Statistical analysis plan	
Study code	D9480C00014
Version	1.0
Date	15 Oct 2021

An Open-Label, Randomised, Controlled, Parallel-Design, Multicentre, Phase IV Study of Sodium Zirconium Cyclosilicate and Enhanced Nutrition Advice Compared to Standard of Care in Dialysis Patients with Hyperkalaemia (GRAZE)

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AZ Study Statistician

PPD

Date

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AE	Adverse Event
ANCOVA	ANalysis of COVAriance
BMI	Body Mass Index
CI	Confidence Interval
CKD	Chronic Kidney Disease
COVID-19	Coronavirus Disease 2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
DBL	Data Base Lock
DCO	Data Cut Off
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ePRO	electronic Patient-Reported Outcomes
EOT	End Of Treatment
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HCP	Healthcare Provider
HK	Hyperkalaemia
HKS	Hyperkalaemia treatment Safety analysis set
HRQoL	Health-Related Quality of Life
ICH	International Council for Harmonisation
CCI	[redacted]
IDWG	Interdialytic Weight Gain
K^+	Potassium
KDQOL-36	Kidney Disease and Quality of Life-36 item
LIDI	Long Interdialytic-Dialysis Interval
LS	Least Squares
M	Month
MCMC	Markov Chain Monte Carlo
MCS	Mental Component Summary
MedDRA	The Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
NK	Normokalaemia

Abbreviation or special term	Explanation
PCS	Physical Component Summary
PGIC	Patients' Global Impression of Change
PRO	Patient Reported Outcome
PT	Preferred Term
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's method
RAASi	Renin-Angiotensin-Aldosterone System Inhibitors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
S-K^+	Serum Potassium
SoA	Schedule of Activities
SoC	Standard of Care
SOC	System Organ Class
SZC	Sodium Zirconium Cyclosilicate
TEAE	Treatment-Emergent Adverse Event
TSQM-9	Treatment Satisfaction Questionnaire for Medication (9 items)
URR	Urea Reduction Ratio
VAS	Visual Analogue Scale

AMENDMENT HISTORY

Date	Brief description of change
15Oct2021	Initial version

1. OBJECTIVES

Table 1: Study Objectives

Objectives	Endpoints
Primary	
• To evaluate the effect of the combination of sodium zirconium cyclosilicate (SZC) and enhanced nutritional advice to consume fruit and vegetables as compared to standard of care (SoC) in reducing S-K^+	• Change in S-K^+ taken at long interdialytic-dialysis interval (LIDI) visits Month 3, Month 4, and Month 5 (M3, M4, and M5) compared to baseline
Secondary	
• To evaluate the effect of the combination of SZC and enhanced nutritional advice as compared to SoC on the consumption of fruit and vegetables	• Change from baseline in fruit and vegetable consumption determined by participant-reported intake using Noom app from M2 to M5
• To evaluate the effect of the combination of SZC and enhanced nutritional advice as compared to SoC on participant-reported chronic kidney disease (CKD) symptoms, physical and mental health, and satisfaction with treatment	• Electronic versions of: • Kidney Disease and Quality of Life-36 item (KDQOL-36; symptoms/problems, Physical Component Summary [PCS] and Mental Component Summary [MCS], Burden of Kidney Disease and Effects of Kidney Disease) (Cohen et al. 2019) • EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) (Herdman et al. 2011) • Abbreviated Treatment Satisfaction Questionnaire for Medication (9 items) (TSQM-9) (Atkinson et al. 2004) • Participants' Global Impression of Change (PGIC)

Objectives	Endpoints
• To evaluate the effect of the combination of SZC and enhanced nutritional advice to consume fruit and vegetables as compared to SoC in maintaining S-K^+ levels within a range of 3.5–5.5 mmol/L, without requiring rescue therapy for hyperkalaemia (HK)	• Binary response (responder/non-responder) with criteria that at least 66% of S-K^+ values taken at LIDI visits in M3, M4, and M5 fall between 3.5 and 5.5 mmol/L Receiving rescue therapy or a K^+ binder for HK during the final 3 months of the study will result in a non-response
Safety	
• To assess the safety and tolerability of SZC and enhanced nutritional advice as compared to SoC	• Safety and tolerability will be evaluated in terms of adverse events (AEs), vital signs, clinical laboratory, interdialytic weight gain (IDWG), and electrocardiogram (ECG) • Assessments related to AEs cover: • Occurrence/frequency • Relationship to SZC as assessed by investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of SZC
Exploratory	
• CCI [redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
• CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2. STUDY DESIGN AND SAMPLE SIZE

2.1 Overall Design

This is a Phase IV, randomised, controlled, open-label, parallel-group, multicentre, prospective study to evaluate the effect of the combination of SZC and enhanced nutritional advice to consume fruit and vegetables as compared to SoC in reducing S-K^+ levels in participants with hyperkalaemia on haemodialysis.

2.1.1 Up to 1-month HK Treatment Phase (all participants)

Participants will follow labelled instructions for dosing dialysis participants, starting at 5 g on non-dialysis days. At weekly intervals participants can be titrated up or down in 5 g steps to a maximum of 15 g on non-dialysis days and a minimum of 5 g on non-dialysis days, to keep S-K^+ in the range of 3.5-5.5 mmol/L.

K^+ will be corrected with SZC as per local label. Participants will receive dietary advice consistent with SoC at that site, including K^+ restriction. Dietary advice will be given by dietitians at study visits.

2.1.2 4-month Diet Comparison Phase (2 arms)

Randomisation will occur at Visit 6. Only participants with S-K^+ ≤5.5 mmol/L on 5 or 10 g SZC will be randomised. Participants on 15 g SZC will be considered as randomisation failures.

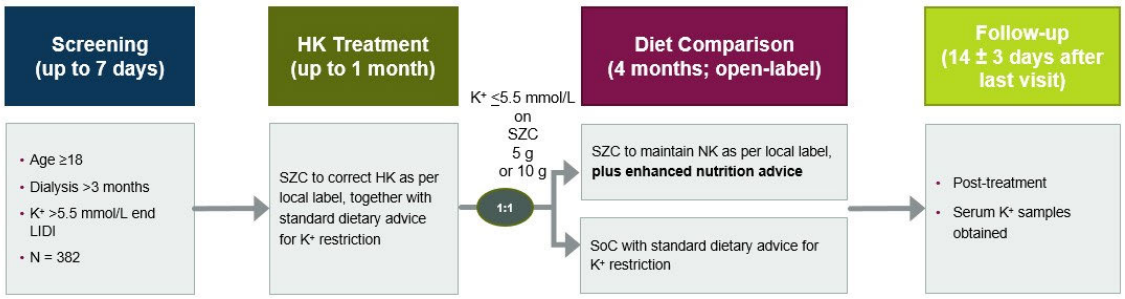
SZC arm: Participants will continue taking SZC, which can be titrated up or down as described in Section 2.1.1 to maintain S-K^+ in the range 3.5-5.5 mmol/L; participants will also receive enhanced nutritional advice to consume fruit and vegetables. Advice will be provided by dietitians at study visits and by Noom app between visits.

