performed. Some sub-group analyses have been removed.
Section 4.2.1.5	24 Apr 2024	Minor change in sub-group analysis approach	Yes	The effect estimates will now be obtained for each sub-group separately, rather than from a global model via application of contrasts. Changed for simplicity of implementation.

Section 4.2	24 Apr 2024	Exclusion of the late measurements	No	Due to the termination of the study, the number of laboratory measurements later in the study is very limited. As such, all the lab-based analyses (majority of efficacy) will be performed on data obtained up to and including visit 17.
4.2.6	24 Apr 2024	Change of the repeated measurements analysis from mixed model to GEE	Yes	Relative ease of interpretation, as GEE works with marginal odds, rather than conditional ones, leading to a closer correspondence to a simple number (%) type of tabulation.
4.5	24 Apr 2024	Actual treatment removed from listings	Yes	
4.5.1	24 Apr 2024	All AEs resented by PT in decreasing frequency, rather than only the most common ones. Sorting now by SZC.	Yes	
4.5.2	24 Apr 2024	For all abnormality tabulations, only patients with normal values at baseline are included.	Yes	
3.3.1.3	29 May 2024	Definitions of phases revised and clarified.	Yes, but there are consequences that are not, see 3.2 below.	More precise definitions of the phases needed.
3.2	29 May 2024	Definitions of the analysis sets revised and clarified.	No	Consequence of the revision of the study phases in 3.3.1.3 mentioned above.
4.1.1.1	29 May 2024	Definition of disposition entries revised and clarified	Yes	Consequence of the revision of the study phases in 3.3.1.3 mentioned above.
4.1.9.1	29 May 2024	Compliance, both for SZC/SZC placebo and IP RAASi will no longer be presented, neither summarised, nor listed.	No	Due to drug-accountability (DA) data being unavailable. DA data are lying behind the derivation of compliance.
4.2.1.1	31 May 2024	The set of sensitivity analyses reduced.	No	Due to early close-down of study.

4.2.1.2--.5	3 June 2024	Subsections 4.2.1.2.--.5 merged into one Subgroup 4.2.1.2	Yes	More clarity, it is hoped.
4.2.2.2	3 June 2024	These two supplementary analyses to Secondary objective #1 removed: • An analysis of time to the first occurrence of sustained ≥ 50% decline in eGFR, onset of ESKD or death from kidney failure, where the censored event times have been imputed. • An analysis of time to the first occurrence of sustained ≥ 50% decline in eGFR, onset of ESKD or death from kidney failure.	Yes	Due to early close-down of study.
4.2.2.3	3 June 2024	These two supportive analyses to Secondary objective #1 removed: • Imputation of events. • Initiation of treatment that affects potassium or eGFR.	Yes	Due to early close-down of study.
4.2.2.4	3 June 2024	Subgroup analyses to Secondary objective #1 removed.	Yes	Due to early close-down of study.
4.2.4.1	3 June 2024	Main analysis to Secondary objective #3 changed from a mixed model to a linear-regression model.	Yes	Due to early close-down of study.
4.2	3 June 2024	All supplementary analyses removed from the analyses to Secondary objective #3.	Yes	Due to early close-down of study.
3.2	3 June 2024	Table revised for better clarity	Yes	More precise definitions of the phases needed.

General	29 May 2024	Text revised.	NA	As is done at any updates.

1 INTRODUCTION

STABILIZE-CKD is a Phase 3, International, Randomised, Double-blind, Placebo controlled Study to Evaluate the Effect of Sodium Zirconium Cyclosilicate on Chronic Kidney Disease (CKD) Progression in Participants with CKD and Hyperkalaemia or at Risk of Hyperkalaemia. For details on study background and rationale, please refer to the Clinical study protocol for STABILIZE-CKD (CSP, D9488C00001, Version 2.0 (16Jun2022)).

This Statistical Analysis Plan (SAP) provides further details of the summaries and analyses to be performed to report the findings in the CSR and should be read in conjunction with the STABILIZE-CKD Clinical Study Protocol (CSP).

2 CHANGES TO PROTOCOL PLANNED ANALYSES

No changes were made to the analyses as described in the CSP.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

Only one set of analyses will be performed to write the CSR. These will be performed at the end of the study after the data base is locked and all data is available.

3.2 Analysis Populations

The study consists of five analysis populations, namely:

Populations for Analysis

Population/analysis set	Description
Enrolled	All participants who sign the ICF.
Safety analysis set, initiation phase (SAS-IP)	All participants receiving at least one dose of Initiation SZC.
Safety analysis set, run-in phase (SAS-RIP)	All participants receiving at least one dose of Run-in SZC, regardless within or without the run-in phase.
Safety analysis set, maintenance phase (SAS-MP)	All randomized participants receiving at least one dose of Maintenance SZC or Maintenance-phase placebo, regardless within or without the maintenance phase.
Full analysis set (FAS)	All randomised participants.

3.3 General Considerations

For the purpose of describing the data, summary statistics illustrating the empirical distribution of the variables will be tabulated for most of the collected measurements.

Continuous variables will be summarised using the following descriptive statistics: n (the number of patients included in the analysis), mean, median, standard deviation, minimum, maximum and quartiles where appropriate. Categorical variables will be summarised using number and percentage of observations in each category, with the denominator for the percentages depending on the type and purpose of analyses (e.g., the number of subjects in an analysis set will be used for the tabulations of the baseline characteristics, but number of subjects with available data at a visit will be used for summary statistics by visit tabulations).

In addition, time to event variables will be summarised using Kaplan-Meier estimators of the CDF function. For a selection of continuous variables, in the absence of censoring, the whole eCDF function, rather than a number of different kinds of summary statistics, might be plotted.

3.3.1 General Study Level Definitions

3.3.1.1 Baseline

Different baselines will be defined for the initiation, run-in and the maintenance phases. For each of these phases, the baseline will be defined as the value obtained on the first day of the phase, or, if such a measurement is missing, within a certain number of days prior to the first day of the phase, namely: within 14 days for the Initiation-Phase, within 1 day for the Run-In Phase and within 5 days for the Maintenance Phase. See Section 3.3.1.3 for the definition of the different phases of the study.

3.3.1.2 Imputation of Missing Dates

No imputation will be done for missing or partial missing dates, except for start and end date for concomitant medication, which will be imputed as indicated below. For the purpose of this imputation, "first dose" refers to the (scheduled) beginning of SZC administration in the initiation phase.

- Missing start day - impute as the 1st of the month unless the month is the same as month of first dose of study drug, then impute start day as date of first dose of study drug.
- Missing start day and month – impute 1st of January unless year is the same as for first dose date, then impute first dose date. Ensure that the start date is prior to the end date of the concomitant medication.

- Start day completely missing - impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st of January of the same year as the end date of the concomitant medication.

When imputing a start date ensure that the new imputed date is sensible, i.e., is prior to the end date of the medication.

- Missing end day - impute the last day of the month unless month is same as the date of contact with the patient, then impute the date of last contact.
- Missing end day and month – impute 31st of December unless year is the same as the date of last contact, then impute the date of last contact.
- End date completely missing - if the ongoing flag is missing, then assume that the medication is still being taken, i.e., do not impute a date. If the medication has stopped and start date is prior to first dose date, then impute the 1st dose date. If it started on or after first dose date, then impute to be the date of last contact.

3.3.1.3 Study Periods

The study consists of five distinct study periods, namely: Screening phase, Initiation phase, Run-In phase, Maintenance phase and Follow-Up phase. Participants will transfer directly between study periods in the order given.

