Statistical Analysis Plan	
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A Double-blind Randomized Placebo-controlled Parallel Design Multicenter Phase IIIb Study of the Effect of Sodium Zirconium Cyclosilicate (SZC) on Serum Potassium and Serum Bicarbonate in Patients with Hyperkalemia and Metabolic Acidosis Associated with Chronic Kidney Disease (NEUTRALIZE)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ACEi	Angiotensin-Converting Enzyme inhibitor
ANCOVA	ANalysis of COVAriance
ARB	Angiotensin II Receptor Blocker
ARNi	Angiotensin Receptor-Neprilysin inhibitor
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	COronaVIrus Disease 2019
CSP	Clinical Study Protocol
ECG	ElectroCardioGram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
EOT	End Of Treatment
FAS	Full Analysis Set
IP	Investigational Product
LOCF	Last Observation Carried Forward
K+	Potassium
MedDRA	Medical Dictionary for Regulatory Activities
POCT	Point-of-Care Test
PPS	Per Protocol Set
QD	once daily
QTcF	QT interval corrected by the Fridericia method
RAASi	Renin-Angiotensin-Aldosterone System Inhibitor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sK+	serum potassium
SoA	Schedule of Activities
SSO	Safety Set Open
SSR	Safety Set Randomized
SZC	Sodium Zirconium Cyclosilicate
TCO2	Total carbon dioxide
TID	Three times daily
UACR	urine albumin-to-creatinine ratio

AMENDMENT HISTORY

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Other	01-Dec-2022	Amended subgroup and sensitivity analyses to be conducted. Amended covariates to be included in sensitivity analysis of primary endpoint.	No	Due to the early termination of study some planned analyses cannot be performed due to small sample size. Updating SAP to clarify which subgroup and sensitivity analyses are no longer being performed.
Multiple Testing Procedure	01-Dec-2022	Clarified data presentation of multiplicity process due to early termination of the study	No	Clarifying how p-values will be displayed in data presentations due to early termination of study.
Other	30-May-2022	Updated language to reflect changes in protocol v6.0. Added details regarding interim analysis.	Yes, v6.0	Protocol update includes interim analysis to be described in the SAP.
Primary or secondary endpoints	09-Aug-2021	Changed i-STAT to Point of Care Test (POCT) throughout SAP in line with CSP	Yes, v4.0	Protocol updated to expand POCT options in addition to i-STAT.
Statistical analysis method for the primary of secondary endpoints	09-Aug-2021	Added POCT type to multivariable analyses of primary and secondary endpoints	Yes, v4.0	Considered important to control for confounding difference from POCT type used by site.
CCI [redacted]				

				gap results but providing variables needed to enable calculation.
Addition of analysis visit windows	09-Aug-2021	Added analysis visit windows	No	This change expands visit windows to allow additional assessments to be included in summaries by visit.

* Pre-specified categories are
Primary or secondary endpoints; Statistical analysis method for the primary or secondary endpoints; Derivation of primary or secondary endpoints; Multiple Testing Procedure; Data presentations; Other

1 STUDY DETAILS

1.1 Study objectives

Objectives	Endpoints
Primary	
• To evaluate the efficacy of sodium zirconium cyclosilicate (SZC) as compared to placebo in maintaining normal serum potassium (sK+) in patients with hyperkalemia and metabolic acidosis associated with chronic kidney disease (CKD)	• Occurrence (yes/no) of patients having normal sK+ between 3.5 and 5.0 mmol/L inclusive at end of treatment (EOT), Day 29, without need for rescue treatment for hyperkalemia at any point during the randomized phase
Secondary	
• To evaluate the efficacy of SZC as compared to placebo in increasing serum bicarbonate in patients with hyperkalemia and metabolic acidosis associated with CKD	• Mean change in serum bicarbonate at Day 29 compared to baseline (Day 1) • Occurrence (yes/no) of patients having an increase in serum bicarbonate of ≥2 mmol/L from baseline (Day 1) to EOT (Day 29) without need for rescue treatment for metabolic acidosis (low bicarbonate) • Occurrence (yes/no) of patients having an increase in serum bicarbonate of ≥3 mmol/L from baseline (Day 1) to EOT (Day 29) without need for rescue treatment for metabolic acidosis (low bicarbonate) • Occurrence (yes/no) of patients having bicarbonate ≥22 mmol/L at EOT (Day 29) without need for rescue treatment for metabolic acidosis (low bicarbonate) •
• To evaluate the efficacy of SZC as compared to placebo in normalizing sK+ and increasing serum bicarbonate in patients with hyperkalemia and metabolic acidosis associated with CKD	• Occurrence (yes/no) of patients having normal sK+ between 3.5 and 5.0 mmol/L inclusive at EOT (Day 29) and an increase in serum bicarbonate of ≥3 mmol/L from baseline (Day 1) to EOT (Day 29) without need for rescue treatment for hyperkalemia or metabolic acidosis (low bicarbonate). • Occurrence (yes/no) of patients having normal sK+ between 3.5 and 5.0 mmol/L inclusive and bicarbonate ≥22 mmol/L at EOT (Day 29) without need for rescue treatment for hyperkalemia or metabolic acidosis (low bicarbonate).
• To describe the need for rescue treatment with sodium bicarbonate for metabolic acidosis (low bicarbonate) in SZC and placebo arms	• Occurrence (yes/no) of patients needing rescue treatment for serum bicarbonate (≤15 mmol/L) any time during the randomized phase
Safety	
• To evaluate the safety and tolerability of SZC as compared to placebo in patients with	• Safety and tolerability will be evaluated in terms of Adverse Events (AEs), vital signs, clinical laboratory

Objectives	Endpoints
hyperkalemia and metabolic acidosis associated with CKD	assessments, and Electrocardiogram (ECG). Assessments related to AEs cover: • Occurrence/frequency • Relationship to SZC/placebo as assessed by investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of SZC/placebo

1.2 Study design

This is a prospective, randomized, double-blind, placebo-controlled, parallel, multicenter, Phase IIIb study to investigate the safety and efficacy of SZC in patients with hyperkalemia and low bicarbonate (or metabolic acidosis).

The study will be conducted in the United States (US) at approximately 35 investigative sites.

This study consists of a short screening visit (Day 1), an open-label correction period (up to 48 hours), a 4-week randomized treatment period, and a follow-up period (7 days after the last administration of study medication). The total study treatment duration, consisting of open-label and randomized periods, will be 29 days.

Screening will be performed using potassium and bicarbonate value from a study-approved point-of-care test (POCT) to determine eligibility of consenting patients to enter the open-label correction phase. Patients who meet the POCT eligibility criteria of serum potassium (sK+) between 5.1-5.9 mmol/L inclusive, AND serum bicarbonate between 16-20 mmol/L

inclusive, will be enrolled into the open-label correction phase. All baseline parameters should be measured/collected prior to administration of the first dose of study drug in the open-label initial phase.

In the open-label initial phase, patients will receive open-label SZC orally at a dose of 10 g three times daily (TID) for up to 48 hours, depending on POCT potassium value.

Patients who achieve normokalemia (K+ between 3.5 and 5.0 mmol/L inclusive) within 24-48 hours will be randomized 1:1 into the double-blind randomized treatment phase to receive 10 g SZC or placebo once daily (QD) starting dose for the following 28 days. Patients who achieve normokalemia after 24 hours will be randomized and will not need to continue on 10 g SZC TID for another 24 hours.