SoC arm: SZC will be withdrawn and participants will receive SoC as per site practice, including dietary K^+ restriction. Dietary advice will be given by dietitians at study visits and by Noom app between study visits.

2.1.3 Follow-up Phase (all participants)

Upon completion of the study, or early discontinuation, all participants that have received study drug, including those who have been enrolled into the HK Treatment Phase but not been randomised into the Diet Comparison Phase, will proceed to the post-treatment follow-up visit after 14±3 days. After completing the study, or early discontinuation, participants will receive SoC and standard diet advice as determined by their treating physician.

Figure 1 Study design



Abbreviations: HK = hyperkalaemia; K = potassium; LIDI = long interdialytic-dialysis interval; N = number of participants; NK = normokalaemia; SoC = standard of care; SZC = sodium zirconium cyclosilicate.
Note: Only participants with S-K^+ ≤5.5 mmol/L on 5 or 10 g SZC at end of HK Treatment Phase will be randomised.

3. ANALYSIS SETS

3.1 Analysis sets

All-Participants Analysis Set

The all-participants analysis set will consist of all participants who are screened for 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.

HK Treatment Safety Analysis Set (HKS)

The HKS will include all participants who receive at least 1 dose of sodium zirconium cyclosilicate (SZC) during the hyperkalaemia (HK) Treatment Phase. The HKS will be used to describe the safety and exposure endpoints during the HK Treatment Phase and certain baseline and demographic characteristics. Summaries will combine all participants together within the SZC treatment group.

Full Analysis Set (FAS)

The FAS, the primary efficacy analysis set, will include all randomised participants, with participants being analysed as randomised, rather than as treated. The FAS will be the primary analysis set used for the primary, secondary and exploratory endpoints and baseline and demographic characteristics. Summaries and analysis will group participants according to their randomized treatment arm.

Safety Analysis Set (SAS)

The SAS will include all randomised participants receiving at least 1 dose of study treatment during the Diet Comparison Phase, for the SZC arm, and all randomised participants completing visit 5 for the standard of care (SoC) arm. The SAS will be the analysis set used for safety and exposure endpoints during the diet comparison phase. Summaries will group

participants according SZC if they received at least one dose of SZC during the Diet Comparison Phase, and to SoC if they were randomized to SoC.

3.2 Analysis Periods

The following periods will be defined for the purpose of reporting.

Screening Phase

Screening refers to the period from the date of the first study specific assessment to the date and time of the first dose of SZC during the HK Treatment Phase or date of screen failure, whichever occurs first.

HK Treatment Phase

The HK Treatment Phase (open-label dosting period) refers to the period from the date and time of first dose of SZC during the HK Treatment Phase until randomisation at the start of the Diet Comparison Phase.

Diet Comparison Phase

The Diet Comparison Phase refers to the period from of randomisation until the earliest date of last assessment during the follow-up period, date of withdrawal of consent, date of last contact with the participant, or date of death.

3.3 Violations and deviations

Important protocol deviations will be defined by the Sponsor before database lock by judging the importance of the deviations upon the primary efficacy endpoint. 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.

- Incorrectly enrolled participant who failed any of the inclusion or exclusion criteria of the study as provided in sections 5.1 and 5.2 of the CSP respectively.
- Inappropriate compliance with study treatment during the HK treatment phase and diet comparison phase of the study, e.g. treatment compliance of less than 80% or greater than 120%
- All restricted medications which are administered during the study when used for a purpose other than those instructed, as detailed in section 6.5 of the CSP.
- Any participant who received incorrect study treatment compared with randomized study treatment at any time during the diet comparison phase. This also includes any participant who received SZC instead of randomized SoC at any time during the diet comparison phase.
- Participant with first dose date prior to baseline evaluations in the diet comparison phase.

In addition, protocol deviations will be defined by the Sponsor before database lock as coronavirus disease 2019 (COVID-19) pandemic related or not by judging the root cause of the protocol deviation, in line with FDA guidance (FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency; March 2020). The following criteria may be considered as 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 sK+ measurements due to COVID-19 illness and/or COVID-19 public health control measures

4. EXPOSURE(S) AND OUTCOMES

4.1 Exposures

4.1.1 Investigational Product - SZC

Participants in the active arm will receive SZC dosed as per the local label to control HK and maintain normokalaemia. Any decision to discontinue SZC will be up to the treating physician's judgement and as advised by the label. Per the label, SZC should only be dosed on non-dialysis days. The recommended starting dose is 5 g once daily. To establish normokalaemia (in the range commonly regarded as acceptable in these participants [3.5-5.5 mmol/L]), the dose may be titrated up or down weekly based on the pre-dialysis S-K^+ value after LIDI. The dose can be adjusted at intervals of 1 week in increments of 5 g up to 15 g once daily on non-dialysis days.

4.1.2 SoC Dietary Advice

All participants during the HK Treatment Phase, and participants randomised to the SoC arm of the Diet Comparison Phase will receive standard dietary advice including K^+ restriction. This advice will be provided by dietitians at study visits and will be consistent with SoC at that site and will use a mobile app (Noom) to track food intake only.

Participants will be encouraged to consume less than 50 mmol K^+ per day.

4.1.3 Enhanced Dietary Advice

Upon randomisation to the SZC arm of the Diet Comparison Phase, participants will receive enhanced dietary advice in addition to taking SZC. This will include advice from dietitians at study visits to consume fruit and vegetables. Participants will receive dietary support from the Noom app between visits. Participants will be encouraged to consume up to 70 mmol K^+ per day.

4.1.4 Diet Mobile App (Noom)

In order to track dietary changes, participants in both arms will be supported by a mobile app (Noom) between study visits. Participants will be required to enter information daily on their food intake. This app will (a) track food intake, including K^+, fruit and vegetables, and fibre, (b) provide feedback regarding an estimate of daily K^+ consumption, and (c) provide live guidance on food consumption by human coaches.

4.2 Outcomes

4.2.1 Primary efficacy outcome - Potassium

Serum potassium ($S\text{-}K^+$) will be measured at each visit prior to dialysis, and the primary outcome will use assessments during the Diet Comparison Phase (including the baseline assessment for the Diet Compaison Phase as defined in Section 5.1). Serum samples will be analysed using local laboratory for the purposes of study inclusion and monitoring.

Serum potassium results after the introduction of rescue theapy of K^+ binder for HK will be collected but excluded from the primary analysis of the primary efficacy outcome.