The five phases are delimited in time like this:

Screening phase

- *First day*: the day of the date of signature on the signed informed-consent form (ICF).
- *Last day* (if participant not going into Intervention period/Initiation phase): the day of last contact.
- *Last day* (if participant going into Intervention period/Initiation phase): the day before first Initiation-phase SZC-dose.

Note: If there is no signed ICF, then there is no Screening phase, and no other phases either.

Initiation phase

- *First day*: the day of first Initiation-phase SZC-dose.
- *Last day* (if not going into Run-in phase): the day of last Initiation-phase SZC-dose.
- *Last day* (if going into Run-in phase): the day before the first day of the Run-in phase (see below).

Run-in phase

- *First day*: the day of first Run-in SZC dose, or the day of first Run-in (IP) RAASi-dose, whichever comes first, however no earlier than the day after last Initiation-phase SZC-dose.

  A consequence of this is that the Run-in phase always has its first day on the day after last Initiation-SZC dose, *at the earliest*; if any Run-in IP (SZC, lisinopril, valsartan, irbesartan), would be initiated before, or on the same day as, the last Initiation SZC dose, then the Run-in phase will start on the day after the day of last Initiation-SZC dose. This means that any Initiation-SZC dosing takes precedence over any Run-in IP dosing when it comes to separating the Initiation phase and the Run-in phase, in favour of the Initiation phase. If – on the other hand – both Run-in SZC and Run-in RAASi would start on a day (potentially different days for Run-SZC and Run-in RAASi) *after* the day of last Initiation SZC then the Run-in phase will have its first day on the day of the earliest initiation of any of the two Run-in IP types (SZC or RAASi). This means that any time "gap" between Initiation SZC and Run-in IP will be assigned to the Initiation phase.
- *Last day* (if not going into Maintenance phase): the day of last Run-in SZC-dose, or the day of last Run-in (IP) RAASi-dose, whichever comes last.
- *Last day* (if going into Maintenance phase): the day before the day of randomisation.

Maintenance phase

- *First day*: the day of randomisation.
- *Last day*: the day of last contact.

Note: No Follow-up phase will follow the Maintenance phase.

Follow-up phase

- *First day*: The day after last day of the immediately preceding phase (Initiation phase or Run-in phase; no Follow-up phase will follow the Maintenance phase and the Screening phase; see above). However, if the day of last contact would occur in a preceding phase, then there will not be any Follow-up phase.
- *Last day*: The day of last contact.

Note 1: A Follow-up phase can only occur following the end of the Initiation phase or following the end of the Run-in phase. No Follow-up phase will occur after the Maintenance phase.
Note 2: There will not be any Follow-up phase if the day of last contact would occur in a preceding phase.

For the purpose of presentation of **safety analyses**, the follow up phase will generally be combined with the phase that directly precedes it.

For the purpose of presentation of **patient disposition**, the study periods as provided by the investigator (such an option exists in the CRF for disposition events in particular) will be used.

3.3.1.4 On-treatment and During Period definitions

An event, or measurement, is said to be occurring during a particular period if the start date of the event, or the date of measurement, falls within the start and end date of the period as defined in Section 3.3.1.3.

An event, or measurement, is said to be occurring on-treatment for a particular period if the start date of the event, or date of measurement, falls within this period and simultaneously occurs between the first dose date and last dose date of SZC/Placebo, for that period, plus one day.

3.3.2 Visit Window

Visit windowing will not be applied for the study. Rather, the assignment of measurements to scheduled visits will be determined by the investigator. Missing measurements at scheduled visits will not be replaced with those obtained on the unscheduled visits in the vicinity of the scheduled ones.

3.3.3 Handling of Unscheduled Visits

Data obtained on unscheduled visits (e.g., safety laboratory evaluations) will be excluded from any analyses and presentations that are based on scheduled visits, an example of these being a presentation summary statistics of laboratory measurements, by visit. It will, however, be included in analyses of extreme values observed during a particular period of time, such as tabulations of high/low/out-of-range test results observed while a subject was on treatment. It will also be included in the analyses of endpoints that are not connected to a particular scheduled visit, such as, for instance, time to the first Lisinopril/Valsartan dose decrease after randomization.

3.3.4 Multiplicity / Multiple Comparisons

Statistical testing will be performed for all primary and secondary hypotheses. In all cases, the null hypothesis will be that of no difference between the treatment arms (SZC vs placebo), with the two-sided alternative of there being a difference. Two primary hypotheses (corresponding to the evaluation of the difference in total and chronic eGFR slope, respectively) are defined in the study.

The family-wise Type I error rate will be controlled in the strong sense over the families of primary and the secondary hypotheses i.e., regardless of whether the hypotheses covered are true or false.

Two co-primary hypotheses (corresponding to the evaluation of the difference in total and chronic eGFR slope, respectively) are defined in the study. The two hypotheses will be tested in parallel (i.e., with no pre-defined order) using the whole significance level alpha.

Provided both primary hypotheses are rejected, the testing will proceed to the secondary hypotheses. A fixed sequence MTP will be applied to the family of all secondary hypotheses, with the order in the sequence following the order specified in Table 2.

In accordance with the fixed sequence MTP, significance for a hypothesis will be declared if the corresponding two-sided p-value is smaller than 0.05, provided that all other preceding hypotheses in the sequence have been rejected.

3.3.5 Handling of Protocol Deviations in Study Analysis

Reasons for PD being classified as Important Protocol Deviations (IPD) will include those related to:

- Inclusion criteria
- Exclusion criteria
- Discontinuation criteria for IP met but subject not withdrawn from study treatment
- Discontinuation criteria for overall study withdrawal met but subject not withdrawn from study
- IP related deviations
- Excluded medication taken
- Deviations related to study procedure
- Incorrect stratification
- Other important protocol deviations

Details regarding protocol deviations, including a finer sub-categorization, as well as methods of detection, will be listed in the Protocol Deviation plan. Since an intention-to-treat principle is applied to the main analyses of the efficacy endpoints, occurrence of an IPD will not imply exclusion of data from these main analyses. However, supplementary analyses to evaluate e.g., the impact of usage of disallowed medications on the efficacy results, might be conducted, and would then exclude data points obtained while a subject is taking such a disallowed medication (see Section 4.2.7 for details).

Deviations related to the Covid-19 pandemic will be identified during the IPD collection.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivations, analyses, and data presentations per domain (study population, efficacy, safety).

4.1 Study Population

This section, "study population", covers presentation of subject disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical history, concomitant medication, and study drug compliance.

Unless specified otherwise, analyses will be performed separately for the initiation, run-in and maintenance phases, using the SAS-IP and SAS-RIP for first two phases, and the full analysis set for the maintenance phase.

Data will be summarised descriptively for each of the phases, by treatment arm (for the maintenance phase) and the overall total population. Categorical variables will have an additional “Missing” category that includes the subjects for which the relevant information is not available. Denominators used to calculate percentages will be the number of subjects in the relevant analysis set and in total (i.e., "missing" category included in the denominator).

4.1.1 Subject Disposition and Recruitment

4.1.1.1 Definitions and Derivations

Subject disposition will be collected as part of the eCRF. The following definitions and derivations are applicable for the table:

- **Enrolled** subjects will be defined as those who have signed the informed consent form.
- Subjects who **entered the initiation phase** will be defined as those who received at least one dose of Initiation SZC.
- Subjects who **entered the run-in phases** will be defined as those who received at least one dose of Run-in SZC or Run-in RAASi (lisinopril/valsartan/irbesartan).
- Subjects who **entered the maintenance phase** will be defined as those who were randomized.
- Subjects who **completed a phase of the study** will be defined as subjects who either are assigned the status “Completed” for the phase by the investigator, or who have a

disposition status as per the eCRF (e.g., "Death", "Withdrawal by subject") that is assigned during a later phase.