Study treatment will end with the Day 29 visit, which will be followed by the end of study visit 7 days after the last administration of study medication.

1.2.1 Randomization

Subjects who are normokalaemic (NK; 3.5≤sK+≤5.0 mmol/L) within 24 to 48 hours of enrolment in the open-label correction phase will be randomized 1:1 to either SZC 10g QD or placebo 10g QD. Randomization will be performed using randomly permuted blocks. The randomization codes will be computer generated and loaded into the IxRS database.

1.3 Number of subjects

- Prior data: Proportion of patients with serum bicarbonate between 16-20 mmol/L inclusive who had a 3 mmol/L or greater increase in serum bicarbonate with SZC versus placebo from ZS-004,[20] Global Harmonize trial,[21] and ZS-005.[22]
- SZC: 92/235 = 0.39 achieved an increase in serum bicarbonate ≥3 mmol/L
- Placebo: 7/40 = 0.175 achieved an increase in serum bicarbonate ≥3 mmol/L
- Sample size estimate*
    - 20% absolute difference:
    - Alpha=0.05, Power=80%
    - Control=0.175 with serum bicarbonate increase of 3mmol/L or more
    - SZC=0.39 with serum bicarbonate increase of 3mmol/L or more
        - *Actual effect size = 0.215
    - N=68 per group (136)
    - N=148 (accounting for 8% drop-out from initial phase to randomized placebo-controlled phase)

*Sample size would be smaller if based on primary endpoint of mean sK+ (N=18 per arm).

Approximately 477 patients will be screened. Approximately 148 patients will be enrolled to the open-label phase of the study to achieve 136 randomly assigned to study intervention.

2 ANALYSIS SETS

2.1 Definition of analysis sets

Screened Set

All subjects who were screened for inclusion in the open-label run-in period of the study. This analysis set will be used to describe the demographics of subjects considered for inclusion in the study. The assignment of subjects to a treatment group for analysis is not applicable.

Safety Set Open

All patients enrolled in the open-label correction phase who took at least 1 dose of study drug. The Safety Set Open (SSO) analysis set will be used to describe the safety characteristics of SZC during the open–label period. Patients will be analyzed as a single group.

Safety Set Randomized

All patients who achieve normokalemia at the end of the open-label correction phase and who received at least one dose of either SZC or placebo during the randomized placebo-controlled phase. The Safety Set Randomized (SSR) analysis set will be used to describe the safety characteristics of SZC or placebo during the randomized placebo-controlled phase. Patients will be analyzed according to the investigational product (IP) received during the randomized placebo-controlled phase.

Full Analysis Set

All patients who achieve normokalemia (K+ between 3.5 and 5.0 mmol/L inclusive) at the end of the open-label correction phase and enter the randomized placebo-controlled phase. The Full Analysis Set (FAS) will be the primary analysis set used for the primary, secondary and CCI [redacted]. Patients will be analyzed on an intent-to-treat basis according to their randomized IP.

Per Protocol Set

The Per Protocol Set (PPS) is defined as all patients in the FAS without any important protocol deviations leading to exclusion from the PPS. Patients will be analysed according to their randomized IP. The PPS will be used for sensitivity analysis of the primary and secondary endpoints.

Protocol deviations are defined as any change, divergence, or departure from the study design of procedures defined in the clinical study protocol (CSP). Important protocol deviations are a subset of protocol deviations and may significantly impact the correctness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Important protocol deviations which should lead to exclusion from the PPS will be defined by the Sponsor before database lock by judging the importance of the deviations upon the primary efficacy endpoint.

2.2 Violations and deviations

Subjects will be assessed by comparison of their electronic case report form (eCRF) data with the criteria below; protocol waivers will not be taken into consideration (e.g. if a subject younger than 18 enters the study on a protocol waiver, the subject would still be excluded from the PPS).

The following criteria may be considered as important protocol deviations which have a major effect on efficacy or that could potentially affect the interpretability of the study results and which should lead to exclusion from the PPS.

- Subjects who failed any of the inclusion or exclusion criteria of the study.
- Inappropriate compliance with study treatment during the randomized placebo-controlled phase of the study, e.g. treatment compliance of less than 80% or greater than 120%
- All prohibited medications which are administered during the randomized placebo-controlled phase of the study. Prohibited medications include patients starting on renin-angiotensin-aldosterone system inhibitor (RAASi) therapy during the trial Note: RAASi therapies: Angiotensin-converting enzyme inhibitor (ACEi), angiotensin II receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNi) are permitted to be continued at the same dose as baseline.
- Errors in treatment allocation. Any subject who received incorrect study treatment compared with randomized study treatment at any time during the study
- Any subject unblinded during the study
- Rules for rescue medication for hyperkalemia or metabolic acidosis violated
- Start of double-blind study medication prior to randomization date
- Subject with first dose prior to baseline evaluations.

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

2.3 Analysis Periods

Analysis periods defined in this section are distinct from those used to describe the study design in the CSP and section 1.2 of the SAP.

Screening Period

The screening period is defined as the period from informed consent to the first dose of open-label study or screen failure.

Open-label correction period

The open-label correction period refers to the period from first dose of open-label study treatment to the earliest date of randomization, withdrawal of consent, last contact with the subject or death.

Randomized placebo-controlled period

The randomized placebo-controlled period refers to the period from randomization to the earliest date of rescue treatment for hyperkalemia or low serum bicarbonate, last assessment during follow-up (day 36 +/- 3), withdrawal of consent, last contact with the subject, or death.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Time Points and Visit Windows

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 day and visit window during the open-label period in Table 1 are with respect to the first dose of open-label study treatment. Baseline is defined as measurements taken at the screening visit on day 1 of the study.

Table 1 Definition of visit windows

Visit	Scheduled Day of Visit	Analysis Period	Protocol Visit Windows	Visit title in TFLs	Analysis Visit Windows
Visit 1	1	Screening/ Open-Label	Day 1	Visit 1 (Baseline)	Day 1
Visit 2	2	Open-Label	Day 2*	Visit 2	Day 2*
Visit 3	2 or 3	Randomized	Days 2 – 3*	Visit 3 (Randomization)	Days 2 – 3*
Visit 4	8	Randomized	Days 7 – 9	Visit 4	Days 4 – 11
Visit 5	15	Randomized	Days 14 – 16	Visit 5	Days 12 – 18
Visit 6	22	Randomized	Days 21 – 23	Visit 6	Days 19 – 25
Visit 7	29	Randomized	Days 28 – 30	Visit 7 (EOT)	Days 26 – 32
Visit 8	36	Randomized	Days 33 – 39	Visit 8 (Follow-up)	Days 33 - 39

* Assessments conducted on day 2 and day 3 will be assigned to visit 2 or 3 based on the nominally entered visit on the eCRF.

3.2 Subject Disposition

Screen failures are defined as subjects who consent to participate in the clinical study but fail inclusion/exclusion criteria and are not entered into the open-label correction phase. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened after >2 weeks if screen failure was due to not meeting inclusion criterion #3 (POCT K+ level >5 mmol/L to ≤5.9 mmol/L and POCT bicarbonate levels between 16-20 mmol/L inclusive prior to the first SZC dose on study Day 1) and/or met exclusion criterion #24 (If the participant has evidence of Coronavirus disease 2019 (COVID-19) within 2 weeks prior to screening). Further, participants who failed, due to not meeting inclusion criteria #3

may be rescreened more than once at investigator's discretion if sK+ and bicarbonate obtained during routine patient care subsequent to the last rescreening are consistent with study entry criteria. Rescreen participants will be assigned the same participant number as in the initial screen so that each participant will appear once in disposition summaries.