Rescue therapy is defined as any therapeutic intervention considered necessary in accordance with local practice patterns to reduce $S\text{-}K^+$ in the setting of severe HK as defined by physician and site.

Treatments considered rescue may include:

- Intravenous insulin/glucose or dextrose, beta adrenergic agonists, intravenous sodium bicarbonate, and any additional dialysis or other forms of renal-replacement treatments when used specifically for the treatment of severe HK as defined locally at site.
- In addition, reduction in the dialysate K^+ concentration that is prescribed for the treatment of severe HK during the study is also considered rescue therapy. Investigators may change dialysate bath as needed.
- Use of other K^+ binders including SPS, CPS, and patiromer.

Rescue medication will be identified using the concomitant medication eCRF page, using pre-specified drug codes.

4.2.2 Secondary outcome(s)

4.2.2.1 Maintaining S-K+ levels within a range of 3.5–5.5 mmol/L without requiring rescue therapy for HK

The secondary endpoint of maintaining $S\text{-}K^+$ levels within the normokalaemic range of 3.5-5.5 mmol/L without requiring rescue therapy for HK will be assessed as a binary (responder/non-responder) variable, with participants being be deemed responders if all of the following are true:

1. The participant provides 2 or more non-missing S-K^+ assessments during the period from M3 to M5, inclusive.

2. At least 66% of their non-missing S-K^+ assessments between the M3 and M5 visits, inclusive, show values within the normokalaemic range.

3. The participant does not receive rescue therapy or a K^+ binder for HK at any point between the M3 and M5 visits, inclusive.

Participants will be deemed non-responders if point 3 is not true, or if point 1 is true and point 2 is not true.

Participants will be excluded from the secondary analysis if point 1 is not true and point 3 is true.

4.2.2.2 KDQOL™-36

The KDQOL-36 is a validated, self-reported questionnaire that combines generic and diseasespecific components for assessing symptoms and health-related quality of life (HRQoL) of participants with CKD, refer Appendix C1 of the CSP (Ricardo et al. 2013). The KDQOL-36 comprises a PCS (12 items), MCS (12 items), Symptoms/Problems (12 items), Burden of Kidney Disease (4 items), and Effects of Kidney Disease (8 items). Higher scores indicate better health/HRQoL.

4.2.2.3 EQ-5D-5L

The EQ-5D-5L will be used to explore the impact of treatment and disease state on health state utility (refer Appendix C2 of the CSP).

The EQ-5D-5L, developed by the EuroQol Group, is a generic questionnaire that provides a simple descriptive profile of health and a single index value for health status for economic appraisal. The EQ-5D-5L questionnaire comprises six questions that cover five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible five options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/ extreme problems). A unique EQ-5D health state, termed the EQ-5D-5L profile, is reported as a five-digit code with a possible 3,125 health states. For example, state 11111 indicates no problems on any of the five dimensions. Respondents also assess their health today using the EQ-VAS, which ranges from 0 (worst imaginable health) to 100 (best imaginable health).

The EQ-5D profile will be converted into a weighted health state utility value, termed the EQ-5D index, by applying a country-specific equation to the EQ-5D-5L profile that represents the comparative value of health states. This equation is based on national valuation sets elicited from the general population and the base case will be the UK perspective. Where

a valuation set has not been published, the EQ-5D-5L profile will be converted to the EQ-5D index using a crosswalk algorithm (EuroQol 2019). The EQ-VAS is reported separately.

4.2.2.4 TSQM-9

The TSQM-9 is a participant-reported instrument to assess participants' satisfaction with medication, providing scores on 3 scales: effectiveness (3 items), convenience (3 items), and global satisfaction (3 items) (refer Appendix C3 of the CSP). The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction on that domain. TSQM-9 is an abbreviated version derived from the TSQM version 1.4 and has shown good psychometric properties (Bharmal et al. 2009).

4.2.2.5 PGIC

The PGIC will be included to assess how a participant perceives his/her change in activity limitations, symptoms, emotions, and overall HRQoL since the start of study treatment (details of the questions are provided in the Appendix C4 of the CSP).

4.2.2.6 Fruits and Vegetable Consumption

Consumption of fruit and vegetables will be tracked within the Noom app. Food consumed in calories by participants per day will be recorded.

Total calories of all fruit and vegetable consumed per person per day will be identified and will be used for the analysis during the Diet Comparison Phase.

The baseline average daily fruit and vegetable consumption at visit 6 will be calculated as below:

Baseline average daily fruit and vegetable consumption = (Total fruit and vegetable consumption from start of the Diet comparison Phase -28 days to the start of the Diet comparison Phase – 1 day in calories) / 28.

28-day period fruit and vegetable consumption will be calculated in 28 day windows, starting from the start of the Diet Comparison Phase until visit 12.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

4.3 Other variables and covariates

4.3.1 Safety variables

4.3.1.1 Adverse Events

All AEs, non-serious and serious adverse events (SAEs) will be collected throughout the study. A treatment-emergent AE (TEAE) in the HK Treatment Phase is defined as an AE with the start date on or after the first dose date of SZC and up to (and including) 14 days after the last dose date of SZC at visit 5, or one day prior to the start of the Diet Comparison Phase, whichever is sooner.

A TEAE in the Diet Comparison Phase is defined as:

- an AE with a start date on or after the date of first dose date of SZC in the diet comparison phase up to (and including) 14 days after the last dose date of SZC for participants randomized to SZC, or

- an AE with a start date on or after the date of randomization in the diet comparison phase up to (and including) the follow-up visit (or 14 days after the last visit if no follow-up visit is performed) for participants either randomized to SoC or who do not enter the Diet Comparison Phase.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, should report the SAE to the sponsor.

The Medical Dictionary for Regulatory Activities (MedDRA) (using the latest or current MedDRA version) will be used to classify AEs according to system organ class (SOC) and preferred term (PT).

4.3.1.2 Clinical Safety Laboratory Assessments

Blood samples for determination of clinical chemistry and haematology will be taken before dialysis at the visits indicated in the protocol SoA. Additional safety samples may be collected if clinically indicated at the discretion of the investigator.

The clinical chemistry and haematology will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured (note that S-K^+ will be summarized and analysed as part of the efficacy objectives).

Table 2 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	Blood urea nitrogen (BUN)
B-Leukocyte differential count (absolute count)	S/P-Bilirubin, total
B-Platelet count	S/P-Alkaline phosphatase (ALP)
	S/P-Aspartate transaminase (AST)
	S/P Gamma-glutamyl transferase (GGT)
	S/P-Albumin
	S/P-Lactate dehydrogenase
	S-K^+

	S-Calcium
	S-Magnesium
	S-Sodium
	S-Phosphate
	S-Bicarbonate
	S/P-Chloride
	S/P-Glucose
	S/P-Creatine kinase (CK)
	S/P-Total protein
	S-Pregnancy test (serum hCG)

Abbreviations: B = blood; hCG = human chorionic gonadotropin; P = plasma; S = serum.