- Subjects who **completed the study** will be defined as subjects who completed all these four phases:
  - the Screening phase,
  - the Initiation phase,
  - the Run-in phase, and
  - the Maintenance phase,

  and, in addition, attended the follow-up visit.

- Subjects who **completed treatment** for a given phase will be defined as subject who did not discontinue treatment prematurely during that phase. Note that, for the initiation and run-in phases, this should coincide with completion of that whole phase, as subjects who discontinue treatment during these phases should also discontinue the whole study as per the study design.

The study period during which a particular disposition event takes place is also indicated directly in the eCRF by the investigators and will be used in the presentations.

4.1.1.2 Presentation

The purpose of this presentation is to provide an overview of the patient flow in the study, i.e., how many patients entered the respective study phases, how many completed the respective phases, the reasons for discontinuing a phase etc.

The tabulation will include the number, and percentage, of subjects falling into different disposition categories, i.e., it will be a descriptive summary in accordance with the rules described in Section 3.3. It will, for instance, include the following categories: subjects enrolled, subjects entering each of the phases, subjects discontinuing each of the phases, as well as reason for discontinuation, subjects completing and discontinuing treatment in the maintenance phase.

Effect of COVID-19 on the disposition

Subjects whose disposition status was affected by COVID-19 will be presented separately, the presentation including the number, and percentage, of subject who discontinued treatment and / or study due to COVID-19. An overview of subjects whose study conduct was affected by COVID-19, e.g., whose visits were impacted and were performed remotely rather than on site, will also be provided.

Recruitment

The recruitment pattern, in terms of the number, and percentage, of subjects per region, country and site, will be provided. This will be described in terms of subjects Screened, Randomized, and Dosed.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

There will be five separate analysis sets in the study. For the definition, see Section 3.2. Explicitly, the FAS set will consist of all patients receiving a randomization number, while the different SAS sets will be determined by whether a patient has at least one dose of SZC provided to them, as per the drug accountability module in the eCRF, during the respective phases of the study.

4.1.2.2 Presentation

The analysis sets will be described descriptively, with the number of subjects in each set displayed by treatment arm, along with the overall total consisting of both treatment arms. In addition, the number of subjects excluded from each analysis set, along with the reason for exclusion, will be displayed in the same manner.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

All protocol deviations will be recorded and stored in Veeva Vault (a component of the unified platform for clinical trial management, that incorporates e.g., the electronic trial master file and the clinical trial management system), regardless of their detection method. The data set containing the PDs will then be exported from this system at the time of the database lock, to be converted into a SAS data set and included in the data base for the purpose of analysis and reporting.

4.1.3.2 Presentation

Important protocol deviations will be summarised descriptively in accordance with the rules described in Section 3.3.

The number of patients with at least one protocol deviation will be presented, and specific protocol deviations will be presented and nested within this. Subjects may have more than one protocol deviation.

Subjects with protocol deviations relating to COVID-19 will be presented in the same format as described above.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographic data will be collected in the eCRF during screening. The variables collected, and summarised, are:

- Age (in years and by age category (18 - <65, ≥65 - <85, ≥ 85 years)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other)
- Country
- Geographic Region (Asia, Europe, North America, South America)

Age group will be derived using the continuous age variable collected in the eCRF. Geographic region will be derived from country.

4.1.4.2 Presentation

The demographic characteristics will be summarised descriptively in accordance with the rules set out in Section 3.3.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

The baseline characteristics that will be summarised include:

- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m2)

The BMI will be derived for each subject by calculating {weight at screening (kg)}/{height (m)}^{2}.

4.1.5.2 Presentation

Baseline characteristics will be summarised descriptively and presented according to the rules described in Section 3.3.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

The disease characteristics that will be summarised include:

- UACR
  - Measured value (mg/g)
  - UACR group (<300, ≥300 - <1000, ≥1000 mg/g)
- eGFR
  - estimated value (mL/min/1.73m2)
  - eGFR group (<15, ≥15 - <30, ≥30 - <45, ≥45 - <60, ≥60 mL/min/1.73m^2)
- S-K
  - Measured value from central laboratory (mmol/l)
  - Measured value from local laboratory S-K (mmol/l)
  - S-K group (≤5.0, >5.0 - ≤6.0, >6.0 - ≤6.5, >6.5 mmol/l) (central laboratory)
  - S-K group (≤5.0, >5.0 - ≤6.1, >6.0 - ≤6.5, >6.5 mmol/l) (local laboratory)
- Diabetes (yes / no)
- Systolic blood pressure (≤ 130, > 130 mmHg)
- CKD aetiology class (see Appendix 7.1 for details)
- SGLT2 inhibitors or finerenone (yes / no)
- Adequate RAASi dose at randomization (yes/no)

The eGFR and UACR values will be provided by central laboratory. The S-K at baseline will be provided by both central and local laboratory.

The measurements included in this summary will depend on which study period the summary corresponds to. For instance, for initiation phase, local laboratory S-K will correspond to the measurement performed at Visit 2. For the run-in phase, both local laboratory S-K corresponding to Visit 2 and value obtained at Visit 3d will be included.

4.1.6.2 Presentation

Disease characteristics will be summarised descriptively and presented according to the rules described in Section 3.3.

In addition, a cross-tabulation of the eGFR and the UACR categories, as described above, will be created, the tabulation including the number and percentage of patients in each eGFR / UACR category. For the percentage calculation, the number of patients SAS-IP will be used as the denominator.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Only specific medical history will be collected in the eCRF (i.e., corresponding to specific terms). It will be classified in terms of preferred term (PT) and system organ class (SOC).

This will be done according the latest MedDRA version the time of database lock. The definition of medical history will not distinguish between prior and ongoing medical history.

4.1.7.2 Presentation

Medical history will be summarised descriptively and presented according to the rules described in Section 3.3.

Subjects will only be counted once per SOC and PT, regardless of the number of occurrences within each category. PT will be nested within the appropriate SOC and sorted by international order of SOC and alphabetically for PT.

4.1.8 Concomitant Medications

4.1.8.1 Definitions and Derivations

Concomitant medications, including medications taken during the screening period, will be collected in the eCRF and classified by ATC classification and generic term.

Baseline medications for a particular phase are defined as medications with a start date no later than the beginning of the phase in question, and a stop date after the beginning of the phase (or ongoing at the end of study).

Concomitant medications for a particular phase are defined as medications which a patient takes during that phase. Explicitly, it is medications with a start date earlier than the end of the specific phase and a stop date during or after the same phase (or ongoing at the end of study). Missing start and stop dates will be handled as set out in Section 3.3.1.2.

A **rescue medication** is defined as a medication used in connection to the adverse event of severe hyperkalaemia requiring rescue as determined by the investigator.

Two types of medications are considered to be disallowed in the study:

- **A potassium binder is disallowed** if it is not a short term (≤ 2 days) rescue medication. Potassium binders are defined by the following ATC codes / ingredients:

  Table 1: Disallowed potassium binders

ATC code	Ingredients
V03AE	SODIUM POLYSTYRENE SULFONATE
V03AE	CALCIUM POLYSTYRENE SULFONATE
V03AE	PATIROMER
V03AE	PATIROMER CALCIUM
V03AE	PATIROMER SORBITEX CALCIUM

- **RAASi medication is disallowed** if it is taken concomitantly with Valsartan or Lisinopril, after the initiation phase, as specified by the CSP.

4.1.8.2 Presentation

Concomitant medications will be summarised descriptively and presented according to the rules in Section 3.3. Disallowed medications and baseline RAASi medications will be summarised in a similar manner.

Medications will be summarised according to ATC classification and then by drug name within each classification. Further, the number of subjects on any medication will also be presented.

