Statistical Analysis Plan	
Study Code	D9480C00018
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Phase IV, Double-Blind, Placebo-Controlled, Randomized-Withdrawal Trial Evaluating Sodium Zirconium Cyclosilicate (SZC) for the Management of Hyperkalaemia in Patients with Symptomatic Heart Failure with Reduced Ejection Fraction and Receiving Spironolactone (REALIZE-K)

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ACEi	Angiotensin-Converting Enzyme inhibitor
AE	Adverse Event
ANCOVA	ANalysis of COVAriance
ARB	Angiotensin II Receptor Blocker
ARNi	Angiotensin Receptor-Neprilysin Inhibitor
BP	Blood Pressure
CEC	Clinical Events Committee
CRO	Contract Research Organisation
CSA	Clinical Study Agreement
COVID-19	Coronavirus Disease 2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Clinical Trial
CV	Cardiovascular
DBL	Data Base Lock
DCO	Data Cut Off
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOT	End Of Treatment
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
FSI	First Subject In
GCP	Good Clinical Practice
GEE	Generalised Estimating Equation
HF	Heart Failure
HFrEF	Heart Failure With Reduced Ejection Fraction
HK	Hyperkalaemia
IB	Investigator's Brochure
ICH	International Council for Harmonisation
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire Clinical Summary Score

Abbreviation or special term	Explanation
KCCQ-OSS	Kansas City Cardiomyopathy Questionnaire Overall Symptom Score
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire Total Symptom Score
LSLV	Last Subject Last Visit
LTFU	Lost To Follow-Up
MID	Minimally Important Difference
NK	Normokalaemia or Normokalaemic
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PGIS	Patient Global Impression of Severity
PI	Principal Investigator
PPS	Per Protocol Set
PRO	Patient Reported Outcome
PSSR	Project Specific Safety Requirements
RAASi	Renin-angiotensin-aldosterone system inhibitors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SOC	Standard of Care
SSO	Safety Set Open
SSR	Safety Set Randomised
SZC	Sodium Zirconium Cyclosilicate
TA	Therapeutic Area
UACR	Urine Albumin-to-Creatinine Ratio
WBDC	Web Based Data Capture

AMENDMENT HISTORY

Category*: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Other	06-August-2024	Added additional analysis population of safety set exploratory for presentation of additional exploratory analyses	No	To allow additional exploratory analysis presentation
Statistical analysis method for the primary or secondary endpoints	06-August-2024	Sensitivity analyses for alternative definitions of responders added	No	Additional sensitivity analysis added
Statistical analysis method for the primary or secondary endpoints	06-August-2024	Subgroup analysis for participants with LVEF > median and ≤median at screening	No	Correction, as it was a mistake to have ><EF 40%
Other	06-August-2024	Amended description of an exploratory endpoint (outcome variable) to refer to domains and subdomains	No	Clarification
Other	06-August-2024	Amended 1.3 Number of participants to clarify the number refers to a minimum of 166	No	Clarification
Other	06-August-2024	Clinical characteristics added to the list of summaries to be presented for Screened Set	Yes	To align with the presentations

Other	06-August-2024	Summary of maximum dose of spironolactone achieved in cohort 2 among subjects who do not become hyperkalaemic added	Yes	To align with the study objectives
Other	06-August-2024	Efficacy of SZC in achieving normokalaemia, and maintaining normokalaemia during the run-in phase added to the list of summaries to be presented for Safety Set	Yes	To align with the study objectives
Other	06-August-2024	Section 3.3.8 revised to refer to loop diuretics; dose conversion formulas added	Yes	Clarification
Other	06-August-2024	Section 4.1 revised to include only a generic statement on the programming validation process; Covance replaced with Fortrea	N/A	Clarification
Other	06-August-2024	Summary of change in mean daily furosemide equivalent loop diuretic dose during randomised-withdrawal period added	Yes	To support the summaries of the furosemide equivalent loop diuretic dose over time

Other	06-August-2024	Summary of subjects achieving normokalaemia, and maintaining normokalaemia during the run-in period added to 4.2.7.4.6	Yes	To support summaries of subject status during and at the end of the open-label run-in period
Other	06-August-2024	Revised definition of safety set open in section 2.1, description of change from protocol added to section 6.	No	Safety summaries in open-label period should include subjects exposed to SZC or spironolactone.
Other	06-August-2024	Revised definition of open-label period for subjects in cohort 2 in sections 2.3 and 3.2.	No	Subjects in cohort 2 do not immediately receive SZC but period is measured from visit 2.
Other	06-August-2024	Amended baseline definition for subjects in cohort 2 in line with changes to open-label period in sections 3.1 and 4.1.	No	Subjects in cohort 2 should have baseline comparable to cohort 1 rather than date of first dose of SZC.
Other	06-August-2024	Missing dates imputation updated in section 4.1.1 for cohort 2 subjects.	No	Missing dates imputation altered in line with change in definition of open-label period in cohort 2.
Other	06-August-2024	Analysis of baseline heart failure medications and diuretics added to section 4.2.5.	No	These medications are of clinical interest to describe.
Statistical analysis method for the primary or secondary endpoints	06-August-2024	Supplementary analysis method updated in section 4.2.7.1.3 to	No	Time-dependent covariates acted as confounder and mediator so

		remove time-dependent dose from statistical model. Description of change from protocol added to section 6.		removed from analysis as induced bias in treatment effect estimate.
Statistical analysis method for the primary or secondary endpoints	06-August-2024	Addition of calculation of median percentage and corresponding modelled percentage described in section 4.2.7.1.	No	Included to give indication of overall population with response.
Statistical analysis method for the primary or secondary endpoints	06-August-2024	Two additional supplementary analyses for primary endpoint added in section 4.2.7.1.3 excluding participants with 15g daily SZC/placebo at randomisation and with an alternate definition of hyperkalaemia.	No	Included to provide further supplementary analyses of the primary endpoint.
Statistical analysis method for the primary or secondary endpoints	06-August-2024	Additional sensitivity analyses added in section 4.2.7.2 for secondary endpoints exploring an alternate definition of hyperkalaemia.	No	Included to provide further supplementary analyses of the secondary endpoint.
Statistical analysis method for the primary or secondary endpoints	06-August-2024	Added log-rank test to Kaplan-Meier figure in sections 4.2.7.2, 4.2.7.3, 4.2.7.4.2 and 4.2.7.4.5.	No	Included as part of Kaplan-Meier plots in AstraZeneca standards.

Other	06-August-2024	Specified log-transformation for NT-pro BNP and aldosterone in statistical methods in section 4.2.7.4.2	No	Both parameters observed to be non normally distributed so transformation will improve model fit.
Other	06-August-2024	Specified backward selection approach for variable selection in section 4.2.7.4.2.	No	Model was over-fitted and terms needed to be reduced.
Other	06-August-2024	Revised categories for presentation of RAASi persistence in section 4.2.7.4.5.	No	Revised based on clinical feedback.
Other	06-August-2024	Exposure calculation updated in section 4.2.8.8.9.	No	Clarified exposure information to use for exposure calculation based on latest exposure record in relation to study visit date.
Primary and secondary endpoints	21-Dec-2023	Added "The monthly visits are used for response assessment from month 1 to month 6" to primary and secondary endpoints and deleted "at the end of treatment (EOT) visit (approximately 6 months post-randomisation)". Updated response and non-response definitions and the non-response imputation rules due to	Yes, v4.0	Definition for primary endpoint amended to a longitudinal analysis which increases the power of study and allows for a reduced sample size.

		the change in endpoint definition.		
Statistical analysis method for the primary and secondary endpoints	21-Dec-2023	GEE model for primary endpoint and secondary efficacy endpoint analyses were added, the logistic regression model was deleted.	Yes, v4.0	Determined to be appropriate statistical method for estimating responses at each time point and fixed treatment effect.
Other	21-Dec-2023	Revised sample size calculation for new primary endpoint definition. Decrease in number of participants who will be randomised and enter the 6 month randomised phase of the trial, from 260 to 166 participants.	Yes, v4.0	Sample size calculation updated to align with the updated primary endpoint definition.
Other	21-Dec-2023	Clarified selection rules for the use of paper PROs versus electronic PROs when both are available or multiple PROs have been recorded.	Yes, v4.0	Clarification based on the recording of PROs during the study.
Other	21-Dec-2023	Clarified selection rules for the use of paper PROs versus electronic PROs when both are available or multiple PROs have been recorded.	Yes, v4.0	Clarification based on the recording of PROs during the study.