4.3.1.3 Vital signs

Vital signs (blood pressure, pulse rate, and oral temperature) will be collected at timepoints as specified in the protocol SoA, after 5 min of lying or sitting down without any distractions.

4.3.1.4 Electrocardiograms

An ECG will be performed at timepoints specified in the protocol SoA. QTc(F) will be collected at each ECG measurement. ECG data and S-K^+ values will be collected and recorded in the eCRF in connection with reporting AEs of S-K^+ below 3.0 mmol/L.

4.3.1.5 Physical Examinations

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Height, lean weight, and triceps skin-fold thickness assessments will be also be collected before dialysis at timepoints as specified in the protocol SoA.

4.3.1.6 Pregnancy

Women of childbearing potential will get a pregnancy test as described in protocol.

All pregnancies and outcomes of pregnancy should be reported, except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants.

4.3.1.7 Interdialytic Weight Gain (IDWG)

IDWG will be calculated as the difference between current pre-dialysis weight minus previous post-dialysis weight (measured at immediate dialysis session prior to the visit) in kilograms.

IDWG will be collected at the times specified in the protocol SoA.

4.3.2 Other variables

4.3.2.1 Dialysis Prescription

Dialysis prescription parameters including blood flow (Qb, mL/min) and time on dialysis (minutes) will be collected at the times specified in the protocol SoA.

4.3.2.2 Dialysis Adequacy

Dialysis adequacy indices including spKt/V and/or urea reduction ratio (URR) will be collected at the times specified in the protocol SoA.

5. ANALYSIS METHODS

5.1 General principles

The principal analyses outlined in this statistical analysis plan will be conducted by Labcorp Drug Development Inc., in accordance with the contract with AstraZeneca Pharmaceuticals LP and following the Excellence in Medical Partnership for Outsourced Worldwide Evidence Research (EMPOWER) description of services.

The below mentioned general principles will be followed for analyses:

In general, all baseline characteristics and efficacy and safety variables will be summarised using descriptive statistics as appropriate. Continuous variables will be summarised by descriptive statistics (including number of participants [n], mean, standard deviation, minimum, median, and maximum). Categorical variables will be summarised using frequencies and percentages, where the denominator of calculation is the underlying analysis set unless stated.

Descriptive statistics of quantitative efficacy and safety parameters by scheduled visits will be provided on observed cases (ie, including only participants who have non-missing assessments at a given visit).

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.

The last observation before the first dose of study treatment in the HK treatment phase will be considered the baseline measurement for HK treatment phase, unless otherwise specified.

The last available assessment prior to or on the date of the randomisation visit for all participants in Diet Comparison phase will be considered the baseline measurement for Diet Comparison phase , unless otherwise specified.

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

The following treatment labels will be used for the analyses during the HK Treatment Phase and Diet Comparison Phase.

- HK Treatment Phase: SZC
- Diet Comparison Phase: SZC and SoC

In general terms, the FAS will be used for the efficacy analyses, while the HKS and SAS will be used for the safety reporting. Study population, baseline and demography data will also be summarized using the FAS and selected summaries will be produced for the HKS.

5.1.1 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. However, for use in calculations (for instance in calculation of the duration of an AE or medication use), dates will be estimated as follows:

5.1.1.1 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 HK treatment phase then impute the month and day of the first dose date.
- Otherwise, if the year matches the year of the first dose date in the Diet Comparison phase then impute the month and day of the first dose date.
- Otherwise, assign the month as January

If the day is unknown, then:

- If the month and year match the month and year of the first dose date in the HK treatment phase, then impute the day of the first dose date.
- Otherwise if the month and year match the month and year of the first dose date in the Diet Comparison phase, then impute the day of the first dose date.
- Otherwise, assign the day as 1st of the month.

5.1.1.2 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 December.

If the day is unknown, then assign the last day of the month.

If the above rules for end dates result in an illogical date with regard to the dates the participant was in the study, then the end date will be replaced with the participant's date of study completion/discontinuation.

5.1.2 Handling of Missing Efficacy Data

Participants with missing data for efficacy analyses will be treated as described under each endpoint's estimand definition. The primary analysis will need to account for missing values, and values recorded for participants after commencement of rescue therapy of a K^+ binder for hyperkalaemia, through a multiple imputation (MI) method using the missing not at random framework separately for each treatment group. Any assessments performed after the introduction of rescue therapy will not be used as inputs for the MI procedure and will be treated as missing. Details of handling missing values for secondary efficacy analysis is detailed in section 5.3.7.4.

5.1.3 Handling of Missing Safety Data

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

5.1.4 COVID-19 Impact

A listing of all participants affected by the COVID-19 related study disruption along with the description of how the individual's participation was altered will be produced.

Depending on the extent of COVID-19 impact, summaries of AEs associated with new onset SARS-CoV-2 infection, discontinuation of study treatment, discontinuation of study, missed visits, COVID-19 related protocol deviations and other missing data will be generated.

Additional sensitivity and supplementary analyses will be performed to determine the impact of the COVID-19 pandemic on this trial and its endpoints. Planned sensitivity analyses will distinguish between pandemic and non-pandemic-related intercurrent events in terms of the approach taken for sensitivity analyses. Further details will be included under each endpoint's estimand definition.

5.2 Visit Windows

For all populations, assessments will be assigned to visits for non-categorical summaries as follows:

- Only assessments recorded with a nominal visit number or recorded as an unscheduled visit will be considered for assignment to visits (i.e. results recorded on the end of treatment and end of study CRF forms will not be used).
- Assessments will be assigned to baseline for the HK Treatment Phase and Diet Comparison Phase as defined in Section **5.1**.
- 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.
- If the initial nominal visit, (defined hereafter as the earliest assessment for a given visit to be recorded as the nominal visit number via the eCRF), has a non-missing response, then that will be chosen for analysis.
- If the initial nominal visit has a missing response, then the earliest of all subsequent assessments with a non-missing response which have either:
  - been recorded as the same nominal visit, or
  - been recorded as an unscheduled visit which is assigned to the given visit as per Table 1

  will be chosen for the analysis.
- If a given visit has no initial nominal visit record, then the earliest of all unscheduled visits which are assigned to the given visit as per Table 1 will be chosen for the analysis.

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 will be used for the summary.

Scheduled Month and visit window during the HK Treatment Phase and Diet Comparison Phase is shown in Table 1. The window for visits will be constructed in such a way that the upper limit of the interval falls half way between the two visits, except in the case where the visit is the first in a phase, or immediately follows the first visit in a phase.