3.3 Efficacy Variables

3.3.1 Potassium

Whole blood samples will be analyzed locally using POCT devices to generate K+ for the purposes of study inclusion, dose adjustments, and monitoring. Samples drawn at the same timepoints will be prepared and shipped to the central laboratory for analysis of sK+. In the event that hemolysis or other artifacts are suspected based on the reported POCT K+ result, the blood samples must be re-drawn to confirm the result and only the confirmatory sample result will be reported.

The primary endpoint will use the central laboratory sK+ measurement from Visit 7 if available and no use of rescue medication for hyperkalaemia has occurred. Missing measurements at Visit 7 will be imputed as follows:

(i) If Visit 7 central laboratory sK+ is missing

Visit 6 (or an unscheduled assessment which occurs between visits 6 and 7) central laboratory sK+ will be used in its place under the principle of last observation carried forward (LOCF). If multiple measurements are available, the closest measurement to the scheduled date of Visit 7 will be used.

(ii) If central laboratory sK+ is missing for Visits 6 and 7

sK+ will be replaced by POCT values adjusted to reflect the mean difference between POCT and sK+ values from all available (including screening, baseline and unscheduled visits) paired laboratory samples in both treatment groups. The mean difference will be estimated using a summary statistic of the difference in all pairs and will not adjust for baseline characteristics. If a Visit 7 POCT value is available the adjusted value for this will be used unless missing, in which case the adjusted Visit 6 POCT will be used. If an unscheduled POCT assessment which occurs between visits 6 and 7 is available, then the closest POCT assessment to the scheduled date of visit 7 will be used.

(iii) No sK+ or POCT K available for Visits 6 or 7

The subject will be classified as non-evaluable for primary and secondary efficacy endpoints which include sK+ measurements in their definition.

Normokalaemia is defined as 3.5 ≤ sK+ ≤ 5.0 and hyperkalaemia is defined as sK+ >5.0 where the sK+ value used will be the result of the imputation approach described above.

3.3.2 Bicarbonate

Whole blood samples will be analyzed locally using POCT devices to generate POCT serum bicarbonate measurements (TCO2). The secondary endpoints will use the POCT serum bicarbonate measurement from Visit 7 if available. For the first secondary endpoint analysing the mean change in serum bicarbonate from baseline, missing measurements at visit 7 will be imputed as follows:

(i) **If Visit 7 POCT serum bicarbonate measurements are unavailable**

Visit 6 (or an unscheduled assessment which occurs between visits 6 and 7) POCT serum bicarbonate will be used in its place under the principle of LOCF. If multiple measurements are available, the closest measurement to the scheduled date of Visit 7 will be used.

As a sensitivity analysis for the secondary endpoint #1, and as standard imputation approach for the other secondary endpoints which include serum bicarbonate measurements, the additional imputation rule will be applied:

(ii) If POCT bicarbonate is missing for Visits 6 and 7

POCT bicarbonate will be replaced by central laboratory bicarbonate values adjusted to reflect the mean difference between POCT and central laboratory bicarbonate values from all available (including screening, baseline and unscheduled visits) paired laboratory samples in both treatment groups. The mean difference will be estimated using a summary statistic of the difference in all pairs and will not adjust for baseline characteristics. If a visit 7 central laboratory value is available the adjusted value for this will be used unless missing, in which case the adjusted Visit 6 central laboratory measurement will be used. If an unscheduled central laboratory assessment which occurs between visits 6 and 7 is available, then the closest available assessment to the scheduled date of visit 7 will be used.

(iii) No POCT or central laboratory bicarbonate available for Visits 6 or 7

The subject will be classified as non-evaluable for secondary efficacy endpoints which include serum bicarbonate measurements in their definition.

Thresholds for the change from baseline for the imputed serum bicarbonate value described above of ≥2 mmol/L and ≥3 mmol/L will be calculated and an absolute value of ≥22 mmol/L or <15 mmol/L.

3.3.3 Additional serum measurements

Whole blood samples will be analyzed locally using POCT devices to generate POCT creatinine and anion gap measurements. If POCT does not generate anion gap values, then anion gap will be derived using the formula:

Anion gap (mEq/L) = sodium (mEq/L) – (chloride (mEq/L) + bicarbonate (mEq/L))

Where sodium, chloride and bicarbonate are measured at the same visits as discussed below.

3.3.4 Urine analysis

When possible, first morning void spot urine will be collected at visits 1, 3-8 and in the event of early withdrawal. Urinary albumin, ammonium, citrate, pH, and creatinine will be measured at the central laboratory. Urine anion gap will be calculated based on sodium, potassium, and chloride ions using the formulate provided in section 3.3.3. Urine albumin-to-creatinine-ratio (UACR) will be calculated based on the measured urinary albumin and creatinine. Ammonium-to-creatinine ratio will be calculated based on the measured urinary ammonium and creatinine. The urine anion gap, UACR and ammonium-to-creatinine ratio will be calculated by the central laboratory.

If visit 7 central laboratory measurements are unavailable, then visit 6 values will be used under the principle of LOCF.

3.4 Safety Variables

3.4.1 Exposure and dose interruptions

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

Total (or intended) exposure of study treatment

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

Actual exposure of study treatment

- Actual exposure = total (or intended) exposure – total duration of dose interruptions, where intended exposure will be calculated as above and a dose interruption is defined as any length of time where the subject has not taken any of the planned daily dose. The duration of each dose interruption will be calculated as interruption stop date – interruption start date + 1.

The actual exposure calculation makes no adjustment for any dose reduction that may have occurred.

3.4.2 Adverse Events

Adverse events (AEs) and Serious adverse events (SAEs) will be collected from start of the open-label correction phase, throughout the treatment period and including during the follow-up period. In addition, SAEs will be recorded from the time of signing the informed consent form and will continue throughout the clinical study until the end of any follow-up prior; this applies even if the subject has not received any study treatment (as per the SOP: Reporting of Individual Safety Events in Clinical Studies). SAEs which occur after the end of the clinical study but with a suspected causal relationship to the IP will be reported by the investigator but will not be included in summary tables and listings.

A treatment emergent AE (TEAE) will be defined as an AE with the start date on or after the first dose date and up to (and including) 7 days after the last dose date or an AE which starts prior to first dose of IP (i.e. before study day 1) which subsequently worsen in severity on or after the date of first dose of IP and up to and including 7 days following the date of last dose of study medication. AEs which occur more than 7 days after the last dose date will only be listed. Similarly, the number of patients experiencing SAEs, AEs that led to withdrawal, AEs that led to death and treatment related AEs, and number of such events, will be summarized by treatment group.

AEs will be further categorized as either occurring during the open-label period, if the start date is on or after the first dose date during the open-label correction period and prior to the date of the first dose of treatment during the randomized placebo-controlled period, or occurring during the randomized placebo-controlled period if the start date is on or after the date of the first dose of treatment during the randomized placebo-controlled period.

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

If the relationship to treatment is missing, then the AE will be considered as possibly related to treatment.