Other	21-Dec-2023	Updated CKD-EPI formula to non-race based CKD-EPI Creatinine Equation 2021.	Yes, v3.0	CSP amendment v3.0, clarified CKD-EPI formula to be used.
Other	08-Jul-2022	Amended visit windowing, restricted concomitant therapy definition, additional subgroup analysis	Yes, v3.0	SAP amended to reflect changes to trial design made in protocol v3.0.
Data presentations	11-Mar-2022	Added details of analysis for peripheral edema and heart failure events. Corrected other errata.	Yes, v2.0	Details of analysis were missing from SAP text and TFL shells.

* 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

Objective	Endpoint (Outcome Variable)
Primary	
• To evaluate the efficacy of SZC as compared with placebo in keeping potassium levels within the normal range (3.5-5.0 mEq/L) while on spironolactone ≥25 mg daily without assistance of rescue therapy for hyperkalaemia (HK)	• Response (yes/no) defined by: ○ Having potassium (sK+) within 3.5-5.0 mEq/L as assessed by central laboratory AND ○ Being on spironolactone ≥25 mg daily AND ○ Not using rescue therapy for HK during the last month. Response means all three bullet points hold. Non-response is indicated if at least one bullet point does not hold. Additionally, for each assessment visit, non-response is indicated for participants who are lost to follow-up at the visit, including due to death. The monthly visits are used for response assessment from month 1 to month 6 (Visits 9-14 during the Randomised Withdrawal Phase, Protocol Table 1). The treatment effect concerns the overall odds ratio.
Secondary	
• To compare the SZC and placebo arms with respect to keeping potassium levels within a normal range (3.5-5.0 mEq/L), keeping same spironolactone dose as used at randomisation, and without having had assistance of rescue therapy for HK	• Response (yes/no), defined by: ○ Having potassium (sK+) within 3.5-5.0 mEq/L as assessed by central laboratory AND ○ Being on the same spironolactone dose as they were at randomisation AND ○ Not using rescue therapy for HK during the last month.

Objective	Endpoint (Outcome Variable)
	Response means all three bullet points hold. Non-response is indicated if at least one bullet point does not hold. Additionally, for each assessment visit, non-response is indicated for participants who are lost to follow-up at the visit, including due to death. The monthly visits are used for response assessment from month 1 to month 6 (Visits 9-14 during the Randomised Withdrawal Phase, Protocol Table 1). The treatment effect concerns the overall odds ratio.
• To compare the SZC and placebo arms with respect to spironolactone dose	• Response (yes/no), defined by: o Being on spironolactone ≥25 mg daily Response means the bullet point holds. Non-response indicates bullet point does not hold. Additionally, for each assessment visit, non-response is indicated for participants who are lost to follow-up at the visit, including due to death. The monthly visits are used for response assessment from month 1 to month 6 (Visits 9-14 during the Randomised Withdrawal Phase, Protocol Table 1). The treatment effect concerns the overall odds ratio.
• To evaluate the efficacy of SZC as compared to placebo in keeping potassium levels ≤5.0 mEq/L	• Time to first HK episode for participants on SZC compared to placebo during the randomised-withdrawal period, with HK defined as sK+ >5.0 mEq/L as assessed by central laboratory
• To compare the SZC and placebo arms with respect to ability to prevent decreases in spironolactone dose	• Time to first instance of decrease or discontinuation of spironolactone dose due to HK for participants on SZC compared to placebo during the randomised-withdrawal period

Objective	Endpoint (Outcome Variable)
• To compare the SZC and placebo arms with respect to change from baseline in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS)	• Change in KCCQ-CSS at EOT visit (approximately 6 months post-randomisation) from randomisation baseline for participants on SZC compared to placebo
Safety	
• To assess the safety and tolerability of SZC as compared to placebo in participants with symptomatic HF with reduced ejection fraction (HFrEF) and HK, who are on renin-angiotensin-aldosterone system inhibitors (RAASi) treatment	• Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory, and electrocardiogram (ECG) Assessments related to adverse events (AEs) cover: ○ Occurrence/frequency ○ Relationship to SZC/placebo as assessed by investigator ○ Intensity ○ Seriousness ○ Death ○ AEs leading to discontinuation of SZC/placebo
Exploratory	
• To explore the SZC/Placebo dosing pattern in the SZC and Placebo arms	• SZC/placebo dose assigned at each visit during the study (e.g., 5 g every other day; 5, 10, 15 g once daily)
• To explore the spironolactone dosing pattern in the SZC and Placebo arms	• The spironolactone dose assigned at each visit during the study
• To explore the potential occurrence of cardiovascular (CV) death, worsening of HF (defined as HF Hospitalizations or Urgent HF visits regardless of intravenous [IV] loop diuretic use), and the individual components in the SZC and placebo arms during the randomised-withdrawal period	• Time to first event of CV death or worsening HF (defined as HF Hospitalizations or Urgent HF visits regardless of IV loop diuretic use), and the individual components during the randomised period: ○ CV Death ○ Worsening HF (HF hospitalizations or urgent HF visits regardless of IV loop diuretic use)

Objective	Endpoint (Outcome Variable)
	○ HF Hospitalizations ○ Urgent HF Visits
• To explore the potential change in mean urine albumin-to-creatinine (UACR) in the SZC and Placebo arms	• Change in mean UACR in SZC group compared with placebo group at: ○ Screening compared to EOT ○ Randomisation compared to EOT • Change in mean UACR at: ○ Screening compared to randomisation
• To explore the change from baseline in KCCQ Total Symptom Score (TSS) and KCCQ Overall Symptom Score (OSS) and other KCCQ sub-domains (including KCCQ physical limitation score) between the SZC and Placebo arms	• Change in KCCQ-TSS, KCCQ-OSS and other KCCQ sub-domains (including KCCQ physical limitation score) at EOT (approximately 6 months post randomisation) compared with randomisation baseline
• To explore the relationship between aldosterone level and PGIS and KCCQ scores, with particular attention to intrapatient consistency, between the SZC and placebo arms at the EOT visit compared to randomisation.	• Change in PGIS and KCCQ scores (across domains and subdomains) from screening to the end of open-label, screening to the EOT and randomisation to EOT adjusted for change in aldosterone levels during the same period
• To explore the potential difference in N-terminal pro-B-type natriuretic peptide (NTpro-BNP) between SZC and Placebo arms (mean difference as compared to baseline, as well as the likelihood of an increase, decrease and stability)	• Change in NTpro-BNP measurements at EOT (approximately 6 months post randomisation) compared with randomisation baseline
• To evaluate the efficacy of SZC as compared to placebo in avoiding the requirement of rescue therapy use for HK	• Time to first instance of use of rescue therapy for HK during the randomised-withdrawal period
• To evaluate the potential change in potassium levels after the EOT in the SZC and Placebo arms	• Change in sK+ at 7 days post EOT compared with EOT
• To evaluate the efficacy of SZC as compared with placebo in keeping	• Response (yes/no) of participants on SZC compared to placebo who, at the end of

Objective	Endpoint (Outcome Variable)
potassium levels within the normal range (3.5-5.0 mEq/L) while on spironolactone ≥25 mg daily without assistance of rescue therapy for hyperkalaemia (HK)	treatment (EOT) visit (approximately 6 months post-randomisation), have serum potassium (sK+) within 3.5-5.0 mEq/L as assessed by central laboratory, are on spironolactone ≥25 mg daily, and did not use rescue therapy for HK at any point during the randomised-withdrawal phase. Participants who are lost to follow-up, including due to death, prior to the EOT visit will be treated as non-response.