Table 1 Definition of visit windows for HK Treatment Phase and Diet Comparison Phase

Analysis Period	Scheduled Month of Visit	Visit	Visit Window[a]
Screening		Visit 1	Up to and including HK Day -1
HK Treatment Phase	Month 1	Visit 2	HK Day 1

		Visit 3	HK Day 2 to 11
		Visit 4	HK Day 12 to 18
		Visit 5	HK Day 19 to DC Day -1
Diet Comparison Phase	Month 2	Visit 6	DC Day 1
		Visit 7	DC Day 2 to 11
		Visit 8	DC Day 12 to 18
		Visit 9	DC Day 19 to DC Day 25
	Month 3	Visit 10	DC Day 26 to DC Day 44
	Month 4	Visit 11	DC Day 45 to DC Day 75
	Month 5	Visit 12	DC Day 76 to FU Visit

[a] Visit window is assigned based upon study day and is calculated as as (date – start of phase date + 1). Date of the start of the phase according to the Analysis Periods in Section 3.2. For participants who do not proceed to the next phase and for whom the study day is after the lower limit of window of the last visit of the phase, the assessment will be assigned to the last visit of the phase.

5.3 Analysis methods

5.3.1 Participant Disposition and Analysis Sets Analyzed

Participant disposition will be listed and summarized for SZC in the HK Treatment Phase and for SZC, SoC and overall for participants in the Diet Comparison Phase. The number of participants in the following categories will be summarized:

- Screened;

The number and percentages of participants in the following categories will be summarized:

- Did not enter HK Treatment Phase (screening failures), and associated reasons
- Entered the HK Treatment Phase and received treatment
- Entered the HK Treatment Phase and did not receive treatment, and associated reasons
- Randomized;
- Not randomized (Diet Comparison Phase failure) and associated reasons;
- Randomized participants who received treatment;
- Randomized participants who did not receive treatment and associated reasons;
- Participants who completed the study;
- Discontinued treatment and associated reasons;
- Terminated study and associated reasons;

The denominator used for percentages will be calculated as follows. The denominator for participants who did not enter the HK Treatment Phase (and associated reasons) will be calculated using the All-participants analysis set. The denominator for participants who entered the HK Treatment Phase and received treatment, who entered the HK Treatment Phase and did not receive treatment (and associated reasons) will be calculated using the number of participants who entered the HK Treatment Phase; randomized and not randomized (and associated reasons) will be calculated using the number of participants who

entered the Diet Comparison Phase. The remaining participant disposition categories will use the number of participants who were FAS for the denominator.

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

5.3.2 Protocol Deviations

All important protocol deviations, defined according to section 3.3, will be listed for the HKS, and summarized by SZC for the HKS and by SZC, SoC and overall for the FAS separately. COVID-19 related important protocol deviations will be listed for the HKS. Each listing of important protocol deviations will include the phase during which the deviation occurred.

5.3.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by SZC for the HKS and by SZC, SoC and overall for the FAS. The demographic and baseline characteristics include the following:

- Age (Years);
- Age groups (18-64, 65-84 and over 85 years);
- 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);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- Country

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

A separate table will summarize the participant characteristics at baseline and will be listed and summarized by SZC for the HKS and by SZC, SoC and overall for the FAS. They will include:

- Baseline height (cm);
- Baseline weight (kg);
- Baseline body mass index (BMI) (kg/m^2) [calculated as (baseline weight/baseline height^2 where weight is in kg and height is in m];
- Prevalent HK ($S\text{-}K^+$: >5.5 mmol/L vs ≤5.5 mmol/L) at baseline
- Dialysis status at baseline (Former / Current / No)

- Current dialysis (Times / Week)
- Dialysis access type (Arteriovenous Fistula / Arteriovenous Graft / Tunneled Catheter / Other)

Other baseline measurements, such as vital signs and ECG results, will be reported with post-baseline measurements.

5.3.4 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 24.0 (or a later version if updated during the study)]. All medical history will be listed, and the number and percentage of participants with any medical history will be summarized by SZC for the HKS and by SZC, SoC and overall for the FAS by SOC and PT.

5.3.5 Previous and Concomitant Medications

Medications received prior to or concomitantly with study treatment will be coded using the WHO Drug Dictionary [Version March 2021 B3 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are as defined as follows:

Prior medications are those taken with a stop date prior to the first dose date of study treatment during the HK Treatment Phase.

Concomitant medications during the HK Treatment Phase are those with a start date anytime before the first dose date of study treatment during the Diet Comparison Phase for SZC randomized participants, or with a start date before the date of randomization for SoC randomized participants.

Concomitant medications during the Diet Comparison Phase are those which are either ongoing at the end of the Diet Comparison Phase, or with a stop date anytime after the first dose date of the Diet Comparison Phase for SZC randomized participants, or with a stop date anytime after the date of randomization for SoC randomized participants.

If a medication cannot be classified as “prior” or “concomitant during the HK Treatment Phase” or “concomitant during the Diet Comparison Phase” after applying imputation rules for missing/incomplete dates, it will be classified as concomitant during the Diet Comparison Phase.

Prior and concomitant medications will be listed for HKS. Concomitant medications during the HK Treatment Phase will be summarized by SZC for the HKS. Concomitant medications during the Diet Comparison Phase will be summarized separately by SZC, SoC and overall for the SAS.

For all summaries of medications, 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.

5.3.6 Measurements of Study Treatment Compliance

The percentage compliance for SZC is calculated for each analysis period as:

100*actual sachets taken/expected sachets taken

, where:

Actual sachet taken is defined as:

Sum of the sachets taken throughout the respective analysis period

And the expected sachets taken throughout the respective analysis period is derived using the study intervention and drug dispensation records (planned study drug dosage) to calculate the number of sachets expected accounting for changes to the prescribed dosage level (5g up to 15g once daily on non-dialysis days) and the unit dose strength dispensed (5g and 10g sachets).

The percentage compliance for SZC will be calculated separately for the HK Treatment Phase and Diet Comparison Phase and will be summarized descriptively by SZC for the HKS and by SZC, SoC and overall for the SAS.

Furthermore, for SZC the number and percentage compliance will be presented separately for the HK Treatment Phase and Diet Comparison Phase using the HKS and SAS respectively with the following compliance categories:

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

Furthermore, at each study visit during the HK Treatment Phase and Diet Comparison Phase there will be a categorical summary of the number and percentage of participants assigned to each dose of SZC (e.g. 5g every other day, 5g daily, 10g daily, 15g daily).

5.3.7 Efficacy

The primary statistical hypothesis of the study is that prescribing SZC with enhanced nutritional advice to participants with hyperkalaemia on haemodialysis will show a non-

inferior difference in the change from baseline in S-K^+ taken at LIDI visits M3, M4, and M5 when compared to participants on SoC (other than K^+ binders).