4.1.9 Study Drug Exposure and Compliance

4.1.9.1 Definitions and Derivations

Study periods definition for exposure and compliance

Duration of exposure will be defined separately for each of the study periods. Exposure will be evaluated both for RAASi and SZC/Placebo (SZC alone for the initiation and the run-in phases).

Total exposure to study drug within a period will be defined as total prescribed time on IP (i.e. the days between the first and the last scheduled dose, inclusive) during that period.

The duration of exposure (months) will be calculated separately for exposure to SZC/placebo and Lisinopril/valsartan.

Exposure excluding interruptions to the study drug will be defined as the number of days a subject was scheduled to be on IP, during the respective periods, excluding any scheduled dose interruptions (i.e., as assigned by the investigator).

Duration of exposure to a particular dose will be defined as the time the dose was prescribed, excluding interruptions.

Compliance to SZC/Placebo will not be presented, neither summarised, nor listed.

Compliance to IP RAASi (lisinopril, valsartan, irbesartan) will not be presented either, neither summarised, nor listed.

4.1.9.2 Presentation

Exposure, total and excluding interruptions will be summarised descriptively and presented according to the rules described in Section 3.3. Duration of exposure to a particular dose level will be summarised in a similar manner, by treatment group and dose level, for each combination of study drug and study period.

Discrete summaries of the number and percentage of patients receiving a particular dose level of SZC/Placebo and lisinopril/valsartan (including dose 0, which would correspond to a temporary, or a permanent, interruption) will be presented for the start of the run-in phase, end of the run-in phase and every 3 months during the maintenance phase.

The mean dose will be plotted over time (per day), for both SZC/Placebo and Lisinopril/valsartan.

4.2 Endpoint Analyses

This section covers details related to the analyses of primary, secondary, and other endpoints, including sensitivity and supportive analyses.

All the efficacy analyses will be aimed at evaluating the potential effect of SZC during the randomized treatment phase of the study (i.e., the maintenance phase). As such, the estimands for these analyses can be described as follows.

Population: For all of the efficacy analyses specified in the Table 2 below, the population, in estimand terminology, consists of the patients satisfying the randomization criteria of the study. That is, patients who satisfy the inclusion and exclusion criteria at study entry, and who achieve, and maintain, normokalaemia after the initiation and the run-in phases.

Treatment: For all the analyses performed on the maintenance phase, the treatment, in the estimand framework, is SZC and placebo while receiving lisinopril/valsartan, as guided by the CSP. For all the comparisons of SZC vs Placebo, the Placebo group will be used as the reference.

Intercurrent events: The following intercurrent events that might have impact on the interpretation or existence of the measurements associated with the clinical question have been identified:

- Death
- Permanent discontinuation of SZC/Placebo
- Initiation of long-term potassium-lowering treatment

- Introduction of a concomitant medication that may directly affect CKD progression (e.g., SGLT2 inhibitors)
- Onset of ESKD (the definition of which can be found in CSP section 8.1.2 and includes initiation of dialysis or a kidney transplant)
- Change in IP dosage (SZC or RAASi)

It may be hypothesized that a change in IP dosage (SZC or RAASi) may cause an acute haemodynamic effect that, although visible in the eGFR profile, might not reflect a true change in CKD progression but only a temporary change in eGFR. A set of analyses aimed at further evaluating the presence, and potential impact, of such effects will be performed, see Section 4.2.7 for details.

The main strategy for handling the intercurrent events in the analysis of the primary objective will be that of treatment policy. That is, the intercurrent events that lead to a potential change in the measurements profile, but for which post-intercurrent event data are available (e.g. treatment discontinuation, introduction of eGFR altering concomitant therapy), will be ignored in the analysis, and all data obtained, both pre and post the intercurrent event, will be included as planned. In the table below, the approach for handling intercurrent events described above is referred to as "main strategy". The exception to this rule will be the events for which it could be argued that, after experiencing these, a participant ceases to belong to the population of interest. For such an event, any data collected post event occurrence will be excluded from the main analyses. Onset of ESKD is the only type of event currently identified in this category.

In addition to the main analyses, a number of supplementary analyses of the primary and secondary endpoints, utilizing a hypothetical intercurrent event strategy, will be carried out. In this case, data from after the intercurrent events that lead to a potential change in the measurements profile will not be used in the analysis. Instead, a hypothetical scenario that the intercurrent event did not have occur will be considered. For example, for the intercurrent event of long-term potassium lowering treatment and a hypothetical strategy, it will correspond to a hypothetical situation where such treatment is not available to participants. An equivalent situation will apply to the remaining hypothetical intercurrent events.

Missing data: If not otherwise specified, no imputation of missing data will be performed. Rather, missing data will be handled indirectly through e.g., application of models for longitudinal data, such as regressions with random effects, and survival analysis approaches. The same applies for missing covariate data used in the sub-group analyses: no imputation will be performed.

One exception to this rule will be the eGFR measurements obtained as re-tests, if, due to operational reasons such as unavailability of kits, the planned eGFR samples could not be taken at a scheduled visit (see Section 4.2.1). Such measurements may be used in the eGFR-based analyses.

Covariates: For each of the model-based analyses detailed below, the following variables are included as covariates in the model:

- Treatment (SZC vs Placebo).
- Geographic region.
- Hyperkalaemia at the beginning of the initiation phase (yes/no), as indicated by the strata applied at randomisation.
- Use of SGLT2i/Finerenone at randomisation (yes/no), as indicated by the concomitant-medications collection.
- Age.

Further covariates may be added as appropriate, and these will be specified in the descriptions below.

Table 2: Overview of the main and the supplementary analyses

Statistical category	Endpoint	Intercurrent event strategy	Population level summary	Details in section
Primary				
Primary objective #1: To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan), is superior to placebo in slowing CKD progression, assessed as the reduction in participant's expected eGFR decline over time				
Main	Total slope: eGFR measurements starting at randomisation (up to visit 17/week 69)	Main strategy	Difference in mean total eGFR slopes	4.2.1.1
	Chronic slope: eGFR measurements, starting at 12 weeks after randomisation (up to visit 17/week 69)	Main strategy	Difference in mean chronic eGFR slopes	4.2.1.1
Supplementary	Total slope: eGFR measurements starting at randomisation (up to visit 17/week 69)	Hypothetical strategy wrt initiation of long-term potassium lowering treatment and initiation of potentially eGFR altering treatment	Difference in mean total eGFR slopes	4.2.1.2
	Chronic slope: eGFR measurements, starting at 12 weeks after randomisation (up to visit 17/week 69)	Hypothetical strategy wrt initiation of long-term potassium lowering treatment and initiation of potentially eGFR altering treatment	Difference in mean chronic eGFR slopes	4.2.1.2

Statistical category	Endpoint	Intercurrent event strategy	Population level summary	Details in section
Secondary				
Secondary objective #1: To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan), is superior to placebo in reducing the incidence of the composite of kidney failure outcomes comprising: sustained ≥ 40% decline in eGFR, onset of ESKD, and death from kidney failure				
Main	Time from randomisation to the first occurrence of any component in the composite of - Sustained ≥ 40% decline in eGFR - Onset of ESKD (kidney transplantation, maintenance dialysis, or sustained low eGFR) - Death from kidney failure	Main strategy	Hazard ratio	4.2.2.1