1.2 Study design

This study is a parallel-group, placebo-controlled, multi-centre study with an open-label run-in period. The population studied will be participants with symptomatic heart failure with reduced ejection fraction (HFrEF) who are taking no spironolactone or low-dose spironolactone or eplerenone (<25 mg daily) at baseline. During the open-label 4- to 6-week run-in period, serum potassium (sK+) will be normalised with sodium zirconium cyclosilicate (SZC) as needed and spironolactone will be initiated/up-titrated to a maximum dose of 50 mg daily. Participants who are normokalaemic (NK; 3.5≤sK+≤5.0 mEq/L) and receiving spironolactone ≥25 mg daily at the end of the open-label run-in period will be randomised to SZC or placebo during the double-blind randomised-withdrawal period with randomisation stratified according to the presence of HK/NK at study entry. Study sites will be located in North and South America and Europe. Total duration of study participation for each participant will be approximately 8 months, including 7 months on treatment. The study consists of 3 periods:

1. Screening period (up to 2 weeks)
   a. Participants receiving low-dose eplerenone will be switched to spironolactone 12.5mg daily during the screening period.
   b. Cohort assignment is based on local lab sK+ on Visit 1.
   c. In participants with hyperkalaemia (Cohort 1), Visit 2 may occur at the same time as, or shortly after Visit 1 (Screening), so that treatment with SZC can be initiated as soon as possible, as per investigator's guidance.
2. Treatment period (approximately 8 months)
   a. Open-label, run-in period (4-6 weeks)

1.Cohort 1 (4 weeks): Participants who are HK at study entry:

- HK Correction Period: Participants will start SZC on Day 1 at a dose of 10 g three times daily for up to 48 hours until sK+ 3.5-5.0 mEq/L (NK). **NOTE:** Participants who do not achieve NK during the 48-hour correction phase will be discontinued from the study.
- sK+ Maintenance Period: Participants who achieve NK will continue on SZC 10 g daily and then titrate between 5 g every other day and
  5 to 15 g daily to maintain sK+ 3.5-5.0 mEq/L per protocol instructions.
- Spironolactone: Participants will initiate or up-titrate spironolactone beginning on Day 2 or 3 when they become NK on SZC. Spironolactone will be systematically uptitrated to a target dose of 50 mg daily, as tolerated per protocol instructions. **NOTE:** Participants who develop HK on spironolactone 50mg daily while receiving maximum dose SZC (15g), but were NK on spironolactone 25mg daily may remain in the open-label, run-in phase for up to 2 additional weeks in order to return to spironolactone 25mg and become NK again.

2.Cohort 2 (4-6 weeks): Participants who are NK at study entry:

- Spironolactone: Participants will initiate or up-titrate spironolactone beginning on Day 1. Spironolactone will be systematically uptitrated to a target dose of 50 mg daily, as tolerated per protocol instructions.
- HK Correction Period: Participants who develop HK during the first 4 weeks of the run-in period will begin SZC 10 g three times daily for up to 48 hours until sK+ 3.5-5.0 mEq/L. **NOTE:** Participants who do not achieve NK during the 48-hour correction phase will be discontinued from the study.
- sK+ Maintenance Period: Participants will continue on SZC 10 g daily and then titrate between 5 g every other day and 5 - 15 g daily to maintain sK+ 3.5-5.0 mEq/L per protocol instructions.

3.NOTE:

- Participants in Cohort 2 who do not develop HK during the first 3 weeks (and as a result do not meet the requirements to receive SZC) will be discontinued from the study during the run-in period.
- Participants who develop HK on spironolactone 50mg daily while receiving maximum dose SZC (15g), but were NK on spironolactone 25mg daily may remain in the open-label, run-in phase for up to 2 additional weeks in order to return to spironolactone 25mg and become NK again.

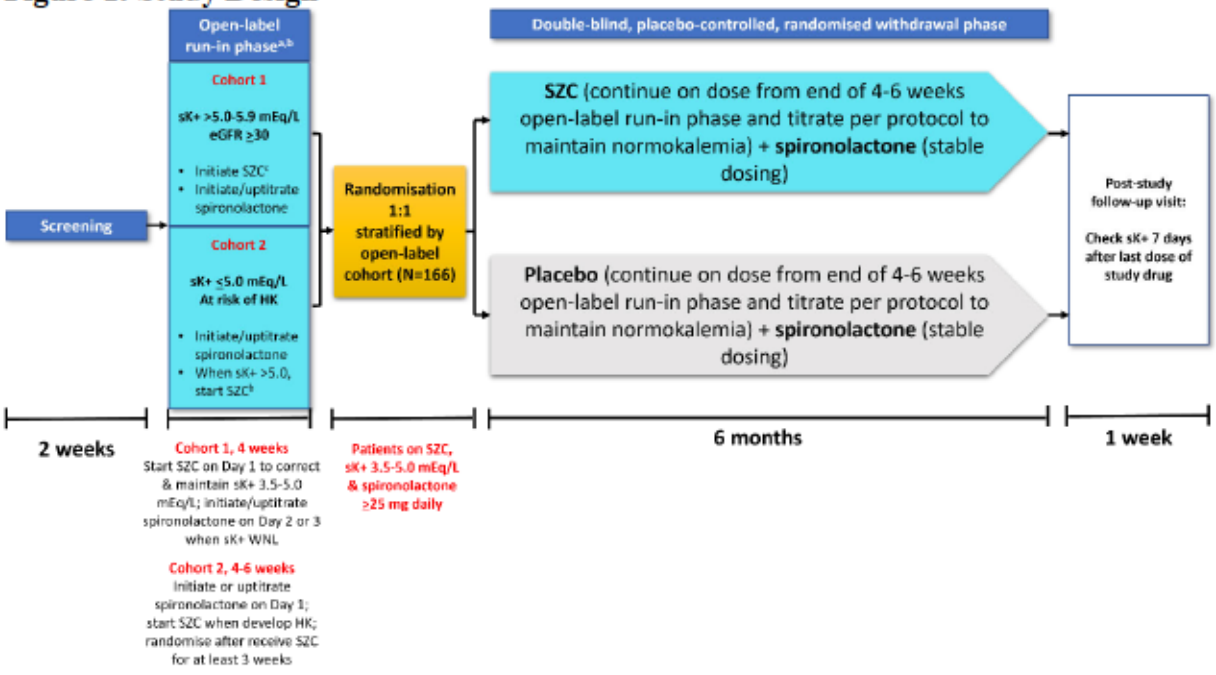
b. Double-blind, placebo-controlled, randomised-withdrawal period (6 months):

1. Participants who are NK on SZC and receiving spironolactone ≥25 mg daily at the end of the run-in period will be randomised 1:1 to SZC or placebo stratified according to the presence of HK/NK (open label cohort 1 vs. cohort 2) at study entry, continuing on the dose they were being administered at the end of the run-in phase.
2. Instructions on how to manage participants who do not qualify for randomisation due to hyperkalaemia are detailed in the CSP, section 6.6.1.
3. Complete information regarding SZC and spironolactone dosing is provided in the CSP, section 6.6.

3. Follow-up period (1 week) after the EOT visit: sK+ will be checked 7 days after last dose of study drug (SZC or placebo). Participants who do not qualify for randomisation due to hyperkalaemia should have a follow-up visit 2 days after their last dose of study drug.

The study schema is displayed in Figure 1.

Figure 1: Study Design



1.2.1 Randomisation

Participants who are normokalaemic (NK; 3.5≤sK+≤5.0 mEq/L) and receiving spironolactone ≥25 mg daily at the end of the open-label run-in period will be randomised 1:1 to either SZC or placebo, continuing on SZC dose from end of 4-6 week open-label run-in period. Randomisation will be stratified according to the presence of hyperkalaemia (Cohort 1)/normokalaemia (Cohort 2) at study entry. Randomisation will be performed using

randomly permuted blocks. The randomisation codes will be computer generated and loaded into the IxRS database.

Drug is dispensed by the IRT system for Visit 2: Open-Label Run-In and Randomisation. Furthermore, drug may be dispensed at Visit 3: Open-Label Week 2, Visit 4: Open-Label Week 3, Visit 5: Open-Label Week 4, Visit 6: Open-Label Week 5, Visit 6.1: Open-Label Week 6 and Visit 9 Double Blind Week 5, Visit 10, Double-Blind Week 9, Visit 11: Double-Blind Week 13, Visit 12: Double-Blind Week 17, Visit 13: Double-Blind Week 21, Visit 14: Double-Blind Week 25, Visit 15: Double-Blind Week 29.