All efficacy endpoints will be analysed using the FAS.

5.3.7.1 Primary Efficacy Analysis

The primary endpoint will be defined as the change in the S-K^+ taken at LIDI visits M3, M4, and M5 compared to the S-K^+ taken at baseline.

The primary objective will test the null hypothesis of [S-K^+ for SZC participants] – [S-K^+ for SoC participants] >= 0.2 mmol/L against the alternative hypothesis that [S-K^+ for SZC participants] – [S-K^+ for SoC participants] <0.2 mmol/L at the 1-sided 0.025 significance level.

Estimand Attributes

In line with the ICH E9 (R1) addendum, 5 attributes (treatment, population, endpoint, intercurrent events, and population level summary) have been specified to translate the primary and secondary efficacy objectives into treatment effects that are to be estimated (estimands).

Endpoint:

The treatment effect is assessed by the primary efficacy endpoint of change from baseline in S-K^+ levels over the M3, M4, and M5 visits.

Population:

The population of participants targeted is adults with HK as defined by the inclusion/exclusion criteria who are able to complete the HK Treatment Phase.

Treatment:

SZC dosed as per local label to control HK and maintain normokalaemia in addition to SoC dietary advice for the up to 1-month HK Treatment Phase followed by the 4-month Diet Comparison Phase (SZC with enhanced nutrition advice versus SoC, including standard dietary advice) for the full 5-month treatment duration.

Intercurrent Event Strategy:

Intercurrent events are handled through a combination of a treatment policy strategy and a composite strategy (whereby the incidence of the intercurrent event is incorporated into the endpoint). Specifically, the following events which preclude the collection of data for the primary estimand will be handled according to the table below:

Intercurrent event	Data collection and analysis
Premature treatment discontinuation due to lack of efficacy or physician's decision	Participants will be followed and data collected will be analysed after the intercurrent event in line with a treatment policy strategy. In the case of missing data after treatment discontinuation, values will be imputed through a MI procedure.
Premature treatment discontinuation due to reasons other than lack of efficacy or physician's decision	Participants will be followed and data collected after the intercurrent event in line with a treatment policy strategy. In the case of missing data after treatment discontinuation, values will be imputed through a MI procedure.
Introduction of rescue therapy of a K^+ binder for HK	Participants will be followed and data collected after the intercurrent event for reporting purposes; however, this data will not be used for the primary analysis of the primary estimand. All values after introduction of rescue medication will be imputed using a composite policy through a MI procedure.

Population Level Summary:

The treatment effect will be quantified by via recombination average of the least squares (LS) mean of the change from baseline in S-K^+ levels across the M3, M4, and M5 visits, obtained from a repeated measures ANCOVA performed multiple times on MI data as described below.

All scheduled assessments during the Diet Comparison Phase (visits 6 to 12) will be used for imputation, and the visits during the LIDI will be used for analysis. Intermittent observed values will be used to generate a full set of imputed values up to and including M5.

The primary analysis will need to account for missing values, and values recorded for participants after commencement of rescue therapy of a K^+ binder for hyperkalaemia, through a MI method with 1000 imputations using the missing not at random framework separately for each treatment group. Any assessments performed after the introduction of rescue therapy will not be used as inputs for the MI procedure and will be treated as missing.

Intermittent observed values will be used to generate a full set of imputed values up to and including M5. In case that a non-monotone missing data pattern exists at the intermediate visits, these data points will be first imputed separately 1000 times for each treatment group using the Markov Chain Monte Carlo (MCMC) method in order to achieve a monotone missing data pattern for all participants. The full set of endpoint values will be subsequently imputed from the multiple copies of the original dataset where each copy will have a monotone missing pattern; if the MCMC method was previously used, this will be done once per existing imputation, otherwise this will be done 1000 times on the existing data.

The following types of missing data will be handled differently:

- Missing values at times where the participant remains on treatment, or after the participant discontinues treatment for reasons other than either the physician's decision or lack of efficacy, will be imputed based on known values for the treatment group the participant was randomized to.
- Missing values at times after discontinuation of treatment for reasons of physician's decision or lack of efficacy, will be imputed based on known values for the treatment group the participant was randomized to, with a penalty of 10% applied to the values used for imputation.
- Values at times whilst the participant remains on treatment and after commencement of rescue therapy of a K^+ binder for hyperkalaemia will be imputed based on known values for the treatment group the participant was randomized to with a penalty of 10%.

A repeated-measures ANCOVA model will be used for each of the 1000 imputed datasets, with fixed terms for the treatment groups for SZC and SoC, visit and baseline S-K^+ for the Diet Comparison Phase as a covariate.. An unstructured variance-covariance matrix will be assumed. The analysis will be performed using post-baseline data from the Diet Comparison Phase (Visit 10 to 12). The results from each model will be recombined using Rubin's rule to provide the estimated change from baseline in S-K^+ for each treatment group over the period of M3 to M5, as well as the average of esitmated mean group differences over visit 10, 11 and 12 and its 95% confidence interval (CI) . The null hypothesis will be rejected if the upper bound of the 95% CI is below 0.2. P-value will be generated as well.

5.3.7.2 Primary Efficacy Analysis – Sensitivity Analyses

The following sensitivity analyses will be pre-specified to be conducted for the primary efficacy endpoint. Aside from the stated amended intercurrent event strategy in each case, the analysis and imputation will be performed in the same way as for the primary analysis.

(i) The intercurrent event strategy will be altered to describe the treatment effect using while on-treatment strategy.

Intercurrent Event Strategy:

Intercurrent event	Data collection and analysis
Premature treatment discontinuation due to lack of efficacy or physician's decision	Participants will be followed and data collected after the intercurrent event for reporting purposes; however, this data will not be used for this sensitivity analysis of the primary estimand. All values after treatment discontinuation will be imputed using a composite policy through a MI procedure.
Premature treatment discontinuation due to reasons other than lack of efficacy or physician's decision	Participants will be followed and data collected after the intercurrent event for reporting purposes; however, this data will not be used for this sensitivity analysis of the primary estimand. All values after treatment discontinuation will be imputed using a composite policy through a MI procedure.
Introduction of rescue therapy of a K^+ binder for HK	Participants will be followed and data collected after the intercurrent event for reporting purposes; however, this data will not be used for the primary analysis of the primary estimand. In the case of missing data whilst the participant is on-treatment, values will be imputed through a MI procedure.

(ii) The intercurrent event strategy will be altered to describe the treatment effect in a COVID-19 pandemic-free world.