Statistical category	Endpoint	Intercurrent event strategy	Population level summary	Details in section
Supplementary	Time from randomisation to the first occurrence of any component in the composite of - Sustained ≥ 50% decline in eGFR - Onset of ESKD (kidney transplantation, maintenance dialysis, or sustained low eGFR) - Death from kidney failure	Main strategy	Hazard ratio	4.2.2.2
Secondary objective #2: To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan), is superior to placebo in reducing the incidence of lisinopril/valsartan dose decrease, in participants on lisinopril/valsartan at randomisation				
Main	Time from randomisation to first lisinopril/valsartan dose decrease	Main strategy	Hazard ratio	4.2.3
Secondary objective #3: To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan), is superior to placebo in reducing albuminuria				
Main	UACR measurements at scheduled visit 13	Main strategy	Difference in means	4.2.4.1

Statistical category	Endpoint	Intercurrent event strategy	Population level summary	Details in section
Supplementary	Logarithm of the ratio between UACR at visit 13 and baseline (pre-randomization) UACR	Main strategy	Ratio of medians of percent change from baseline	4.2.4.2
Secondary objective #4: To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan), is superior to placebo in increasing serum bicarbonate levels				
Main	Serum bicarbonate measurements at scheduled visits after randomisation (up to visit 17/week 69)	Main strategy	Difference in means, overall (across visits)	4.2.5.1
Supplementary	Serum bicarbonate measurements at scheduled visits after randomisation (up to visit 17/week 69)	Main strategy	Difference in means, at each visit	4.2.5.2
Supplementary	Serum bicarbonate classification; normal (> 22.0 mmol/L) or non-normal (≤ 22.0 mmol/L) at scheduled visits after randomisation (up to visit 17/week 69)	Main strategy	Difference in probabilities, at each visit	4.2.5.2

Statistical category	Endpoint	Intercurrent event strategy	Population level summary	Details in section
Secondary objective #5: To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan), is superior to placebo on maintenance of normokalaemia				
Main	S-K level classification; normal (3.5-5.0 mmol/L) or non-normal (< 3.5 or > 5.0 mmol/L) at scheduled visits after randomisation (up to visit 17/week 69)	Main strategy	Odds ratio, overall (across visits)	4.2.6.1
Supplementary	S-K level classification; normal (3.5-5.0 mmol/L) or non-normal (< 3.5 or > 5.0 mmol/L) at scheduled visits after randomisation (up to visit 17/week 69)	Main strategy	Odds ratio, at each visit	4.2.6.2
Supplementary	S-K level classification; normal (3.5-5.0 mmol/L) or non-normal (< 3.5 or > 5.0 mmol/L) at scheduled visits after randomisation (up to visit 17/week 69)	Main strategy	Difference in probabilities, at each visit	4.2.6.2

Note: In case of a local market valsartan shortage, irbesartan will be temporarily used instead.

4.2.1 Analyses of Primary objectives

Primary objective #1: *To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan), is superior to placebo in slowing CKD progression, assessed as the reduction in participant's expected eGFR decline over time.*

4.2.1.1 Main analyses

To evaluate the primary objective a linear mixed effects model will be fitted for each of the primary endpoints. It will be based on the eGFR values obtained at the scheduled visits at and after randomisation (total slope) and at and after 12-week visit (chronic slope) respectively as the dependent variable. The following covariates will be included as fixed effects in the model, in addition to the ones specified above:

- Time (continuous) since randomisation (days)
- Time and treatment interaction
- UACR at randomization

If the model as specified above becomes ill-conditioned or encounters issues with convergence due to too few observations in one of the categories, the corresponding fixed effect will be removed from the model.

In addition, two random effects, intercept and slope corresponding to the time since randomisation, will be incorporated, with an underlying assumption of an unstructured covariance matrix between the two. A covariance matrix that assumes independence between the residuals within each participant but allows for a different standard deviation at each visit, will be applied. Because of that dependence on visit, and due to the early close-down of the study and the ensuing unavailability of late eGFR measurements, only measurements taken up to and including visit 17 (week 69) will be included in the mixed-effects model; however, all available data, including the (quite few) late eGFR measurements beyond visit 17 (week 69), will be summarised descriptively and listed.

The null hypothesis of no difference in slope between SZC and placebo will be tested by considering the fixed effect of time and treatment interaction term in the model. The estimates of the mean slopes obtained from the model, as well as the estimate of the difference between the two slopes, together with two-sided 95% confidence intervals, will be presented. For the difference in slope, the corresponding p-value will also be provided.

4.2.1.2 Sensitivity analyses and supplementary analyses

The following sensitivity analyses and supplementary analyses of the primary endpoint will be performed:

Impact of estimation by means of two separate models

The impact that the choice utilizing two separate models for the total and the chronic slope has on the results of the main analysis will be evaluated following the approach described in Vonesh et al 2019. Explicitly, rather than fitting two separate models, one for the total and one for the chronic slope, a single model that assumes a piecewise linear trend in eGFR in the two treatment arms (two slopes, acute and chronic) will be fitted.

The presentation of the results will include estimates of the difference in mean chronic and total slopes (the latter obtained through a weighted combination of the chronic and the acute slope estimates, with weights corresponding to the relative durations of the slopes, see Vonesh et al 2019, Equation 3). The corresponding standard deviations, confidence intervals and p-values will also be provided.

Again, due to the early close-down of the study and the ensuing unavailability of late eGFR measurements, only measurements taken up to and including visit 17 (week 69) will be included in the mixed-effects model.

Impact of choice of acute-chronic slope separation

The impact that the different choices of the starting point of the chronic slope have on the results of the main analysis will be evaluated by means of constructing a series of two-slopes models, as described above, where the point of connection between the acute and the chronic slopes, the “knot”, will be allowed to move. The models will be compared by means of AIC.

The results for each of these models will include estimates of the difference in mean chronic and total slopes, the corresponding standard deviations, confidence intervals and p-values, as well as AIC.

Again, due to the early close-down of the study and the ensuing unavailability of late eGFR measurements, only measurements taken up to and including visit 17 (week 69) will be included in the mixed-effects model.

Impact of eGFR calculation methodology

During the course of the study, the method of calculating eGFR was changed, excluding race from the calculation. The main eGFR based analyses will be using the eGFR obtained according to the new approach. However, a sensitivity analysis, in which the main analysis of the primary endpoints will be replicated using the original eGFR calculations (i.e., where race was included), will be performed in order to evaluate the potential impact of the difference in eGFR calculation methodologies.

Again, due to the early close-down of the study and the ensuing unavailability of late eGFR measurements, only measurements taken up to and including visit 17 (week 69) will be included in the mixed-effects model.

4.2.1.3 Supplementary analyses

The following supplementary analyses of the primary endpoint will be performed:

Impact of introduction of concomitant medications

Two supplementary analyses (one for each of the primary endpoints) will be performed for the evaluation of the potential impact that the intercurrent events of an introduction of a long-term treatment that affects either potassium, or eGFR profile, will have on the treatment effect of SZC.

For the analyses, the eGFR measurements that are obtained after the introduction of long-term potassium-lowering concomitant treatment or concomitant medication that has direct effect on CKD progression will be removed. That is, the time point at which such treatments are introduced will be regarded as a point of censoring.

The main analysis of the primary endpoint will then be replicated using the resulting data set.

Again, due to the early close-down of the study and the ensuing unavailability of late eGFR measurements, only measurements taken up to and including visit 17 (week 69) will be included in the mixed-effects model.