1.3 Number of participants

The sample size calculation is based on the primary objective, i.e. *To evaluate the efficacy of SZC as compared with placebo in keeping potassium levels within the normal range (3.5 – 5.0 mEq/L as assessed by central laboratory) while on spironolactone ≥25 mg daily without assistance of rescue therapy for hyperkalaemia*.

Assuming that the probability of response is 0.7 in the SZC group and 0.5 in the placebo group, and a correlation of 0.55 between scheduled visits, then a generalised estimating equation (GEE) model, with an estimate of response for each time point and fixed treatment effect, using a binomial distribution with exchangeable correlation matrix with a 5% two-sided significance level and 90% power will require 158 participants to be randomised. Clinical data suggests that the rate of death in this participant population is approximately 10 deaths per 100 person-years. With 79 participant-years of observation (158*6/12), approximately 8 deaths are anticipated (79*10/100) during the 6-month randomised phase. Therefore, the sample size will be increased to a minimum of 166 randomised participants to ensure n=158 in the main sensitivity analysis for the primary endpoint. Participants will be entered into the open-label phase until the required number of randomised participants is reached, at which point the recruitment will stop. Tentatively, it is expected that approximately 400 participants will enter the open label phase in order to achieve the goal of at least 166 randomised participants.

2 ANALYSIS SETS

2.1 Definition of analysis sets

Screened Set

All participants 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 and clinical characteristics of participants considered for inclusion in the study. The assignment of participants to a treatment group for analysis is not applicable.

Safety Set Open

All participants who meet inclusion/exclusion criteria and enter the open-label period of the study and receive at least one dose of SZC or Spironolactone. The Safety Set Open (SSO) analysis set will be used to describe the safety characteristics of SZC.. The assignment of participants to a treatment group for analysis is not applicable.

Safety Set Randomised

All randomised participants who received at least one dose of either SZC or placebo during the randomised-withdrawal period of the study. The Safety Set Randomised (SSR) analysis set will be used to describe the safety characteristics of SZC or placebo during the randomised-withdrawal period. Participants will be analyzed according to the treatment actually received during the randomised-withdrawal phase.

Safety Set Exploratory

All participants who meet inclusion/exclusion criteria and enter the open-label period of the study and receive at least one dose of SZC. The Safety Set Exploratory (SSE) analysis set will be used to describe the efficacy of SZC in achieving normokalaemia, maintaining normokalaemia and achieving at least 25mg of spironolactone during the open-label run-in period.. The assignment of participants to a treatment group for analysis is not applicable.

Full Analysis Set

All randomised participants, irrespective of treatment and any protocol deviations, who have one or more post randomisation central laboratory sK+ measurements available. The Full Analysis Set (FAS) will be used at the primary population for the primary and secondary efficacy objectives. Participants will be analyzed according to the randomised treatment, regardless of the treatment actually received.

Per Protocol Set

The Per Protocol Set (PPS) is defined as participants in the FAS who do not have any important protocol deviations considered to have a major effect on efficacy. The PPS will be used as a sensitivity analysis for the primary and secondary endpoints.

Protocol deviations are defined as any change, divergence, or departure from the study design of procedures defined in the study protocol. 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 participant's rights, safety, or well-being.

2.2 Violations and deviations

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

Important protocol deviations leading 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. 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.

- Participants who failed any of the inclusion or exclusion criteria of the study.
- All prohibited medications which are administered during the study. Prohibited medications include any potassium sparing diuretics other than spironolactone (e.g. eplerenone, triamterene, amiloride)
- All restricted medications which are administered during the study when used for a purpose other than those instructed in section 6.5 of the CSP.
- Errors in treatment allocation. Any participant who received incorrect study treatment compared with randomised study treatment at any time during the study
- Any participant unblinded in error, i.e. not due to emergency unblinding for safety concerns, during the study
- Start of double-blind study medication prior to randomisation date
- Participant with first dose date prior to baseline evaluations

In addition, protocol deviations will be defined by the Sponsor before database lock as 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

2.3 Analysis Periods

Screening Period

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

Open-label period

In cohort 1, the open-label period refers to the period from the date of first dose of open-label study treatment (SZC) to the earliest date of randomisation, withdrawal of consent, last contact with the participant or death. In cohort 2, the open-label period refers to the period from the date of the visit 2 study visit to the earliest date of randomisation, withdrawal of consent, last contact with the participant or death.

Randomised-withdrawal period

The randomised-withdrawal period refers to the period from the date of randomisation to the earliest date of discontinuation of study treatment (SZC/Placebo), withdrawal of consent, last contact with the participant, or death.

Follow-up period

The follow-up period refers to the period from the date of study treatment discontinuation (SZC/Placebo) to the earlier date of last assessment during follow-up (scheduled to be 7 days after the EOT visit), withdrawal of consent, last contact with the participant, 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.

- In the TFL shells, "Time Point" is used interchangeably with "Visit" as multiple observations are not made at the same visit.

Scheduled day and visit window during the open-label period in Table 1 are in cohort 1 with respect to the first dose of open-label study treatment and in cohort 2 with respect to the date of the study 2 visit.

Table 1 Definition of visit windows for open-label period

Visit	Scheduled Day of Visit	Analysis Period	Expected?	Protocol Visit Window	Analysis Visit Window
Visit 1	-14 to 1	Screening	Yes	Days -14 to 1	Days -14 to 1
Visit 2	1	Open-Label	Yes	Day 1	Day 1
Visit 2.1[i]	2	Open-Label	Optional if Cohort 1	Day 2	Day 2
Visit 2.2[i]	3	Open-Label	All Cohort 1 except those NK at visit 2.1	Day 3	Day 3
Visit 3	7 (±2)	Open-Label	Yes	Days 5 to 9	Days 4 to 9
Visit 3.1	8	Open-Label	Optional if Cohort 2	Day 8	Day 8
Visit 3.2	9	Open-Label	All Cohort 2 except those NK at visit 3.1	Day 9	Day 9
Visit 4	14 (±3)	Open-Label	Yes	Days 11 to 17	Days 10 to 17
Visit 4.1	15	Open-Label	Optional if Cohort 2	Day 15	Day 15
Visit 4.2	16	Open-Label	All Cohort 2 except those NK at visit 4.1	Day 16	Day 16
Visit 5	21 (±2)	Open-Label	Yes	Days 19 to 23	Days 18 to 23
Visit 5.1	22	Open-Label	Optional if Cohort 2	Day 22	Day 22
Visit 5.2	23	Open-Label	All Cohort 2 except those NK at visit 5.1	Day 23	Day 23
Visit 6	28 (±3)	Open-Label	Yes	Days 25 to 31	Days 24 to 31
Visit 6.1	35 (±3)	Open-Label	If not randomised and Cohort 2	Days 32 to 38	Days 32 to 38
Visit 6.2	42 (±3)	Open-Label	If not randomised and Cohort 2	Days 39 to 45	Days 39 to 45
Visit 6a [ii]	35 (±3)	Open-Label	If not randomised and Cohort 1	Days 32 to 38	Days 32 to 38
Visit 6b [ii]	42 (±3)	Open-Label	If not randomised and Cohort 1	Days 39 to 45	Days 39 to 45
Visit 6a	49 (±3)	Open-Label	If not randomised and Cohort 2	Days 46 to 52	Days 46 to 52
Visit 6b	56 (±3)	Open-Label	If not randomised and Cohort 2	Days 53 to 59	Days 53 to 59

[i] Visits 2.1 and 2.2 will only be assigned if visit 2 has already had a value allocated.
[ii] Participants who develop HK on spironolactone 50mg daily while receiving maximum dose SZC (15g), but were NK on spironolactone 25mg daily may remain in the open-label, run-in phase for up to 2 additional weeks in order to return to spironolactone 25mg and become NK again.