Intercurrent Event Strategy:

Intercurrent event	Data collection and analysis
Premature treatment discontinuation not related to the COVID-19 pandemic	Participants will be followed and data collected will be analysed after the intercurrent event in line with a treatment policy strategy. In the case of missing data after treatment discontinuation, values will be imputed through a MI procedure.
Premature treatment discontinuation related to the COVID-19 pandemic	Participants will be followed and data collected after the intercurrent event for reporting purposes; however, this data will not be used for this sensitivity analysis of the primary estimand. All values after diagnosis of COVID-19 will be imputed using a composite policy through a MI procedure.
Introduction of rescue therapy of a K^+ binder for HK	Participants will be followed and data collected after the intercurrent event for reporting purposes; however, this data will not be used for this sensitivity analysis of the primary estimand. All values after introduction of rescue medication will be imputed using a composite policy through a MI procedure.

(iii) Missing values at times after discontinuation of treatment or values at times whilst the participant remains on treatment and after commencement of rescue therapy of a K^+ binder for hyperkalaemia will be imputed based on known values for the

treatment group the participant was randomized to, with a penalty of 15%. The intercurrent event strategy will otherwise be the same as the primary analysis.

5.3.7.3 Secondary Efficacy Analyses

A multiplicity correction procedure that covers the primary and the secondary endpoints will be applied, with the method being a fixed-sequence hierarchical testing procedure where the primary hypothesis is tested first. If the primary endpoint or any of the secondary endpoints listed in the order of importance are negative, then all endpoints beneath them in the hierarchy are then reduced to being exploratory endpoints. The order of importance for the secondary endpoints is as follows:

- Maintaining S-K^+ levels within a range of 3.5–5.5 mmol/L without requiring rescue therapy for HK
- Consumption of fruit and vegetables
- EQ-5D-5L score
- KDQOL-36 PCS
- KDQOL-36 MCS
- TSQM-9
- PGIC

Maintaining S-K^+ levels within a range of 3.5–5.5 mmol/L without requiring rescue therapy for HK

The first secondary objective (Maintaining S-K^+ levels within a range of 3.5–5.5 mmol/L without requiring rescue therapy for HK) will test the null hypothesis of [Proportion of SZC responders] – [Proportion of SoC responders] < -0.1 against the alternative hypothesis that [Proportion of SZC responders] – [Proportion of SoC responders] ≥ - 0.1 at the 1-sided 0.025 significance level.

The proportions of responders and non-responders and 95% 2-sided Wilson CI for responders will be calculated for each treatment arm, and a difference in proportions (SZC - SoC) constructed. A 95% 2-sided Newcombe CI for the risk difference will be created, and the null hypothesis will be rejected if the lower bound of the CI is ≥ -0.1.

Estimand Attributes for the secondary endpoint of maintaining S-K^+ levels within the normokalaemic range of 3.5-5.5 mmol/L without requiring rescue therapy for HK

In line with the ICH E9 (R1) addendum, 5 attributes (treatment, population, endpoint, intercurrent events, and population level summary) have been specified to translate the primary and secondary efficacy objectives into treatment effects that are to be estimated (estimands).

Endpoint:

The treatment effect is assessed by the secondary endpoint of maintaining S-K^+ levels within the normokalaemic range of 3.5-5.5 mmol/L without requiring rescue therapy for HK will be assessed as a binary (responder/non-responder) variable, with participants being be deemed responders if all of the following are true:

1. The participant provides 2 or more non-missing S-K^+ assessments during the period from M3 to M5, inclusive.

2. At least 66% of their non-missing S-K^+ assessments between the M3 and M5 visits, inclusive, show values within the normokalaemic range.

3. The participant does not receive rescue therapy or a K^+ binder for HK at any point between the M3 and M5 visits, inclusive.

Participants will be deemed non-responders if point 3 is not true, or if point 1 is true and point 2 is not true.

Participants will be excluded from the secondary analysis if point 1 is not true and point 3 is true.

Population:

The population of participants targeted is adults with HK as defined by the inclusion/exclusion criteria who are able to complete the HK Treatment Phase.

Treatment:

SZC dosed as per local label to control HK and maintain normokalaemia in addition to SoC dietary advice for the up to 1-month HK Treatment Phase followed by the 4-month Diet Comparison Phase (SZC with enhanced nutrition advice versus SoC, including standard dietary advice) for the full 5-month treatment duration.

Intercurrent Event Strategy:

Intercurrent events are handled through a combination of a treatment policy strategy and a composite strategy. Specifically, the following events which preclude the collection of data for the secondary estimand will be handled according to the table below:

Intercurrent event	**Data collection and analysis**
Premature treatment discontinuation due to lack of efficacy or physician's decision	Participants will be followed and data collected will be analysed after the intercurrent event in line with a treatment policy strategy.

Intercurrent event	Data collection and analysis
Premature treatment discontinuation due to reasons other than lack of efficacy or physician's decision	Participants will be followed and data collected after the intercurrent event in line with a treatment policy strategy.
Introduction of rescue therapy of a K^+ binder for HK	Participants will be followed and data collected after the intercurrent event for reporting purposes; however, this data will not be used for the secondary analysis and participant will be treated as non-responder in line with a composite strategy.

Population Level Summary:

The proportions of responders and non-responders will be calculated for each treatment arm, and a difference in proportions (SZC - SoC) constructed. A 95% 2-sided CI for the difference will be created, and the null hypothesis will be rejected if the lower bound of the CI is ≥ -0.1.

Consumption of fruit and vegetables

The average daily fruit and vegetable consumption per 28 days during the Diet Comparison Phase will be analysed using a repeated-measures ANCOVA model with fixed terms for treatment, 28-day period, baseline average daily consumption, and treatment by 28-day period interaction. An unstructured variance-covariance matrix will be assumed.The baseline average daily fruit and vegetable consumption and the 28-day period consumption will be calculated as described in section 4.2.2.6.The comparison between treatment groups will be based upon the p-value associated with the treatment by 28-day period interaction term at M5, which will be presented alongside the LS mean of the M5 treatment difference and its associated 95% CI. Further, descriptive statistics, LS mean estimates, 95% CIs, and p-values will be provided per each 28-day period.

EQ-5D-5L

The EQ-5D-5L questionnaire score change from study baseline at M2 (visit 6) and M5 will be analysed using a ANCOVA model with fixed terms for treatment, and baseline EQ-5D-5L . The comparison between treatment groups will be assessed based upon the p-value associated with the treatment at the M5 visit, which will be presented alongside the LS mean of the overall treatment difference and its associated 95% CI. Further, descriptive statistics, LS mean estimates, 95% CIs, and p-values will be provided at the M2 visit and overall.

KDQOL-36

The change from study baseline at M2 (visit 6) and M5 for KDQOL-36 scores for symptoms, PCS, and MCS will be analysed using a ANCOVA model with fixed terms for treatment and baseline KDQOL-36. The comparison between treatment groups will be assessed based upon the p-value associated with the treatment at the M5 visit, which will be presented alongside the LS mean of the overall treatment difference and its associated 95% CI. Further,

descriptive statistics, LS mean estimates, 95% CIs, and p-values will be provided at the M2 visit and overall.