4.2.1.4 Supportive analyses

The following supportive analyses of the primary endpoint will be performed:

Impact of subgroups

The homogeneity of effect observed in the main analysis will be examined in the following sub-groups:

- Normokalaemia yes/no, as determined by the screening potassium measurement (i.e., the stratification factor)
- Geographic Region (see Section 4.1.4.1 as well as Appendix 7.2)
- Diabetes at screening (Yes/No)
- SZC dose at randomization (5g QOD or 0, 5, 10, 15 g QD)
- RAASi dose at randomisation (guideline-directed / less than guideline-directed as per CSP Appendix B3)
- RAASi dose at screening (guideline-directed / less than guideline-directed as per CSP Appendix B3)

- Age at screening (< 65, ≥ 65 years)
- Sex (Male, Female)
- eGFR at screening (< 45, ≥ 45 ml/min/1.73 m^2)
- eGFR at randomisation (< 45, ≥ 45 ml/min/1.73 m^2)
- UACR classification at screening (<1000, ≥1000 mg/g)
- Systolic blood pressure classification at screening (see Section 4.1.4.1)
- CKD aetiology class at screening (see Appendix 7.1 for details)
- SGLT2 inhibitors and/or finerenone at randomisation (yes / no)

All the subgroup analyses will be performed by means of fitting two sets of mixed models. In order to obtain the effect estimates as well as the corresponding CIs for a particular sub-group, a mixed model, as described in Section 4.2.1.1, will be fitted to each sub-group separately. In order to evaluate the statistical significance of the potential difference in effect between the sub-groups, a separate model will be created. In addition to the covariates used in the main analysis, it will also include the sub-group as a factor, as well as an interaction between the sub-group factor and each of the three main covariates (treatment, time, and the interaction between the two). The homogeneity of effect will be tested by applying a likelihood ratio test corresponding to the subgroup-by-treatment interaction term.

Again, due to the early close-down of the study and the ensuing unavailability of late eGFR measurements, only measurements taken up to and including visit 17 (week 69) will be included in the mixed-effects models.

4.2.2 Analyses of Secondary objective #1

Secondary objective #1: *To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan), is superior to placebo in reducing the incidence of the composite of kidney failure outcomes comprising: sustained ≥ 40% decline in eGFR, onset of ESKD, and death from kidney failure*.

4.2.2.1 Main analysis

Derivations:

Time to the first occurrence of the components as listed in Table 2, namely sustained ≥ 40% decline in eGFR, onset of ESKD or death from kidney failure, will be derived as the difference between the date of the occurrence and the randomization date, plus one day.

Explicitly, for the different components as listed in CSP Section 8.1.2:

Sustained percent decline in eGFR, is defined as percent decline in eGFR of ≥ 40% from the point of randomisation over at least 4 weeks, as evidenced by 2 consecutive central

laboratory measurements taken at least 4 weeks apart. The start date of the event is the date of the first central laboratory measurement.

Onset of ESKD, is defined as meeting any of the three of the following conditions:

- Kidney transplantation, the date of which is collected directly in the eCRF in a dedicated renal event module.

- Maintenance dialysis, defined as dialysis performed for at least 4 weeks. The date of the start of the dialysis will be used as onset of ESKD date.

- Sustained low eGFR, defined as eGFR < 15 mL/min/1.73 m2 over at least 4 weeks, as confirmed by 2 consecutive, non-missing central laboratory measurements < 15 mL/min/1.73m2 taken at least 4 weeks apart. The date of the first such measurement will be used as the date of onset of ESKD.

Death from kidney failure is defined directly by the investigator in the eCRF, as an AE, with the AE date being considered as the date that the event has occurred.

Analysis:

The evaluation of the secondary objective of reducing the incidence of composite outcome of ≥40% sustained decline in eGFR, onset of ESKD, and death from kidney failure, will be performed by means of a Cox regression.

The patients will be censored at the end of the maintenance phase, or at the time they leave the study prematurely for any reason (e.g., the date of ICF withdrawal, or the date of last contact in case of a patient lost to follow-up), if such an event occurs. The null hypothesis of no difference between the treatment arms will be tested by considering the hazard ratio (HR) estimate corresponding to treatment. As for other analyses, the estimates of the treatment effect (i.e., hazard ratio between the two treatment arms) alongside the corresponding 95% CI and a p-value, will also be provided.

4.2.2.2 Supplementary analyses

There will be a supplementary analysis of time to the first occurrence of sustained ≥ 50% decline in eGFR, onset of ESKD or death from kidney failure.

The approach to performing this analysis will be identical to the one described in Section 4.2.2.1, where the main analysis of this objective is detailed, with the only difference being a re-definition of the endpoint to include a ≥ 50% decline in eGFR, rather than ≥ 40%.

4.2.2.3 Supportive analyses

Time to sustained ≥ 40% (as well as 50%) decline in eGFR, onset of ESKD, and death from kidney failure will be illustrated with Kaplan-Meier plots.

4.2.3 Analysis of Secondary objective #2

Secondary objective #2: *To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan), is superior to placebo in reducing the incidence of lisinopril/valsartan dose decrease, in participants on lisinopril/valsartan at randomisation.*

Patients not on RAASi at randomization will be excluded from this analysis.

Time to dose reduction used in the model will be derived as the difference between the date of the first instance of RAASi dose decrease post-randomization and the randomization date, plus one day.

The analysis of this objective will be performed by means of a Cox regression, as described in Section 4.2.2.1.

4.2.4 Analysis of Secondary objective #3

Secondary objective #3: *To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan), is superior to placebo in reducing albuminuria.*

4.2.4.1 Main analysis

The evaluation of the secondary objective of assessing the UACR level will be performed by means of a linear regression model. The model will have UACR levels obtained post randomization (at visit 13, corresponding week 24 post randomization) as response and include baseline (pre-maintenance phase) UACR as an explanatory variable, in addition to the ones specified in the beginning of Section 4.2. Provided will be the estimate of the treatment difference together with a 95 % CI and a p-value for a test of no treatment difference.

4.2.4.2 Supplementary analysis

The supplementary analysis will examine the UACR percent change from baseline. This will be done by means of fitting a linear regression model to the natural logarithm of fold-change from baseline in UACR at Visit 13, i.e., to ln(UACR[visit 13]/UACR[baseline]), on patient level. Besides the ones specified above, the model will also include the natural logarithm of baseline (pre-maintenance phase) UACR as explanatory variable.

The results will be back-transformed via application of $(e^{<<value>>} - 1) \times (100\ \%)$, with <<*value*>> referring to the estimates, as well as the upper and lower CI limits, of the model fitted to the log transformed values, expressing the results as a percent change/difference.

4.2.4.3 Supportive analyses

Cross-tabulations of UACR class at baseline (<300, 300 – 1000, >1000, missing [mg/g]) against the post-baseline UACR class will also be provided.

4.2.5 Analysis of Secondary objective #4

Secondary objective #4: *To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan), is superior to placebo in increasing serum bicarbonate levels.*

4.2.5.1 Main analysis

The evaluation of the secondary objective of assessing the serum bicarbonate level will be performed by means of a linear mixed model. The model will have bicarbonate levels obtained at scheduled visits post randomization as response and include the following covariates in the fixed-effects part, in addition to the ones specified in the beginning of Section 4.2 above:

- Visit (factor)
- Baseline (pre-maintenance phase) bicarbonate

The model will also include a random intercept within patient. Note that the model assumes a constant treatment effect over time, this assumption evaluated in the supplementary analysis described below. The null hypothesis of no difference between the treatment arms will be tested by considering the treatment effect estimate in this model. As for other analyses, the estimates for the two treatment arms, as well as the treatment effect (i.e., difference in means between the two treatment arms) alongside the corresponding 95% CIs and p-value, will be provided.

Again, due to the early close-down of the study and the ensuing unavailability of late bicarbonate measurements, only measurements taken up to and including visit 17 (week 69) will be included in the mixed-effects model; however, all available data, including the (quite few) late bicarbonate measurements beyond visit 17 (week 69), will be summarised descriptively and listed.