The day of randomisation is variable depending upon the time required to achieve NK. In Cohort 1 the randomisation will occur at visit 6 but can occur at visit 6, 6a or 6b. For participants in Cohort 2, the open-label period continues for up to 8 weeks. Scheduled day and visit window during the randomised-withdrawal period in Table 2 are with respect to the date of randomisation. In summary tables, values from the day of randomisation will be displayed

a Randomisation (Visit 6) regardless of the subvisit where randomisation occurs. When a visit could fall in the analysis visit window for both visits 14 and visit 15 the visit will be assigned based on treatment status (if visit date > treatment end date then assign to visit 15).

Table 2 Definition of visit windows for randomised-withdrawal and follow-up period

Visit	Scheduled Day of Visit[i]	Analysis Period	Protocol Visit Window*	Analysis Visit Window
Visit 7	3 (±2)	Randomised-withdrawal	Days 2 to 4	Days 2 to 4
Visit 8	7 (±3)	Randomised-withdrawal	Days 5 to 9	Days 5 to 14
Visit 9	30 (±7)	Randomised-withdrawal	Days 23 to 37	Days 15 to 45
Visit 10	61 (±7)	Randomised-withdrawal	Days 54 to 68	Days 46 to 75
Visit 11	91 (±7)	Randomised-withdrawal	Days 84 to 98	Days 76 to 105
Visit 12	121(±7)	Randomised-withdrawal	Days 114 to 128	Days 106 to 135
Visit 13	152 (±7)	Randomised-withdrawal	Days 145 to 159	Days 136 to 165
Visit 14 (EOT)	182 (±7)	Randomised-withdrawal	Days 175 to 189	Days 166 to 195
Visit 14a[ii]	212 (±7)	Randomised-withdrawal	Days 205 to 219	Days 196 to 225
Visit 14b[ii]	243 (±7)	Randomised-withdrawal	Days 236 to 250	Days 226 to 255
Visit 15[iii]	7 days post EOT (±3)	Follow-Up	7 days post EOT ± 3 days	7 days post EOT ± 7 days
Visit 15a[iii]	21 days post EOT (±7)	Follow-Up	21 days post EOT ± 7 days	21 days post EOT ± 7 days

[i] Scheduled day and visit window are with respect to the date of randomisation
[ii] Visits 14a and 14b during the randomised-withdrawal period occurred for participants enrolled prior to version 3 of the protocol and were labelled as Visits 15 and 16 respectively
[iii] For participants enrolled prior to version 3 of the protocol there were two follow-up period visits at 2 days post EOT ± 7 days and 21 days post EOT ± 7 days labelled as visits 17 and 18 respectively. The Visit 15 analysis visit window includes the first scheduled visit during follow-up for all participants and visit 15a should only occur in participants enrolled prior to version 3 of the protocol.

3.2 Participant Disposition

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomly assigned to study intervention. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened twice if:

- Screen failure is due to not meeting sK+ or MRA dose inclusion criteria at baseline,
- Screening procedures cannot be completed within the 2-week period,
- Technical issues encountered at enrolment site visit.

Participants who are rescreened should be assigned the same participant number as for the initial screening. Rescreened participants informed consent date will be presented as the

rescreened informed consent date. Rescreened participants will appear once in disposition summaries.

3.3 Efficacy Variables

3.3.1 Death Classification

The Clinical Events Committee (CEC) will adjudicate and classify all deaths based on definitions described in the CEC charter. The CEC charter will be specified separately to the SAP. For the purposes of the efficacy analysis, deaths will be sub classified by cardiovascular (CV), non-CV, or undetermined cause of death. The investigator will record the classification of death as CV, non-CV or undetermined in the eCRF. For the purposes of this analysis the CEC adjudicated decision will be used.

3.3.2 Heart Failure Events

All potential heart failure (HF) endpoint events (hospitalization for HF or urgent HF visits) will be recorded as an AE and also on a separate page in the eCRF. Potential HF endpoint events will be adjudicated by the CEC as specified in the CEC charter. The definition of a HF event will be according to the latest CDISC definition (Hicks et al 2014), but will exclude the fifth requirement of treatment specifically for HF such as a IV loop diuretic, and may be updated during the course of this study.

3.3.3 Potassium

Serum samples will be analysed using local laboratory to generate local lab potassium (K) for the purposes of study inclusion and monitoring. Samples drawn at the same time points will be prepared and shipped to the central laboratory for the analysis of serum potassium (sK). All statistical analyses will use central laboratory sK values. Normokalaemia is defined as $3.5 \leq sK \leq 5.0$ and hyperkalaemia is defined as $sK > 5.0$.

3.3.4 Patient Reported Outcomes (PROs)

Two PROs are used in this study: The Kansas City Cardiomyopathy Questionnaire (KCCQ) and Subject Global Impression of Severity (PGIS-HF) questionnaire.

3.3.4.1 Collection of PROs

Participants will either complete the PRO assessment on paper or using an electronic table during clinic visits at the time points indicated in the CSP. Where PROs are available as both paper and electronic records at a study visit, the electronic assessment will be used. Furthermore, if PRO assessments are available for more than one visit of visit 6, 6a and 6b then the earliest visit where an assessment are available will be used for the randomisation visit in analyses described in sections 4.2.7.4.3.

3.3.4.2 KCCQ

The KCCQ instrument quantifies both the frequency of four cardinal HF-symptoms (fatigue, peripheral edema, dyspnoea, and orthopnoea) and how bothersome three of the cardinal HF-symptoms (fatigue, peripheral edema and dyspnoea) are to participants, as well as HF-related physical limitations, social limitations, self-efficacy, and health-related quality of life. The KCCQ consists of 23 items measuring, from the participants' perspectives, their HF-related symptoms, physical limitations, social limitations, self-efficacy, and health-related quality of life over the prior 2 weeks. All items are measured on a Likert scale with 5-7 response options. The KCCQ will be scored as follows:

- Physical Limitation Score (question 1a-f)
- Symptom Stability Score (question 2)
- Symptom Frequency Score (questions 3, 5, 7 and 9)
- Symptom Burden Score (questions 4, 6 and 8)
- Self Efficacy Score (questions 10 and 11)
- Quality of Life (QoL) Score (questions 12, 13 and 14)
- Social Limitation Score (question 15a-d)

The KCCQ is scored by assigning each response an ordinal value, beginning with 1 for the response that implies the lowest level of functioning and 5-7 for the highest level of functioning. To calculate a score, the responses are summed within each domain and the average is taken. Missing values within each domain are assigned the average of the answered items within that domain. Scale scores are transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100. Scores for a domain are only calculated for a participant if more than 50% of responses are available at a visit.

Three summary scores will be calculated:

- Total Symptom Score (KCCQ-TSS): Average of Symptom Frequency and Symptom Burden Scores
- Clinical Summary Score (KCCQ-CSS): Average of Physical Limitation Score and Total Symptom Score
- Overall Summary Score (KCCQ-OSS): Average of Physical Limitation Score, Total Symptom Score, QoL Score, Social Limitation Score

3.3.4.3 PGIS-HF

The PGIS-HF is a one item question which assesses a participant's perception of his/her severity of HF symptoms in the last 2 weeks. This item will be used to enable anchor-based assessments of within-participant clinically meaningful change for the KCCQ-TSS. The ordinal responses to PGIS-HF will be assigned the following numeric values:

- 1 ("no symptoms")
- 2 ("very mild")
- 3 ("mild")
- 4 ("moderate")
- 5 ("severe")
- 6 ("very severe")

3.3.5 NYHA Class

The definition of New York Health Association (NYHA) class is specified in Appendix H of the CSP. This will be assessed according to the SoA and the response as recorded in the CRF will be analysed.

3.3.6 Urine Analysis

Urinary albumin and creatinine will be collected as specified in the SoA of the CSP. Urinary albumin, creatine and urinary albumin creatine ratio (UACR, defined as urinary albumin/urinary creatinine) will be assessed at each visit of collection. UACR will be measured as the mean of three consecutive first morning spot urine collections. The fractional excretion of sodium (Na+) will be measured as the mean of the three consecutive first morning spot urine collections.