TSQM-9

The change from baseline at M2 (visit 6) and M5 for TSQM-9 total score will be analysed using a ANCOVA model with fixed terms for treatment and baseline TSQM-9 total score. The comparison between treatment groups will be assessed based upon the p-value associated with the treatment at the M5 visit, which will be presented alongside the LS mean of the overall treatment difference and its associated 95% CI. Further, descriptive statistics, LS mean estimates, 95% CIs, and p-values will be provided at the M2 visit and overall.

PGIC

The categorical response (much better, a little better, about the same, a little worse, much worse) to each PGIC question will be summarised at each scheduled visit during the Diet Comaprison phase by SZC and SoC using the FAS.

5.3.7.4 Secondary Efficacy Analyses – Sensitivity Analyses

The following sensitivity analysis will be pre-specified to be conducted for the secondary efficacy endpoint, maintaining S-K^+ levels within the normokalaemic range of 3.5-5.5 mmol/L without requiring rescue therapy for HK.

Participants who discontinued study prior to providing a response for the secondary endpoint, maintaining S-K^+ levels within the normokalaemic range of 3.5-5.5 mmol/L without requiring rescue therapy for HK, (i.e.) those for whom point 1 in section 5.3.7.3 is not true, will be treated as non-responders.

CCI [redacted]

CCI [redacted]

5.3.8 Safety

All safety analyses will be performed on the SAS and HKS.

5.3.8.1 Adverse Events

An overall summary table of the number of participants experiencing each category of AEs will be produced using the HKS and SAS. Analyses using the HKS will be restricted to AEs which occurred during the HK Treatment Phase and will be presented overall. Analyses using the SAS will include AEs which occurred during the Diet Comparison Phase and will be presented by treatment group received during the Diet Comparison Phase and overall.

AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) SOC and PT. Only TEAEs will be included in table 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.

- Any AEs
- Any AEs assessed by investigator as possibly related to SZC treatment
- Any AEs with outcome of death
- Any SAEs (including events with outcome of death)
- Any SAEs leading to treatment discontinuation
- Any AEs leading to treatment discontinuation
- Any AEs leading to dose reduction of study treatment

- Any AEs leading to dose interruption of study treatment
- Any AEs leading to study discontinuation

The number and percentage of participants reporting each AE will be summarized by SOC and PT. Tables will be sorted by international order for SOC, and PTs will be sorted alphabetically. The following summaries will be produced using the HKS and SAS:

- AEs by SOC and PT;
- Most common AEs (>5% overall for HKS, >5% in any treatment group for SAS) by SOC and PT;
- AEs assessed by investigator as possibly related to SZC treatment, by SOC and PT;
- AEs by relationship to treatment, by SOC and PT;
- AEs by maximum intensity, by SOC and PT;
- AEs assessed by investigator as possibly related to SZC treatment, by maximum intensity, SOC and PT;
- AEs leading to treatment discontinuation, by SOC and PT;
- AEs assessed by investigator as possibly related to SZC treatment leading to treatment discontinuation, by SOC and PT;
- SAEs, by SOC and PT;
- SAEs related to SZC treatment, by SOC and PT;
- AEs leading to death, by SOC and PT;

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 both HK Treatment Phase and Diet Comparison Phase, study treatment at the time of event.

5.3.8.2 Deaths

A summary of deaths will be provided with number and percentage of participants categorized as:

- Number of participants with any AE with outcome = death
- AEs with outcome of death only

All deaths will be listed.

5.3.8.3 Laboratory Data

Laboratory data (clinical chemistry and haematology) will be summarized 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 first non-missing scheduled value will be used for the summary. 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 summarized at each scheduled assessment time during the Diet Comparison Phase using SAS.

Shift tables will be provided for parameters with available reference range, where shift from baseline to the worst value with respect to the reference range will be summarized, where worst is defined to low or high in preference to normal categorization. Where a participant has both high and low responses, they will be summarized in both categories. This will be provided for the SAS, summarizing the worst overall value across all visits during the Diet Comparison Phase.

5.3.8.4 Vital Signs

Vital sign values will be summarized and listed. Vital sign data absolute and change from baseline will be summarized at each scheduled timepoint. The continuous vital sign parameters will be summarized with descriptive statistics. If a participant has multiple results for a particular test at a particular time point, the first non-missing scheduled value will be used for the summary. These will be provided for the HKS which will be limited to visits during the HK Treatment Phase and be presented overall, and the SAS, which will include all visits during the Diet Comparison Phase with scheduled vital sign assessment and be presented by treatment group.

5.3.8.5 Electrocardiograms

ECG data will be summarized and listed. Absolute and change from baseline in ECG parameters will be summarized at each scheduled timepoint. The continuous ECG parameters will be summarized with descriptive statistics. If a participant has multiple results for a particular test at a particular time point, the first non-missing scheduled value will be used for the summary. These will be provided for the HKS, limited to visits during the HK Treatment Phase and presented overall, and the SAS which will include all visits during the Diet Comparison Phase with ECG assessments and be presented by treatment group.

5.3.8.6 Physical Examination

Physical examination assessments where a new or worsening abnormality is observed will be reported as an AE and included within the AE summaries detailed in section 5.3.8.1.

Height (Visit 2 only), weight and BMI will be summarized overall for the HKS, restricted to visits during the HK Treatment Phase, and by treatment received during the Diet Comparison Phase using the SAS.

5.3.8.7 Exposure

Exposure (in days) to IP i.e. total amount of study drug will be summarized overall for the HKS and by treatment group for the SAS.

Actual and total exposure (days) will be summarized by the following: mean, standard deviation, minimum, maximum, median and number of observations.

5.3.8.8 Pregnancy Test

Serum pregnancy test results will be listed only using the HKS.

5.3.8.9 Dialysis Prescription

Dialysis prescription parameters including blood flow (Qb, mL/min) and time on dialysis (minutes) will be summarized and listed by treatment group for the SAS.

5.3.8.10 Dialysis Adequacy

Dialysis adequacy indices including spKt/V and/or urea reduction ratio (URR) will be summarized and listed by treatment group for the SAS.

5.3.8.11 Interdialytic Weight Gain (IDWG)

IDWG will be summarized overall for the HKS and by treatment group for the SAS.

Change in IDWG from visit 2 to visit 6, and visit 6 to visit 12 will also be summarized by treatment group for the SAS.

6. INTERIM ANALYSES

No interim analysis is planned for this study.

7. REFERENCES

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Document Title:	Statistical Analysis Plan Version 1	
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