Other significant adverse events

An overview of edema-related events (grouped terms include preferred terms of edema, edema peripheral, generalized edema, fluid overload, fluid retention, hypervolemia, localized edema, and peripheral swelling)and instances of sK+ <3.5 will be presented.

Deaths

All AEs leading to death will be collected until the end of the study.

Laboratory Data

Deterioration as compared to baseline in protocol-mandated laboratory values will only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the IP or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, e.g., dose adjustment or drug interruption).

Vital Signs Data

Deterioration as compared to baseline in protocol-mandated vital signs
should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the IP or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, eg, dose adjustment or drug interruption).

3.4.3 Laboratory Data

Absolute change from baseline in haematology and clinical chemistry variables will be calculated for each post-dose visit. CTC and maximum post-baseline grade will be calculated at each visit, where appropriate. Absolute values will be compared to the local laboratory reference range and classified as low (below range), normal (within range or on limits of range) and high (above range). All values classified as high or low will be flagged on the listings.

Urinalysis and blood for the determination of clinical chemistry and haematology will be taken at the visits indicated in the Schedule of Activities (SoA) Tables 1 of the CSP. Presentations and summaries will use central laboratory results except for urinalysis dipstick results which will be local. Laboratory parameters include:

Table 2: Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum)
B-Haemoglobin (Hb)	S-Creatinine (sCr)
B-Leukocyte count	S-Potassium (K+)
B-Leukocyte differential count (absolute count)	S-Bicarbonate (Total CO_2)
B-Platelet count	S-Chloride (Cl-)
B-Hematocrit (Hct)	S-Glucose
	S-Creatinine
Urinalysis (dipstick, non central)	S-Blood Urea Nitrogen (BUN)
U-Hb/Erythrocytes/Blood	Urea (BUN)/Creatinine Ratio
U-Protein/Albumin	eGFR using the CKD-EPI formula
U-Glucose	Anion gap (blood, from POCT if available)
	S-Albumin
	S-Total Protein
	S-Calcium (Ca++)
	S-Magnesium (Mg++)
	S-Phosphate (PO_4)
	S-Bilirubin, total
	S-Alkaline phosphatase (ALP)
	S-Alanine amino transferase (ALT)
	S-Aspartate amino transferase (AST)

Estimated eGFR will be calculated using the CKD-EPI (chronic kidney disease epidemiology collaboration equation) formula for each time-point and will be analysed as provided by Covance Central Laboratory Services:

$$\text{eGFR (CKD-EPI)} = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if Black]}$$

Where S_{Cr} (standardized serum creatinine) = mg/dL, $\kappa = 0.7$ (females) or 0.9 (males), $\alpha = -0.329$ (females) or -0.411 (males), min = indicates the minimum of S_{Cr}/κ or 1, max = indicates the maximum of S_{Cr}/κ or 1 and age = years. eGFR at study entry will be calculated based on either POCT or local laboratory creatinine values.

3.4.4 Vital Signs

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

3.4.5 Electrocardiograms

Electrocardiogram (ECG) assessments will be performed at screening, randomization, EOT, and follow-up (as specified in the SoA), and according to clinical judgement in connection with severe hypokalaemia (sK+ <3.0 mmol/L), severe hyperkalemia (sK+>6.0 mmol/L) or any symptoms or clinical events suggesting cardiac arrhythmia. ECG parameters will include mean, minimum and maximum heart rate (beats/min), aggregate PR interval (msec), P wave duration (msec), QRS duration (msec), QT interval (msec), QTcB interval (msec), QT interval corrected by the Fridericia method (QTcF) interval (msec) and RR interval (msec). The absolute change from baseline will be calculated for each post-dose visit.

3.4.6 Physical Exam

A complete physical examination is performed at screening, randomization and all further study visits according to the SoA, Tables 1 of the CSP. Physical examination will include an assessment of general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems. Body weight and height are measured at the screening visit and weight will then be measured at randomization and all further study visits according to the SoA.

4 ANALYSIS METHODS

The principal analyses outlined in this statistical analysis plan will be conducted by Covance 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:

Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, Q1, Q3, minimum and maximum. Categorical variables will be summarized by frequency counts and percentages for each category.

Unless otherwise stated, percentages will be calculated out of the analysis set total for the treatment group.

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

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

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

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

In general, for all endpoints the last observation before the first dose of study treatment in the open-label period will be considered the baseline measurement, unless otherwise specified. For assessments on the day of first dose, where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose.

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

In all quantitative summaries from baseline, 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. Absolute and percentage change will be summarized.

Safety and treatment exposure data will be summarised based upon the SSO and SSR analysis sets separately. Analyses using the SSO analysis set will be restricted to visits 1 and 2 (if applicable). Study population and demography data will also be summarized using the SSO and SSR analysis sets.

4.1.1 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:

4.1.1.1 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 open-label period, 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 open-label period, then impute the day of the first dose date.
- Otherwise, assign the day as 1st of the month.

4.1.1.2 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 subject was in the study, then the end date will be replaced with the subject's date of completion/discontinuation.

4.2 Analysis methods

4.2.1 Subject Disposition and Analysis Sets Analyzed

Subject disposition will be listed and summarized by treatment group and overall. The number and percentage of subjects in the following categories will be summarized for subjects in the screened set:

- Screened;
- Did not enter open-label period (Screening failures) and associated reasons;
- Entered the open-label period and received treatment
- Entered the open-label period and did not receive treatment and associated reasons
- Randomized;
- Not randomized (Open-label period failure) and associated reasons;
- Randomized and received treatment;
- Randomized, did not receive treatment and associated reasons;
- Completed the study;
- Discontinued treatment and associated reasons (including use of rescue treatment);
- Terminated study and associated reasons;

The denominator used for percentages will be calculated as follows. The denominator for subjects who are screened or who did not enter the open-label period (and associated reasons) will be calculated using the number of screened subjects. The denominator for subjects who entered the open-label period and received treatment, who entered the open-label period and did not receive treatment (and associated reasons), randomized and not randomized (and associated reasons) will be calculated using the number of subjects who entered the open-label period. The remaining subject disposition categories will use the number of subjects who were randomized for the denominator. Categories will still be presented if 0 subjects satisfy the criteria.

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

4.2.2 Protocol Deviations

All important protocol deviations (Section 2.2) leading to exclusion from the PPS will be listed and summarized by treatment group and overall for the FAS. Important protocol deviations will be further classified as either pandemic-related or excluding pandemic related important protocol deviations and will be summarized by treatment group and overall for the FAS.

4.2.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized in total for the SSO and by treatment group and total for the SSR and FAS. The demographic and baseline characteristics include the following:

- Age (years);
- Age groups (>18 to ≤65, >65 to ≤85 and >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);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- CKD status at baseline (3, 4 or 5);
- Chronic Heart Failure at baseline (No, Yes) [Determined as medical history with MedDRA coded preferred term of cardiac failure chronic]
- Diabetes status at baseline (No, Yes);

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

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

- Baseline height (cm);
- Baseline weight (kg);
- Baseline body mass index (kg/m^2) [calculated as (baseline weight/baseline $height^2$ where weight is in kg and height is in m];

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

4.2.4 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 23.0 (or a later version if updated during the study)]. The number and percentage of subjects with any medical history will be summarized for the SSO by system organ class (SOC) and preferred term (PT) overall. The number and percentage of subjects with any medical history will be summarized for the SSR by system organ class (SOC) and preferred term (PT) for each treatment group overall.