4.2.5.2 Supplementary analysis

Inhomogeneity of treatment effect

A supplementary analysis that includes a treatment-by-visit interaction term in the model specified above will also be performed. The aim of this supplementary analysis would be to explore potential differences in treatment effect between visits, and thus the results of this analysis will be presented in the form of treatment effect estimate, with the corresponding 95% CIs, at each visit separately, and the p-value originating from a test of the treatment-by-visit interaction term.

Again, due to the early close-down of the study and the ensuing unavailability of late bicarbonate measurements, only measurements taken up to and including visit 17 (week 69) will be included in the mixed-effects model.

Probability as population summary measure

For each visit and treatment arm, the probability of bicarbonate > 22 mmol/L will be estimated with a simple percentage. For each visit, the difference in probability of bicarbonate > 22 mmol/L will also be estimated, together with a 95 % CI.

Again, due to the early close-down of the study and the ensuing unavailability of late bicarbonate measurements, only measurements taken up to and including visit 17 (week 69) will be included in the mixed-effects model.

4.2.6 Analysis of Secondary objective #5

Secondary objective #5: *To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan), is superior to placebo on maintenance of normokalaemia.*

4.2.6.1 Main analysis

The secondary objective of evaluating the maintenance of normokalaemia will be evaluated by means of a GEE model that uses a logit link function and unstructured working correlation structure. This model will have the dichotomous classification in normokalaemic (S-K, as evaluated by c-lab, between 3.5 and 5 mmol/L) and non-normokalaemic (S-K <3.5 or S-K >5 mmol/L) at each visit as response. Similarly to the analysis of Secondary objective #4, the model will have visit and baseline potassium as covariates, as well as the ones specified earlier. The null hypothesis of no difference between the treatment arms will be tested by considering the estimate of the odds ratio for the treatment effect in this model. As for other analyses, the estimates of the treatment effect (i.e., odds ratios) alongside the corresponding 95% CI and p-values, will also be provided.

Again, due to the early close-down of the study and the ensuing unavailability of late potassium measurements, only measurements taken up to and including visit 17 (week 69) will be included in the GEE model; however, all available data, including the (quite few) late potassium measurements beyond visit 17 (week 69), will be summarised descriptively and listed.

4.2.6.2 Supplementary Analyses

Inhomogeneity of treatment effect

A supplementary analysis similar to that described in Section 4.2.5.2 for Secondary objective #4 will be performed. That is, a model that includes a treatment-by-visit interaction

term in the model specified above will also be constructed, and the treatment effect estimates for each visit, the corresponding CIs and the p-value for the test of significance of the interaction term, will be provided.

Again, due to the early close-down of the study and the ensuing unavailability of late bicarbonate measurements, only measurements taken up to and including visit 17 (week 69) will be included in the mixed-effects model.

Probability as population summary measure

Similarly, to analyses of Secondary objective #4, a supportive analysis that examines the difference in probability of normokalaemia between treatment arms will be performed.

4.3 Pharmacodynamic Endpoint(s)

Not applicable.

4.4 Pharmacokinetics

Not applicable.

4.5 Safety Analyses

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

Tables will be provided for the safety sets, listings are provided for all enrolled subjects, or the safety sets, depending on the availability of data. For the tabular summaries, subjects that erroneously received incorrect IP during the maintenance phase of the study (SZC or Placebo) will be analysed as belonging to the treatment group they were randomized to.

As a rule, safety analysis will be presented for both On Treatment and During Study. Further, as a rule, the safety analyses will be presented separately for different phases, with events occurring during follow-up assigned to the study phase directly preceding the follow-up period.

4.5.1 Adverse Events

4.5.1.1 Definitions and Derivations

Oedema-related events are defined as AEs with the following PT terms: Fluid retention, Generalised oedema, Hypervolemia, Localised oedema, Oedema, Oedema Peripheral, Peripheral swelling.

Hypokalaemia is collected as an adverse event in the appropriate eCRF form. In particular, investigators are advised to report it as an AE if it leads to temporary or permanent discontinuation of SZC or SZC/placebo.

Hyperkalaemia is collected as an adverse event in the appropriate eCRF form.

Note that both hypokalaemia and hyperkalaemia could also be determined based on the central lab potassium evaluation, and would then be reported separately, see Section 4.5.2.

Severe hyperkalaemia requiring rescue is collected as an adverse event and is indicated directly by the investigator in the appropriate eCRF form.

Duration variables to be presented, where applicable (e.g., key subject information tables), are defined as follows:

- Time from planned treatment start date (in the respective treatment period) to onset of AE (days)
- Time from planned treatment start date (in the respective treatment period) to death (days)
- Time from planned treatment start date (in the respective treatment period) to AE becoming serious (days)
- Time from planned treatment start date (in the respective treatment period) to discontinuation of IP (days)
- Time from actual last dose date to death (days)
- Time from actual last dose date to AE start date (days)

The derivations for these variables will be the difference between the two dates stated above + 1 day.

4.5.1.2 Presentations

Adverse events (AE) will be summarised descriptively in accordance with the rules described in Section 3.3. Estimates of differences in AE profiles (e.g., hazard ratios, difference in probability of an event occurring within a pre-specified time interval) may also be presented, along with the corresponding CIs.

All AEs will be summarised by SOC and PT according to the latest MedDRA version available at the time of database lock.

Overall overview

An AE overview table will be created, with AEs falling within the following categories summarized by treatment group.

- Any AE
- Any SAE

- Any AE with outcome death
- Any AE leading to discontinuation of SZC or SZC/placebo
- Any AE leading to discontinuation of Lisinopril/valsartan
- Any AE leading to dose interruption of SZC or SZC/placebo
- Any AE leading to dose interruption of Lisinopril/valsartan
- Any AE leading to dose reduction of SZC or SZC/placebo
- Any AE leading to dose reduction Lisinopril/valsartan
- Any AE possibly related to SZC or SZC/placebo
- Any AE possibly related to Lisinopril/valsartan
- Any SAE possibly related to Lisinopril/valsartan
- Any SAE possibly related to SZC or SZC/Placebo

AEs, SAEs, DAEs and deaths, by system organ class and preferred term

A detailed overview of number, and percentage, of subjects with AEs, SAEs, DAEs and deaths in a particular SOC and PT class will be presented.

Most common AEs
A tabulation of the PT terms sorted by decreasing frequency (most common AEs in SZC arm on top) will be provided.

Intensity of AEs
An overview of the number and the percentage of subjects with AEs in a particular SOC, PT and intensity class (mild, moderate, severe) will be created. Subjects will be counted only once in each category. A subject with two AE in the same SOC and PT class of, e.g., both high and moderate intensity will be assigned the “high” intensity category, i.e., the more severe class.

Causality of AEs
Number and percentage of subjects with AEs considered as possibly related to each of the IPs (SZC/Placebo and Lisinopril/valsartan) will be tabulated by SOC and PT, in separate tabulations.

Events related to oedema, hypokalaemia, or hyperkalaemia
An overview of oedema-related AEs, with number and percentage of subjects with an event with a particular PT term, will be presented.

Number of subjects with AE classified as hypokalaemia, hyperkalaemia, or hyperkalaemia requiring rescue, will be tabulated in a similar manner.

Key subject information tables
Key subject information will be provided for all SAEs, AEs with an outcome of death, and all AEs leading to IP discontinuation. This will include, e.g., the duration variables defined in the beginning of this section, outcome of an AE and action taken with respect to IP.

Listings

The listings provided may include, but may not be limited to:

- All AE
- All AE of hypokalemia.
- SAE for subjects who were enrolled but did not enter initiation phase.

All listings will be created for during the study time period, and will include, among others, planned treatment arm and planned dose of both of the IPs.