3.3.7 Plasma analysis

NT-pro-BNP, serum aldosterone, plasma renin activity, total renin, angiotensinogen, atrial natriuretic peptide and high sensitivity troponin I will be collected as specified in the SoA of the CSP.

3.3.8 Furosemide Equivalent Loop Diuretic Dose

Furosemide Equivalent Loop Diuretics Dose will be identified using the concomitant medications eCRF where the WHO Drug Dictionary generic term equals "Furosemide". The cumulative dose will be collected as:

(Min(end of diuretic, end of study treatment) – max(start of diuretic, start of study treatment)+1) x dose x frequency

All non-furosemide loop diuretic doses will be converted to mg/day furosemide equivalents based on published equivalent dose conversions, as listed in the Table 3 below. Participants not taking loop diuretics at baseline or at subsequent follow-up visits will be coded using a dose of 0 mg/day furosemide equivalents.

Table 3: Loop diuretic dose conversion

Loop diuretic	Furosemide-equivalent dose
Bumetanide	Dose × 40
Torsemide	Dose × 2
Azosemide	Dose × 2/3
Ethacrynic acid	Dose × 4/5

3.4 Safety Variables

3.4.1 Exposure and dose interruptions

Exposure (i.e. duration of treatment) will be defined as follows for SZC/Placebo:

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 participant has not taken any of the planned daily dose.

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

3.4.2 Adverse Events

All Adverse events, (non-serious and Serious adverse events (SAEs) will be collected from start of the open-label period, throughout the randomised-withdrawal period including during the follow-up period. In addition, SAEs will be recorded from the time of signing the informed consent form. A treatment emergent AE (TEAE) will be defined as an AE with the start date on or after the first dose (SZC) date during the open-label period up to (and including) 14 days after the last dose date (SZC/Placebo), and events with start date prior to

the date of first dose of study treatment (SZC) whose severity worsens on or after the date of first dose during the open-label period.

TEAEs will be further categorised as either (i) occurring during the open-label period, if the start date is on or after the first dose date during the open-label period and prior to the date of randomisation, (ii) occurring during the randomised period if the start date is on or after the date of randomisation and prior to the date of study treatment discontinuation+14.

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).

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

Other significant adverse events

Targeted oedema assessments will occur at screening, randomisation, 1-month post randomisation, 4 months post-randomisation, and EOT. N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, body weight, and diuretic use yes/no; if yes, dose) will also be collected at the same time oedema assessments are conducted. Oedema-related adverse events (OAEs) will be collected as other significant AEs.

Deaths

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

3.4.3 Laboratory Data

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

Blood and urine samples for determination of haematology/haemostatis, clinical chemistry and urinalysis will be taken as per Schedule of Activities (SoA) Tables 1 of the CSP for the timing and frequency. Presentations and summaries will use central laboratory results.

Laboratory parameters include:

Table 4: Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum)
B-Haemoglobin (Hb)	S-Sodium (Na+)
B-Leukocyte count	S-Potassium (K+)
B-Leukocyte differential count (absolute count)	S-Bicarbonate Total (Total CO_2)
B-Platelet count	S-Glucose
B-Hematocrit (Hct)	S-Creatinine
	S-Blood Urea Nitrogen (BUN)
Urinalysis (dipstick)	Urea (BUN)/Creatinine Ratio
U-Hb/Erythrocytes/Blood	Estimated glomerular filtration rate (eGFR) using the non-race-based CKD-EPI formula
U-Protein/Albumin	Anion gap
U-Glucose	S-Albumin
	S-Total Protein
Morning void urine	S-Calcium (Ca++)
Urinary albumin	S-Magnesium (Mg++)
Urinary creatinine	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) 2021 formula for each time-point and will be analysed as entered on the eCRF:

$$\text{eGFR (CKD-EPI)} = 142 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012 \text{ [if female]}$$

Where S_{Cr} (standardised serum creatinine) = mg/dL, $\kappa = 0.7$ (females) or 0.9 (males), $\alpha = -0.241$ (females) or -0.302 (males), $\min(S_{Cr}/\kappa, 1)$ = indicates the minimum of S_{Cr}/κ or 1, $\max(S_{Cr}/\kappa, 1)$ = indicates the maximum of S_{Cr}/κ or 1 and age = years.

3.4.4 Vital Signs

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

3.4.5 Electrocardiograms

Electrocardiogram (ECG) assessments will be performed at screening, randomisation, EOT, and follow-up (as specified in the SoA), and according to clinical judgement in connection with severe hypokalaemia (sK+ <3.0 mEq/L), severe hyperkalaemia (sK+>6.0) or any symptoms or clinical events suggesting cardiac arrhythmia. ECG parameters will include heart rate (beats/min), PR interval (msec), RR interval (msec), QRS duration (msec), QT interval (msec) and QTcF interval (msec). The absolute change from baseline will be calculated for each post-dose visit. The baseline measurement for each ECG parameter will be calculated based on the average of all recorded measurements made at the baseline visit.

4 ANALYSIS METHODS

4.1 General principles

The principal analyses outlined in this statistical analysis plan will be conducted by Fortrea, in accordance with the contract with AstraZeneca AB and following the Excellence in Medical Partnership for Outsourced Worldwide Evidence Research (EMPOWER) description of services. External validation of endpoints will be conducted by Saint Luke's Hospital of Kansas City, and may include fully independent programming.

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. For log transformed data it is more appropriate to present geometric mean, coefficient of variation (CV), median, minimum and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.

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 cohort 1, 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. In cohort 2, for all endpoints, the last observation before the date of the visit 2 study visit will be considered the baseline measurement, unless otherwise specified. In cohort 1, for assessments on the day of first dose or in cohort 2, for assessments on the day of the visit 2 study visit, where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose. Any observation made after the first dose of study treatment will be considered post-baseline.

Assessments on the day of the first dose (cohort 1)/visit 2 study visit (cohort 2) 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.

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 which occur during the open-label analysis period. Study population, demography data will also be summarised 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 (cohort 1) or the date of the visit 2 study visit (cohort 2), then impute the month and day of the first dose date or visit 2 study visit 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 (cohort 1) or the date of the visit 2 study visit (cohort 2), then impute the day of the first dose date or visit 2 study visit 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 illogical date with regards to the dates the participant was in the study, then the end date will be replaced with the participant's date of completion/discontinuation.

4.1.2 Handling of Missing Efficacy Data

Participants with missing data for efficacy analyses will be treated as described under each endpoint's estimand definition. Exploratory efficacy analyses using an ANCOVA model will use complete cases only, so participants without a measurement at a specific visit will be excluded from the analysis. Exploratory efficacy analyses using mixed-effect models repeated-measures will assume that missing outcomes are missing at random (MAR).

4.1.3 Handling of Missing Safety Data

In general, missing clinical laboratory data, vital signs, and ECG data will not be imputed. Adverse event imputations for missing severity or relationship are provided in section 3.4.2. 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.

4.2 Analysis methods

4.2.1 Subject Disposition and Analysis Sets Analysed

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

- 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
- Randomised;
- Not randomised (Open-label period failure) and associated reasons;
- Randomised subjects who received treatment;
- Randomised subjects who did not receive treatment and associated reasons;
- Subjects 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 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), randomised and not randomised (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 randomised for the denominator.

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

4.2.2 Protocol Deviations

All important protocol deviations, defined according to section 2.2, leading to exclusion from the PPS will be listed and summarised by treatment group and overall for the FAS. Important protocol deviations will be further classified as either pandemic-related or excluding pandemic related important protocol deviations.