4.2.5 Previous and Concomitant Medications

Medications received prior to or concomitantly with study treatment will be coded using the WHO Drug Dictionary [Version March 2020 (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 open-label correction period.

Concomitant medications during the open-label correction period are those with a start date anytime before the first dose date of study treatment during the randomized placebo-controlled period and a stop date on or after the first dose of study treatment during the open-label correction period.

Concomitant medications during the randomized placebo-controlled period are those with a stop date on or after the first dose date of study treatment during the randomized placebo-controlled period.

If a medication cannot be classified as “prior” or “concomitant during the open-label correction period” or “concomitant during the randomized placebo-controlled period” after applying imputation rules for missing/incomplete dates, it will be classified as concomitant during the randomized placebo-controlled period.

Concomitant medications during the open-label correction and randomized placebo-controlled periods will be further categorized by those allowed and disallowed. Disallowed concomitant medications are defined in the CSP Section 6.8 as starting on RAASi therapy during the trial (ATC level 2 code C09) or sodium-glucose transport protein 2 inhibitor therapy. Furthermore, several medications which are described as restricted will also be included as disallowed concomitant medications.

Prior medications, allowed/disallowed concomitant medications during the open-label correction period and allowed/disallowed concomitant medications during the randomized placebo-controlled period will be listed together. Allowed/disallowed concomitant medications during the open-label correction period will be summarized using the SSO and presented in total. Allowed/disallowed concomitant medications during the randomized placebo-controlled period will be summarized separately by treatment group and overall using the SSR.

The number and percentages of subjects using each medication will be displayed together with the number and percentage of subjects using at least one medication within each therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term.

4.2.6 Measurements of Study Treatment Compliance

The percentage compliance for SZC and placebo 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 to calculate the number of sachets expected accounting for changes to the prescribed dosage level (from 10g three times daily to 5g every other day) and the unit dose strength dispensed (5g and 10g sachets).

The percentage compliance for SZC and placebo will be calculated separately for the open-label and placebo-controlled periods and will be summarized descriptively overall using the SSO and treatment group using the SSR respectively.

Furthermore, for SZC/placebo the number and percentage compliance will be presented separately for the open-label and placebo-controlled periods using the SSO and SSR respectively with the following compliance categories:

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

Furthermore, at each study visit during the open-label and placebo-controlled periods there will be a categorical summary of the number and percentage of subjects assigned to each dose of SZC/placebo (e.g. 5g every other day, 5g daily, 10g daily, 15g daily).

4.2.7 Efficacy

To control for type I error, a hierarchical testing procedure will be followed when formally testing primary and secondary efficacy analysis endpoints. The hierarchical testing procedure will follow a stepwise algorithm where each endpoint is only formally tested if the preceding null hypothesis is rejected ($p<0.05$). The first secondary endpoint will only be formally tested if the null hypothesis for the primary endpoint is rejected at $p<0.05$. Endpoints which are not formally tested will have a p-value displayed when one can be calculated. However, a footnote will indicate that the "P-value is descriptive only due to a previous endpoint in the hierarchical testing procedure failing to have the null hypothesis rejected ($p\geq0.05$). The final order for hierarchical testing will be the order displayed below.

4.2.7.1 Primary Efficacy Analysis

The primary efficacy endpoint is the occurrence (yes/no) of patients having normal sK+ (between 3.5 and 5.0 mmol/L inclusive) on Day 29 (Visit 7) without rescue treatment for hyperkalemia at any point during the randomized phase in the SZC versus placebo arm. Patients with missing sK+ will have these imputed as described in section 3.3.1. The number and percentage of subjects who achieved a response (Yes, No, Non-evaluable) will be summarized by randomized treatment group in the FAS.

The occurrence will be compared between treatment groups in the FAS using a logistic regression model (excluding non-evaluable responses) including response as the dependent variable and randomized treatment as an independent factor, it will be tested using a two-sided

alpha = 0.05. The common odds ratio will be derived together with the two-sided 95% confidence interval.

Documentation will be provided to check the underlying assumptions for the logistic regression model. Standardized residuals will be presented in a scatter plot by alphanumerical subject ID. Subjects with standardized residuals > 3.0 will be listed. Influential observations on the regression coefficients will be detected by calculating Cook's D statistic (In SAS applied with proc reg with the plots=cooksd option) and presented in a diagnostic plot by alphanumerical subject ID. Subjects with Cook's D statistic > 4/sqrt(n) will be listed.

Estimand Attributes

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

Endpoint:

- Hyperkalaemia response, defined as an observed sK+ within 3.5-5.0 mEq/L at Day 29 (Visit 7)

Population:

- All subjects who achieve normokalemia at the end of the open-label correction phase, and are randomized

Treatment:

- SZC or Placebo. Patients with sK+ ≥ 6.0 mmol/L will be managed with rescue therapy employing local standard of care.

Intercurrent Event Strategy:

- Discontinuation of treatment (Treatment policy strategy, i.e. regardless of the intercurrent event)
- Use of rescue therapy for hyperkalaemia at any point during the randomized placebo-controlled period (Composite variable strategy, i.e. considered to be non-response).
- Use of rescue therapy for low bicarbonate at any point during the randomized placebo-controlled period (Treatment policy strategy, i.e. regardless of the intercurrent event).
- Death prior to Day 29 (Visit 7) (Composite variable strategy, i.e. considered to be non-response).
- Subject lost to follow-up prior to Day 29 (Visit 7) (Hypothetical strategy, i.e. assume response is not evaluable).
- Subject with no sK+ or POCT K measurement at visit 6 or visit 7 (Hypothetical strategy, i.e. assume response is not evaluable).

Population Level Summary:

- Odds ratio of the proportion of responders in the SZC treatment group compared to the placebo group.

4.2.7.2 Primary Efficacy Analysis – Sensitivity Analyses

Three sensitivity analyses will be pre-specified to be conducted for the primary efficacy endpoint. Upon review of the trial data, additional post-hoc or subgroup analyses may be performed.

(i) Primary analysis as described above. In addition to randomized treatment, the originally specified logistic regression model would have included: race, gender, age at baseline (<65, ≥65), CKD stage at baseline (3, 4), diabetes status (Yes, No), POCT bicarbonate level at entry (16-18, 19-20), POCT type (i-STAT, Piccolo) and baseline use of RAASi therapy (Yes, No) as independent factors. Due to the early termination of the study only POCT type will be included as an independent factor.

(ii) Primary analysis as described above but conducted in the PPS.

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

Intercurrent Event Strategy:

- Discontinuation of treatment not related to the COVID-19 pandemic (Treatment policy strategy, i.e. regardless of the intercurrent event).
- Discontinuation of treatment related to the COVID-19 pandemic (Hypothetical strategy, i.e. assume response is missing).
- Use of rescue therapy for hyperkalaemia at any point during the randomized-withdrawal period (Composite variable strategy, i.e. considered to be non-response).
- Use of rescue therapy for low bicarbonate at any point during the randomized placebo-controlled period (Treatment policy strategy, i.e. regardless of the intercurrent event).
- Death prior to Day 29 (Visit 7) not related to the COVID-19 pandemic (Composite variable strategy, i.e. considered to be non-response).
- Death prior to Day 29 (Visit 7) related to the COVID-19 pandemic (Hypothetical strategy, i.e. considered to be non-response).
- Subject lost to follow-up prior to Day 29 (Visit 7) irrespective of relationship to COVID-19 pandemic (Hypothetical strategy, i.e. assume response is not evaluable).
- Subject with no sK+ or POCT K measurement at visit 6 or visit 7 irrespective of relationship to COVID-19 pandemic (Hypothetical strategy, i.e. assume response is not evaluable).