4.5.2 Clinical Laboratory, Blood Sample

Clinical Laboratory results will be summarised descriptively in accordance with the rules described in Section 3.3. The definition of baseline is found in Section 3.3.1.1.

4.5.2.1 Definitions and Derivations

Abnormalities

Abnormal values will be determined by comparing the lab values to standard ranges, as provided by the central laboratory.

Hypokaelaemia and Hyperkalaemia

Potassium values will be used to summarise patients who are Hypokalaemic (S-K < 3.5 mmol/L) or Hyperkalaemic (S-K > 5.0 mmol/L), with the following sub-categories also being presented:

Hypokalaemia:

- S-K < 3.5 mmol/L
- S-K < 3.0 mmol/L
- S-K < 2.5 mmol/L

Hyperkalaemia:

- S-K > 5 mmol/L
- S-K > 5.5 mmol/L

- S-K > 6.0 mmol/L
- S-K > 6.5 mmol/L

4.5.2.2 Presentations

Haematology and Clinical Chemistry

Hematology results, collected at Screening Visit and Randomization, will be summarized descriptively in accordance with the rules described in Section 3.3. The values collected at Screening Visit could further be summarised by hyperkalaemia status (screening SK > 5 mmol/L, Yes/No).

A summary of the distribution of haematology and clinical chemistry profiles during the maintenance phase, over time, will be provided, the presentation including a summary of the values themselves, by visit, and change from baseline, also by visit.

The number, and percentage, of patients with abnormal haematology and clinical chemistry values at any point during the maintenance phase, but with normal baseline (pre-randomization) values, will be presented.

Hypokalaemia and Hyperkalaemia

The number of subjects who were Hypokalaemic or Hyperkalaemic at any point in the study will be summarised according to the categorization provided above. This may be complemented by a presentation of the number of subjects who were Hypokalaemic or Hyperkalaemic at each visit.

4.5.3 Vital Signs

4.5.3.1 Definitions and Derivations

Vital signs, if abnormal, will be classified by whether the abnormality is clinically significant or not, the classification indicated directly in the eCRF by the investigator. Furthermore, five categories, corresponding to the number of occasions that a clinically significant abnormality in vital signs was observed for a patient, will be defined:

- 0 Clinically Significant abnormalities
- ≥ 1 Clinically Significant abnormalities
- ≥ 2 Clinically Significant abnormalities
- ≥ 3 Clinically Significant abnormalities
- ≥ 4 Clinically Significant abnormalities

4.5.3.2 Presentations

Vital signs will be summarised descriptively and presented according to the rules described in Section 3.3. The presentation will include a summary of both the distribution of values

themselves, by visit, and the distribution of change from baseline, also by visit. A summary according to the criteria described in Section 4.5.3.1 will also be provided and will be presented for the study periods described in Section 4.6.

Additionally, the change in vital sign abnormality status from the one observed at baseline to the one observed in connection to the minimum, or maximum, vital sign value, will also be presented.

4.5.4 Electrocardiogram

ECG measurements are taken at the Screening and Randomization visits only, and will be summarised together with other Baseline Characteristics, according to the rules described in Section 3.3.

4.6 Immunogenicity

Not applicable.

5 INTERIM ANALYSIS

Not applicable.

6 REFERENCES

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7 APPENDIX

7.1 The mapping of CKD aetiology class

For the purpose of convenience, some of the categories of the CKD aetiology as collected in the eCRF will be combined for the sub-group analyses. It will be done as follows:

Etiology in eCRF	Sub-group analysis class
Cystic kidney disease	Cystic kidney disease
Diabetic nephropathy	Diabetic nephropathy
Ischaemic/Hypertensive nephropathy	Ischaemic/Hypertensive nephropathy
Chronic glomerulonephritis	Chronic glomerulonephritis
Renal artery stenosis	Other
Chronic pyelonephritis (infectious)	Other
Chronic interstitial nephritis	Other
Obstructive nephropathy	Other
Unknown	Other
Other	Other

7.2 The assignment of countries to regions

The division of countries into regions, for the purpose of, e.g., sub-group analyses, will be performed as follows:

Country	Region
Argentina	South America
Brazil	South America
Bulgaria	Europe
Canada	North America
China	Asia
India	Asia
Italy	Europe
Japan	Asia
Malaysia	Asia
Mexico	North America
Poland	Europe
Philippines	Asia
Russia	Europe
Spain	Europe
Taiwan	Asia
Thailand	Asia
Turkey	Asia
Ukraine	Europe
USA	North America
Vietnam	Asia

7.3 Sample size determination and the different causes for missing data during the randomized treatment phase

Approximately 3000 participants will be enrolled (screened) to achieve approximately 1500 participants receiving at least one dose of SZC during the initiation phase, consequently leading to a target of 1360 participants randomly assigned to SZC or placebo.

Note that "enrolled" refers to a participant's, or their legally acceptable representative's, agreement to participate in the study following completion of the informed consent process.

The assumptions for variability of the eGFR measurements between and within participants used in the calculation below are taken from the DECLARE study (D1693C00001 [NCT01730534]): between-participant SD (i.e., SD of the random slopes) of 2.6 and within-participant SD (i.e., SD of the residuals) of 7.7. The difference in slopes in the 2 treatment arms is assumed to be 0.75, a magnitude that is deemed clinically relevant. It is also assumed that no acute effects are present, i.e., that the decline in eGFR over time in both treatment arms is well-approximated by a single line with a particular slope.

Given this, and assuming a two-sided test of a difference in slopes based on a linear mixed model, with a two-sided significance level of 0.05, is performed, then approximately 1220 participants with complete eGFR data will provide a power of 91% for the evaluation of total slope. This is true provided the following time points for eGFR assessment, in terms of weeks since randomisation, are observed for each participant as a minimum: 0 (randomisation), 6, 12, 16, 20, 24, 46, 69, 92, 96, 100, and 104.

Under the same assumptions (i.e., a difference in slopes of 0.75, no acute effect), the power for the chronic slope will be approximately 85%. The evaluation of the chronic slope is assumed to start at 12 weeks.

It is expected that approximately 20% of the eGFR data will be missing. As the eGFR data is correlated within participant, it is assumed that the data points available for a participant will provide information on the missed evaluations, and 20% of missed data would roughly correspond to approximately 10% of randomised participants with no eGFR data available. Hence, 1360 participants will be randomised in the maintenance phase.

Possible Causes for Missing Data during the Randomised Treatment Phase

The initial expectation that approximately 20% of eGFR measurements during the randomised treatment phase will be missing, is largely inferred from DAPA-CKD (Heerspink et al 2020). Death from any cause and ESKD were identified as the 2 potential main contributors for missing eGFR data. Looking at the placebo group in the aforementioned publication, it is expected that approximately 7% of participants will reach ESKD during the 2 years of randomised treatment phase, and approximately 6% of participants will die. It should be noted that the DAPA-CKD study had a somewhat healthier patient population that included patients with eGFR between 25 and 75 mmol/L (10% of the patient population in the study had an eGFR > 60 mmol/L). In addition, the hyperkalaemia requirement in the STABILIZE-CKD study might lead to a lower baseline eGFR in general, so a somewhat larger percentage of missing data due to the reasons mentioned above is expected. Tentatively, the expectation is that approximately 15% of the missing values will originate from ESKD or death.

In addition to these 2 major reasons, it is expected that data points will also be missing due to a number of smaller issues, such as participants not attending visits, blood samples not being analysable, and participants discontinuing the study, or discontinuing treatment and choosing an alternative follow-up option that precludes blood sampling. The magnitude of such smaller issues is difficult to predict, but it is tentatively expected that they might, cumulatively, lead to an additional 5% of the data points being missing, which would, together with ESKD and death, add up to approximately 20% of missing data.

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