4.2.3 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarised by open-label cohort and total for the SSO and treatment group and total for the SSR and 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);
- 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 subject characteristics at baseline and will be listed and summarised by open-label cohort and total for the SSO and 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];

A separate table will summarize the subject characteristics at baseline related to heart failure and will be listed and summarised by open-label cohort and total for the SSO and treatment group and total for the SSR and FAS. They will include:

- Time from diagnosis of HF to enrolment (0-3 months,>3-6 months, >6-12 months, >1-2 years, >2-5 years, >5 years)
- HF hospitalization prior to randomisation (No/Yes)
- Time from last HF hospitalization to randomisation (,>3-6 months, >6-12 months, >1-2 years, >2-5 years, >5 years, No prior HF hospitalization)
- NYHA class at enrolment (II,III,IV)
- LVEF (%)
- LVEF groups (≤25, 26-30, 31-35,36-40)
- Main etiology of HF (Ischaemic, Non-Ischaemic, Valvular, Arrythmia, Unknown, Other)

- History of Atrial Fibrillation/Flutter (Yes, Chronicity: Paroxysmal, Persistent, Permanent)
- QRS Duration, aggregate at enrolment ECG (msec)
- QRS duration (≥150 msec, ≥130 msec)
- NT-proBNP at enrolment (pg/mL)
- NT-proBNP (pg/mL) at enrolment in participants with Atrial Fibrillation/Flutter at enrolment
- NT-proBNP (pg/mL) at enrolment in participants without Atrial Fibrillation/Flutter at enrolment
- Cardiac Pacemaker Insertion (Yes)
- Pacemaker type (Conventional pacemaker, CRT-P, CRT-D, Pacemaker type not recorded)
- CRT-D or CRT-P (Yes)
- Pulse rate (Beats/min)
- Pulse rate (Beats/min) in Participants with Atrial Fibrillation/Flutter at enrolment
- Pulse rate (Beats/min) in Participants without Atrial Fibrillation/Flutter at enrolment
- Systolic blood pressure (mmHg)
- Systolic blood pressure (mmHg) category (≥140, ≥130)
- Diastolic blood pressure (mmHg)
- eGFR (ml/min)
- Serum potassium (mEq/L)

All baseline measurements, such as vital signs and ECG results, will also be reported with post-baseline measurements. Categories for subjects with reported baseline characteristics which are contrary to the inclusion/exclusion criteria for the study will be marked with a footnote.

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)]. All medical history will be listed, and the number and percentage of subjects with any medical history will be summarised by system organ class (SOC) and preferred term for the open-label cohort and total for the SSO and treatment group and total for the SSR and FAS

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 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 period.

Concomitant medications during the open-label period are those with a stop date prior to the first dose of study treatment during the randomised-withdrawal period and either a start date on or after the first dose date of study treatment during the open-label period, or those with a start date before, and a stop date on or after the first dose date of study treatment during the open-label period.

Concomitant medications during the randomised-withdrawal period are those with a start date on or after the first dose date of study treatment during the randomised-withdrawal period, or those with a start date before, and a stop date on or after the first dose date of study treatment during the randomised-withdrawal period.

If a medication cannot be classified as "prior" or "concomitant during the open-label period" or "concomitant during the randomised-withdrawal period" after applying imputation rules for missing/incomplete dates, it will be classified as concomitant during the randomised-withdrawal period.

Concomitant medications during the open-label and randomised-withdrawal periods will be further categorised by those allowed and disallowed. Disallowed concomitant medications are defined in the CSP Section 6.5 as potassium sparing diuretics other than spironolactone and eplerenone (triamterene and amiloride). Furthermore, several medications are described as restricted, such as potassium binders, potassium supplements, drugs with pH-dependent absorption and nonsteroidal anti-inflammatory drugs, and will also be included as disallowed concomitant medications.

Prior medications, allowed/disallowed concomitant medications during the open-label period and allowed/disallowed concomitant medications during the randomised-withdrawal period will be listed together. Allowed/disallowed concomitant medications during the open-label period will be summarised separately by open-label cohort and overall using the SSO and presented in total. Allowed/disallowed concomitant medications during the randomised-withdrawal period will be summarised 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.

A separate summary will present prior medication related to heart failure or diuretics for the SSO and SSR. This summary will present the number and percentage of subjects by cohort (SSO) and randomised treatment group (SSR) who were receiving ACE inhibitor therapy at screening (identified from eCRF "Heart Failure Status" and question "Is the subject taking ACE inhibitor"), ARB therapy at screening (identified from eCRF "Heart Failure Status" and question "Is the subject taking ARB (Angiotensin Receptor Blockers"), ARNi therapy at screening (identified from eCRF "Heart Failure Status" and question "Is the subject taking Neprilysin inhibitor/ARB (ARNI)"), ACE inhibitor therapy or ARB therapy at screening, beta blockers at screening (identified from eCRF "Heart Failure Status" and question "Is the subject taking beta blockers"), low-dose MRA at screening, (identified from eCRF "Heart Failure Status" and question "Mineralocorticoid/Aldosterone Antagonist Treatment?"), SGLT2i at screening (identified from prior/concomitant medication eCRF page using ATC code A10BK where prior medication definition is fulfilled), loop diuretics at screening (identified from prior/concomitant medication eCRF page using the terms "Furosemide", "Bumetanide", "Torsemide", "Azosemide" and "Ethacrynic acid" where prior medication definition is fulfilled) and all diuretics at screening (identified from prior/concomitant medication eCRF page and ATC codes "C03" excluding "C03D").

4.2.6 Measurements of Study Treatment Compliance

The percentage compliance for SZC and placebo is calculated 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 sum of the sachets taken during the open-label period is calculated as: number of sachets dispensed-number of sachets returned where dates are before randomisation. The number of sachets taken during the randomised-withdrawal period is calculated as: number of sachets dispensed-number of sachets returned where dates are after randomisation. The number of sachets taken is calculated based upon the dose and frequency of SZC or placebo prescribed:

Dose and frequency	**Number of sachets expected**
5g every other day	Number of days between visits/2
5g daily	Number of days between visits
10g daily	Number of days between visits
10g three times per day (Open-label)	3*Number of days between visits
15g daily	2*Number of days between visits

The percentage compliance for SZC and placebo will be calculated separately for the open-label and randomised-withdrawal periods and will be summarised descriptively by open-label cohort using the SSO and treatment group (including overall) using the SSR respectively.

The percentage compliance for spironolactone is calculated as:

100*actual tables taken/expected tablets taken

, where:

Actual tablets taken is defined as:

Sum of the tablets taken throughout the respective analysis period

And the expected tablets taken throughout the respective analysis period is derived using the study intervention and drug dispensation records to calculate the number of tablets expected accounting for changes to the prescribed dosage level (from 12.5g daily to 50g daily) and the unit dose strength dispensed (25mg and 50mg tablets). The percentage compliance for spironolactone will be calculated separately for the open-label and randomised-withdrawal periods and will be summarised descriptively by open-label cohort using the SSO and by treatment group (including overall) using the SSR respectively.

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

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

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 testing if the preceding null hypotheses 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 $p<0.05$. The current order for testing the subsequent secondary endpoints is the order presented below but may be amended prior to database lock.

4.2.7.1 Primary Efficacy Analysis

The primary efficacy endpoint is response (yes/no) of participants on SZC compared to placebo who, during the maintenance phase (≥ month 1 and ≤6 months), have sK+ within 3.5-5.0 mEq/L as assessed by central laboratory, are on spironolactone ≥25 mg daily, and did not use rescue therapy for HK at any point during the randomised-withdrawal phase. A response is defined by (i) having sK+ within 3.5-5.0 mEq/L as assessed by central laboratory AND (ii) being on spironolactone ≥ 25mg daily AND (iii) not using rescue therapy for hyperkalaemia at any point during the last month. Response means all three requirements are met. Non-response is indicated if at least one requirement is not met. Additionally, for each assessment visit, non-response is indicated for participants who are lost to follow-up at the visit, including due to death. The monthly visits are used for response assessment from month 1 to month 6 (Visits 9-14 during the Randomised Withdrawal Phase, Protocol Table 1)..

The number and percentage of subjects who achieved a response (Yes, No, Missing) for each monthly visit will be summarised by randomised treatment group in the FAS.

The treatment effect concerns the overall Odds Ratio and will be analysed using a GEE model, with a binomial distribution family and a logit link with exchangeable correlation matrix and tested using a two-sided alpha = 0.05. The dependent variable will be response at each visit. Fixed treatment effects will include randomised treatment, subject recruitment country, a per visit indicator variable (e.g. visit 7, 8, 9, 10, 11, 12, 13 and 14) and open-label period cohort. The common odds ratio will be derived together with two-sided 95% confidence intervals.