4.2.7.3 Secondary Efficacy Analyses

1 Mean change in serum bicarbonate from baseline (Day 1) to Day 29 (Visit 7) in SZC versus placebo arm.

Serum bicarbonate will be summarized and listed in the FAS using the visits of Baseline (Visit 1), randomization (Visit 3) and Day 29 (Visit 7). Patients with missing serum bicarbonate values at visit 7 will have these imputed with serum bicarbonate values from visit 6 if available, as described in section 3.3.2. The mean change in serum bicarbonate from baseline (Day 1) will be analyzed using analysis of covariance (ANCOVA) analyses at the significance level 5% (2-sided), with randomized treatment as main effect and baseline bicarbonate as covariate. For patients needing rescue treatment for low bicarbonate, the last value of the POCT bicarbonate during the randomized period prior to rescue treatment will be analyzed. The analysis will be based on the FAS.

Documentation will be provided on the underlying assumptions for the ANCOVA model. This will include a check that the residuals are approximately normally distributed by plotting a histogram of the residuals for the model as well as a Shapiro-Wilk test which will reject the null hypothesis that the residuals are normally distributed if $p<0.05$. Secondly, the homogeneity of variance will be visually checked through an inspection of a plot of residuals versus predicted values from the model. Finally, the homogeneity of slopes will be determined by conducting an ANCOVA analysis where the dependent variable is Day 29 (Visit 7) serum bicarbonate and the independent variables are randomized treatment group, baseline serum bicarbonate and an interaction term between randomized treatment group and baseline serum bicarbonate. If $p>0.05$ for the interaction term, then we will accept the homogeneity of the treatment slopes.

Estimand Attributes

Endpoint:

- Change in serum bicarbonate at Day 29 (Visit 7) from baseline

Population:

- All subjects who achieve normokalemia at the end of the open-label correction phase, meet inclusion/exclusion criteria and are randomized

Treatment:

- SZC or Placebo. Patients with sK+ $\geq$ 6.0 mmol/L will be managed with rescue therapy employing local standard of care.

Intercurrent Event Strategy:

- Discontinuation of treatment (Treatment policy strategy, i.e. regardless of the intercurrent event)
- Use of rescue therapy for hyperkalaemia at any point during the placebo-controlled period (Treatment policy strategy, i.e. regardless of the intercurrent event).

- Use of rescue therapy for low bicarbonate at any point during the randomized controlled period (While on treatment strategy, e.g. last observation carried forward).
- Death prior to Day 29 (Visit 7) (While on treatment strategy, e.g. last observation carried forward).
- POCT bicarbonate measurement unavailable for Visits 6 and 7 (Hypothetical strategy, assume response is missing).
- Subject lost to follow-up prior to Day 29 (Visit 7) (Hypothetical strategy, assume response is missing).

Population Level Summary:

- Least squares mean estimate in the SZC treatment group compared to the placebo group.

2 *Occurrence (yes/no) of patients having an increase in serum bicarbonate of ≥2 mmol/L on Day 29 (Visit 7) from baseline without need for rescue treatment for low bicarbonate in SZC versus placebo arm.*

For secondary efficacy endpoints #2 - #7 the number and percentage of subjects with the endpoint (Yes, No, Non-evaluable) will be summarized by randomized treatment group in the FAS. Patients with missing sK+ or serum bicarbonate values at visit 7 will have these imputed as described in sections 3.3.1 and 3.3.1. The occurrence of each secondary efficacy endpoint will be compared between treatment groups in the FAS using a logistic regression model including the binary response endpoint as the dependent variable and randomized treatment as an independent factor, it will be formally tested using a two-sided alpha = 0.05 if the hierarchical testing strategy supports conducting a formal hypothesis test. The common odds ratio will be derived together with the two-sided 95% confidence interval.

For each secondary efficacy endpoint #2 - #7, documentation will be provided to check the underlying assumptions for the logistic regression model. Standardized residuals will be presented in a scatter plot by alphanumerical subject ID. Subjects with standardized residuals > 3.0 will be listed.

Endpoint:

- Serum bicarbonate response, defined as an increase from baseline in serum bicarbonate value ≥2 mmol/L at Day 29 (Visit 7)

Population:

- All subjects who achieve normokalemia at the end of the open-label correction phase, meet inclusion/exclusion criteria and are randomized

Treatment:

- SZC or Placebo. Patients with sK+ ≥ 6.0 mmol/L will be managed with rescue therapy employing local standard of care.

Intercurrent Event Strategy:

- Discontinuation of treatment (Treatment policy strategy, i.e. regardless of the intercurrent event)
- Use of rescue therapy for hyperkalaemia at any point during the placebo-controlled period (Treatment policy strategy, i.e. regardless of the intercurrent event).
- Use of rescue therapy for low bicarbonate at any point during the randomized controlled period (While on treatment strategy, e.g. last observation carried forward).
- Death prior to Day 29 (Visit 7) (Composite variable strategy, i.e. considered to be non-response).
- Subject lost to follow-up prior to Day 29 (Visit 7) (Hypothetical strategy, i.e. assume response is not evaluable).
- Subject with no POCT or central laboratory bicarbonate measurements at visit 6 or visit 7 (Hypothetical strategy, i.e. assume response is not evaluable).

Population Level Summary:

- Odds ratio of the proportion of responders in the SZC treatment group compared to the placebo group.

3 *Occurrence (yes/no) of patients having an increase in serum bicarbonate of ≥3 mmol/L on Day 29 (Visit 7) from baseline without need for rescue treatment for low bicarbonate in SZC versus placebo group.*

Endpoint:

- Serum bicarbonate response, defined as an increase in serum bicarbonate value ≥3 mmol/L at Day 29 (Visit 7) from baseline

Population:

- All subjects who achieve normokalemia at the end of the open-label correction phase, meet inclusion/exclusion criteria and are randomized

Treatment:

- SZC or Placebo. Patients with sK+ ≥ 6.0 mmol/L will be managed with rescue therapy employing local standard of care.

Intercurrent Event Strategy:

- Discontinuation of treatment (Treatment policy strategy, i.e. regardless of the intercurrent event)
- Use of rescue therapy for hyperkalaemia at any point during the placebo-controlled period (Treatment policy strategy, i.e. regardless of the intercurrent event).
- Use of rescue therapy for low bicarbonate at any point during the randomized controlled period (While on treatment strategy, e.g. last observation carried forward).
- Death prior to Day 29 (Visit 7) (Composite variable strategy, i.e. considered to be non-response).

- Subject lost to follow-up prior to Day 29 (Visit 7) (Hypothetical strategy, i.e. assume response is not evaluable).
- Subject with no POCT or central laboratory bicarbonate measurements at visit 6 or visit 7 (Hypothetical strategy, i.e. assume response is not evaluable).

Population Level Summary:

- Odds ratio of the proportion of responders in the SZC treatment group compared to the placebo group.

4 *Occurrence (yes/no) of patients having a normal sK+ (between 3.5 and 5.0 mmol/L inclusive) on Day 29 (Visit 7) and an increase in serum bicarbonate of ≥3 mmol/L on Day 29 (Visit 7) from baseline without need for rescue treatment for hyperkalemia or low bicarbonate.*

Endpoint:

- Hyperkalaemia response, defined as an observed sK+ within 3.5-5.0 mEq/L at Day 29 (Visit 7) and serum bicarbonate response, defined as an increase in serum bicarbonate value of ≥3 mmol/L at Day 29 (Visit 7) from baseline.

Population:

- All subjects who achieve normokalemia at the end of the open-label correction phase, meet inclusion/exclusion criteria and are randomized

Treatment:

- SZC or Placebo. Patients with sK+ ≥ 6.0 mmol/L will be managed with rescue therapy employing local standard of care.

Intercurrent Event Strategy:

- Discontinuation of treatment (Treatment policy strategy, i.e. regardless of the intercurrent event)
- Use of rescue therapy for hyperkalaemia at any point during the placebo-controlled period (While on treatment strategy, e.g. last observation carried forward).
- Use of rescue therapy for low bicarbonate at any point during the randomized controlled period (While on treatment strategy, e.g. last observation carried forward).
- Death prior to Day 29 (Visit 7) (Composite variable strategy, i.e. considered to be non-response).
- Subject lost to follow-up prior to Day 29 (Visit 7) (Hypothetical strategy, i.e. assume response is not evaluable).
- Subject with no sK+ or POCT K measurement at visit 6 or visit 7 (Hypothetical strategy, i.e. assume response is not evaluable).
- Subject with no POCT or central laboratory bicarbonate measurements at visit 6 or visit 7 (Hypothetical strategy, i.e. assume response is not evaluable).

Population Level Summary:

- Odds ratio of the proportion of responders in the SZC treatment group compared to the placebo group.

5 Occurrence (yes/no) of patients having serum bicarbonate ≥22 mmol/L on Day 29 (Visit 7) without need for rescue treatment for low bicarbonate in SZC versus placebo group

Endpoint:

- Serum bicarbonate response, defined as a serum bicarbonate value of ≥22 mmol/L at Day 29 (Visit 7)

Population:

- All subjects who achieve normokalemia at the end of the open-label correction phase, meet inclusion/exclusion criteria and are randomized

Treatment:

- SZC or Placebo. Patients with sK+ ≥ 6.0 mmol/L will be managed with rescue therapy employing local standard of care.

Intercurrent Event Strategy:

- Discontinuation of treatment (Treatment policy strategy, i.e. regardless of the intercurrent event)
- Use of rescue therapy for hyperkalaemia at any point during the placebo-controlled period (Treatment policy strategy, i.e. regardless of the intercurrent event).
- Use of rescue therapy for low bicarbonate at any point during the randomized controlled period (While on treatment strategy, e.g. last observation carried forward).
- Death prior t Day 29 (Visit 7) (Composite variable strategy, i.e. considered to be non-response).
- Subject lost to follow-up prior to Day 29 (Visit 7) (Hypothetical strategy, i.e. assume response is not evaluable).
- Subject with no POCT or central laboratory bicarbonate measurements at visit 6 or visit 7 (Hypothetical strategy, i.e. assume response is not evaluable).

Population Level Summary:

- Odds ratio of the proportion of responders in the SZC treatment group compared to the placebo group.

6 Occurrence (yes/no) of patients having a normal sK+ (between 3.5 and 5.0 mmol/L inclusive) on Day 29 (Visit 7) and a serum bicarbonate of ≥22 mmol/L on Day 29 (Visit 7) without need for rescue treatment for low bicarbonate or hyperkalemia

Endpoint:

- Hyperkalaemia response, defined as an observed sK+ within 3.5-5.0 mEq/L at Day 29 (Visit 7) and serum bicarbonate response, defined as a serum bicarbonate value of ≥22 mmol/L at Day 29 (Visit 7).

Population:

- All subjects who achieve normokalemia at the end of the open-label correction phase, meet inclusion/exclusion criteria and are randomized

Treatment:

- SZC or Placebo. Patients with sK+ ≥ 6.0 mmol/L will be managed with rescue therapy employing local standard of care.

Intercurrent Event Strategy:

- Discontinuation of treatment (Treatment policy strategy, i.e. regardless of the intercurrent event)
- Use of rescue therapy for hyperkalaemia at any point during the placebo-controlled period (While on treatment strategy, e.g. last observation carried forward).
- Use of rescue therapy for low bicarbonate at any point during the randomized controlled period (While on treatment strategy, e.g. last observation carried forward).
- Death prior to Day 29 (Visit 7) (Composite variable strategy, i.e. considered to be non-response).
- Subject lost to follow-up prior to Day 29 (Visit 7) (Hypothetical strategy, i.e. assume response is not evaluable).
- Subject with no sK+ or POCT K measurement at visit 6 or visit 7 (Hypothetical strategy, i.e. assume response is not evaluable).
- Subject with no POCT or central laboratory bicarbonate measurements at visit 6 or visit 7 (Hypothetical strategy, i.e. assume response is not evaluable).

Population Level Summary:

- Odds ratio of the proportion of responders in the SZC treatment group compared to the placebo group.

7 *Occurrence (yes/no) of patients needing rescue treatment for low bicarbonate (serum bicarbonate from POCT ≤15 mmol/L) during the randomized phase between SZC and placebo.*

Endpoint:

- Use of rescue treatment for low bicarbonate, where low bicarbonate is defined as a serum bicarbonate value of ≤15 mmol/L during the randomized placebo-controlled period

Population:

- All subjects who achieve normokalemia at the end of the open-label correction phase, meet inclusion/exclusion criteria and are randomized

Treatment:

- SZC or Placebo. Patients with sK+ ≥ 6.0 mmol/L will be managed with rescue therapy employing local standard of care.

Intercurrent Event Strategy:

- Discontinuation of treatment (Treatment policy strategy, i.e. regardless of the intercurrent event)
- Use of rescue therapy for hyperkalaemia at any point during the placebo-controlled period (Treatment policy strategy, i.e. regardless of the intercurrent event).
- Death prior to Day 29 (Visit 7) (Hypothetical strategy, i.e. assume response is not evaluable).
- Subject lost to follow-up prior to Day 29 (Visit 7) (Hypothetical strategy, i.e. assume response is not evaluable).
- Subject with no POCT or central laboratory bicarbonate measurements at visit 6 or visit 7 (Hypothetical strategy, i.e. assume response is not evaluable).

Population Level Summary:

- Odds ratio of the proportion with rescue treatment for low bicarbonate in the SZC treatment group compared to the placebo group.

4.2.7.4 Secondary Efficacy Analysis – Sensitivity Analyses

Two sensitivity analyses will be conducted for secondary efficacy endpoint #1:

(i) Analysis as described for secondary endpoint #1 using PPS

(ii) Analysis as described above but with full imputation of bicarbonate using central laboratory measurements, as described in section 3.3.2, is conducted before the response is assumed to be missing. In addition, the ANCOVA model will include a binary variable to indicate if the dependent variable is central laboratory measurement.

Two sensitivity analyses will be conducted for each of the secondary efficacy endpoints #2-#7.

- Principal secondary analysis as described where the logistic regression model will include: race, gender, age at baseline (<65, ≥65), CKD stage at baseline (3, 4), diabetes status at baseline (Yes, No), POCT bicarbonate level at entry (16-18, 19-20), POCT type (i-Stat, Piccolo) and baseline use of RAASi therapy (Yes, No) as independent factors.

- Principal secondary analysis as described but conducted in the PPS.

Due to the early termination of the trial, the sensitivity analyses described above will not be conducted due to an insufficient sample size.

4.2.8 Safety

4.2.8.1 Adverse Events

An overall summary table of the number of subjects experiencing each category of AEs will be produced using the SSO and SSR. Analyses using the SSO will be restricted to AEs which occurred during the open-label correction period and will be presented overall. Analyses using the SSR will include AEs which occurred during the randomized placebo-controlled period and will be presented by treatment group received during the randomized placebo-controlled period and overall.

Any AE occurring within the defined 7-day follow-up period after discontinuation of IP will be included in the AE summaries. Treatment emergent adverse events (TEAEs) occurring prior to first dose of IP (i.e. before study day 1) which subsequently worsen in severity following dosing will be presented in the summary tables.

An overview table will summarize the number and percentage of subjects with at least one of the following AEs, where patients 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. For the overall summary of subjects with any AEs, in the safety set randomized analysis group, the event rate will be displayed. This will be calculated as the Number of subjects with AEs divided by the total number of days at risk for AEs across all subjects in given group, multiplied by 365.25 multiplied by 100.

- Any AEs
- Any AEs assessed by investigator as possibly related to 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 subjects reporting each AE will be summarized by system organ class (SOC) and preferred term (PT). Tables will be sorted by international order for SOC and PTs will be sorted alphabetically. The following summaries will be produced using the SSO and SSR:

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

All AE data will be listed appropriately for all subjects 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 open-label correction period, study treatment at the time of event.

4.2.8.2 Deaths

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

- Number of subjects with any AE with outcome = death
- AEs related to disease under investigation and with AE outcome of death
- AEs with outcome of death only (AE start date falling > 21 days after last treatment dose)
- Deaths > 21 days after last treatment dose, unrelated to AE or disease under investigation
- Deaths > 21 days after last treatment dose, AE related to disease under investigation and with AE outcome of death

All deaths will be listed.

4.2.8.3 Laboratory Data

Laboratory data (clinical chemistry, haematology and urinalysis) will be summarized and listed. Laboratory data outside the reference ranges will be indicated in the listings. If a subject 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, haematology and urinalysis parameters will be summarized at each scheduled assessment time. Separate tables will be provided for the SSO, restricted to visits during the open-label period and presented overall and for the SSR which will include all visits and be presented by treatment received during the randomized placebo-controlled period.

Shift tables will be provided for select tests, where shift from baseline to the maximum value will be summarized. These will be provided separately for the SSO which will be limited to visits during the open-label period and the SSR which will summarize the worst overall value across all visits. Shift tables for laboratory values by worst common toxicity criteria (CTC) grade will be produced for all parameters with grading. These will be provided separately for the SSO which will be limited to visits during the open-label period and be presented overall and the SSR which will summarize the worst CTC grade across all visits and be presented by treatment received during the randomized-withdrawal period.

In addition, the number and percentage of subjects with markedly abnormal clinical laboratory values will be summarized for each parameter by timepoint. These will be provided separately for the SSO, which will be limited to visits during the open-label period and be presented overall, and the SSR, which will summarize abnormal clinical laboratory values across all visits and be presented by treatment received during the randomized placebo-controlled period.

4.2.8.4 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 subject 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 SSO, limited to visits during the open-label correction period and presented overall, and the SSR which will include all visits with scheduled vital sign assessment and be presented by treatment received during the randomized placebo-controlled period.

4.2.8.5 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 subject 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 SSO, limited to visits during the open-label correction period and presented overall, and the SSR which will include all visits with ECG assessments and be presented by treatment received during the randomized placebo-controlled period.

4.2.8.6 Physical Examination

Physical examination assessments where a new or worsening abnormality is observed will be reported as an AE.

Height (Screening visit only), weight and BMI will be summarized overall for the SSO, restricted to visits during the open-label correction period, and by treatment received during the randomized placebo-controlled period using the SSR.

4.2.8.7 Exposure

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

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

The dosage will be calculated for the open-label correction period and randomized placebo-controlled periods respectively:

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

SZC/Placebo will be summarized by the following: range, mean, range of mean doses. Total cumulative dose received (g) will be summarized by mean and range. The range of the maximum dose received (g/day) will be summarized. For each study visit period (e.g. from visit 1 to visit 2, visit 2 to visit 3) the total number (%) of subjects who received dose will be presented and the prescribed daily dose.

4.2.8.8 Pregnancy Test

Serum pregnancy and urine pregnancy test results will be listed only using the SSO analysis set.

5 INTERIM ANALYSES

An informal interim analysis for the purpose of Sample Size Re-estimation (SSR) will be conducted when approximately 68 person-months of follow-up time of the total 136 person-months have occurred (an information time of 0.5) to adjust for potential deviations from the

pre-specified expected effect sizes based on updated knowledge provided by the observed effect sizes which inform the key secondary efficacy endpoint (occurrence of patients having an increase in serum bicarbonate of ≥3 mmol/L from baseline (Day 1) to Day 29 without need for rescue treatment for metabolic acidosis).

This analysis will estimate the true effect sizes and re-estimate the additional numbers of subjects that need to be accrued to achieve sufficient power based on this new information. At sponsor's discretion, enrolment may be extended to accrue this number of additional subjects if it is determined that this can be achieved in a cost-effective manner. The analysis will be unblinded to the party who executes it but blinded to the study team.

The SSR will follow the approach outlined in Herson and Wittes (1993). Once 68 person-months of follow-up time have elapsed an analysis will be conducted by a separate unblinded team. The current proportion of subjects in the placebo arm for secondary endpoint #3 "The occurrence (yes/no) of patients having an increase in serum bicarbonate of ≥3 mmol/L on Day 29 (Visit 7) from baseline without need for rescue treatment for low" will be estimated as $\widehat{\theta_C}$. The sample size, N, required to detect a difference between:

$\theta_E = \widehat{\theta_C}$ versus $\theta_E = \min((\widehat{\theta_C} + .215, 1)$

will be calculated using nQuery to determine the suggested sample size requires adjustment and a report provided to the sponsor detailing this calculation. N_{min}, the minimum sample size for the trial will be set at the original sample size calculation of 136. Based on estimates of the total sample size needed to detect a difference of 0.215 with 80% power for varying proportions for the control arm ($\widehat{\theta_C}$), a maximum sample size of 168 is required when $\widehat{\theta_C}$=0.4, so N_{max}, the maximum proposed sample size for the trial will be set at 168. The sponsor will have oversight and will make the decision whether an increase in sample size is economically and scientifically viable.

However, due to the early termination of the study the interim analysis will not be conducted.

6 CHANGES OF ANALYSIS FROM PROTOCOL

Due to the early termination of this study all sensitivity analyses described in section 4.2.7.4, subgroup analyses described in section 4.2.7.5 and the interim analysis described in section 5 will not be conducted due to insufficient sample size.

7 REFERENCES

FDA. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic: Guidance for Industry, Investigators, and Institutional Review Boards. https://www.fda.gov/media/136238/download. Accessed 25 May 2021.

Herson, J. and Wittes, J., 1993. The use of interim analysis for sample size adjustment. Drug Information Journal, 27(3), pp.753-760.

8 APPENDIX

Not applicable.

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