From the percentage of responders per visit, in the placebo group, the median percentage of responders for placebo and SZC will be calculated and presented. The median percentage of responders for placebo will also be presented as the corresponding modelled percentage for placebo. From this value, odds for placebo =(median probability of responders for placebo)/(1-median probability of responders for placebo). The modelled odds for SZC will be calculated as the raw odds for placebo (derived above) × common odds ratio from the GEE model. The modelled odds will then be used to calculate the corresponding modelled percentage for SZC as (modelled odds for SZC)/(1+modelled odds for SZC). The corresponding modelled percentage for SZC will be presented.

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 at each visit, defined as an observed sK+ within 3.5-5.0 mEq/L AND being on spironolactone ≥ 25mg daily AND (iii) not using rescue therapy for hyperkalaemia at any point during the last month.

Population:

- Participants with symptomatic HFrEF who meet inclusion/exclusion criteria. Participants have either hyperkalaemia (sK+ 5.1-5.9 mEq/L) or normokalaemia (sK+ 3.5-5.0 mEq/L) who become hyperkalaemic during the first 4 weeks of the open-label period, and who maintain sK+ 3.5-5.0 when dosed with SZC, who are randomised and have one or more post randomisation central laboratory sK+ measurement available

Treatment:

- SZC or Placebo administered daily with spironolactone. Participants with sK+ ≥ 6.0 mEq/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)
- Discontinuation of spironolactone≥25mg daily prior to the EOT visit (Composite variable strategy i.e. considered to be non-response).
- Use of rescue therapy for hyperkalaemia at any point during the randomised-withdrawal period (Composite variable strategy, i.e. considered to be non-response).
- Death prior to the EOT visit (Composite variable strategy, i.e. considered to be non-response).
- Participant lost to follow-up for any reason prior to the EOT visit Composite variable strategy, i.e. considered to be non-response).

Population Level Summary:

- The common odds ratio of the occurrence (yes/no) of response in the SZC treatment group compared to the placebo group.

4.2.7.1.1 Primary Efficacy Analysis – Sensitivity Analyses – PPS

Two sensitivity analyses will be conducted using the PPS.

i. Analyses will be conducted as described above for the primary efficacy endpoint.
ii. Deaths prior to the EOT will be treated as missing response. Analyses will be conducted as described above using the FAS as for the primary efficacy endpoint.

4.2.7.1.2 Primary Efficacy Analysis – Sensitivity Analyses – COVID-19 intercurrent events

As a sensitivity analysis, 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 during the last month not related to the COVID-19 pandemic (Treatment policy strategy, i.e. regardless of the intercurrent event)
- Discontinuation of treatment during the last month related to the COVID-19 pandemic (Hypothetical strategy, i.e. assume response is missing).
- Discontinuation of spironolactone≥25mg daily during the last month not related to the COVID-19 pandemic (Composite variable strategy i.e. considered to be non-response).
- Discontinuation of spironolactone≥25mg daily during the last month related to the COVID-19 pandemic (Hypothetical strategy, i.e. assume response is missing).
- Use of rescue therapy for hyperkalaemia during the last month (Composite variable strategy, i.e. considered to be non-response).
- Death during the last month not related to the COVID-19 pandemic (Composite variable strategy, i.e. considered to be non-response).
- Death during the last month related to the COVID-19 pandemic (Hypothetical strategy, i.e. assume response is missing).
- Participant lost to follow-up prior during the last month irrespective of relationship to COVID-19 pandemic (Composite strategy, i.e. considered to be non-response).

4.2.7.1.3 Primary Efficacy Analysis – Supplementary Analyses

A supplementary analysis will be conducted with the same analysis method as the primary analysis but with the addition of an interaction term between treatment received and dose received at randomisation (5g every other day, 5g daily, 10g daily, 15g daily) to allow for the effect of dose to be assessed.

An additional supplementary analysis will be conducted with the same analysis method as the primary analysis but excluding participants who received 15g daily at randomisation.

An additional supplementary analysis will be conducted with the same analysis method as the primary analysis but with response (yes/no) defined as the number of participants on SZC compared to placebo who, during the maintenance phase (≥ month 1 and ≤6 months), have sK+ within 3.5-5.5 mEq/L as assessed by central laboratory, are on spironolactone ≥25 mg daily, and did not use rescue therapy for HK at any point during the randomised-withdrawal phase.

4.2.7.2 Secondary Efficacy Analyses

1. The first secondary efficacy endpoint is response (yes/no) of participants on SZC compared to placebo who, during the maintenance phase (≥month 1 and <6 months), have sK+ within 3.5-5.0 mEq/L as assessed by central laboratory, are on the same spironolactone dose as they were at randomisation and did not use rescue therapy for hyperkalaemia at any point during the randomised-withdrawal phase.

Response is defined by (i) having sK+ within 3.5-5.0 mEq/L as assessed by central laboratory AND (ii) being on the same spironolactone dose as they were at randomisation AND (iii) not using rescue therapy for hyperkalaemia at any point during the last month. Response means all three requirements are met. Non-response is indicated if at least one requirement is not met. Additionally, for each assessment visit, non-response is indicated for participants who are lost to follow-up at the visit, including due to death. The monthly visits are used for response assessment from month 1 to month 6 (Visits 9-14 during the Randomised Withdrawal Phase, Protocol Table 1).

The number and percentage of subjects who achieved a response (Yes, No, Missing) for each monthly visit will be summarised by randomised treatment group in the FAS.

The treatment effect concerns the overall Odds Ratio and will be analysed using a GEE model, with a binomial distribution family and a logit link with an exchangeable correlation matrix and tested using a two-sided alpha = 0.05. Fixed treatment effects will include randomised treatment, subject recruitment country, a per visit indicator variable (e.g. visit 7, 8, 9, 10, 11, 12, 13 and 14) and open-label period cohort. The common odds ratio will be derived together with two-sided 95% confidence intervals.

Estimand Attributes

Endpoint:

- Hyperkalaemia response at each visit, defined as an observed sK+ within 3.5-5.0 mEq/L AND being on the same spironolactone dose as they were at randomisation AND (iii) not using rescue therapy for hyperkalaemia at any point during the last month.

Population:

- Participants with symptomatic HFrEF who meet inclusion/exclusion criteria. Participants have either hyperkalaemia (sK+ 5.1-5.9 mEq/L) or normokalaemia (sK+ 3.5-5.0 mEq/L) who become hyperkalaemic during the first 3 weeks of the open-label period, and who maintain sK+ 3.5-5.0 when dosed with SZC, who are randomised and have one or more post randomisation central laboratory sK+ measurement available.

Treatment:

- SZC or Placebo administered daily with spironolactone. Participants with sK+ ≥ 6.0 mEq/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)
- Change in dose of spironolactone prior to the EOT visit (Composite variable strategy e.g. considered to be non-response).
- Use of rescue therapy for hyperkalaemia at any point during the randomised-withdrawal period (Composite variable strategy, e.g. considered to be non-response).
- Death prior to the EOT visit (Composite variable strategy, e.g. considered to be non-response).
- Participant lost to follow-up prior to the EOT visit (Composite variable strategy, considered to be non-response).

Population Level Summary:

- The common odds ratio of the occurrence (yes/no) of response in the SZC treatment group compared to the placebo group.

Secondary Efficacy Endpoint Analysis – Sensitivity Analysis

As a supplementary analysis the analysis of this secondary endpoint will be repeated but with response defined as (i) having sK+ within 3.5-5.5 mEq/L as assessed by central laboratory AND (ii) being on the same spironolactone dose as they were at randomisation AND (iii) not using rescue therapy for hyperkalaemia at any point during the last month.

2. The second secondary efficacy endpoint is response (yes/no) of participants on SZC compared to placebo who, during the maintenance phase (≥month 1 and <6 months), are on spironolactone ≥25 mg daily.

A response (yes) is defined by (i) being on spironolactone ≥25 mg daily. Response means that this requirement is met. Non-response (no) indicates this requirement is not met. Additionally, for each assessment visit, non-response (no) is indicated for participants who are lost to follow-up at the visit, including due to death. The monthly visits are used for response assessment from month 1 to month 6 (Visits 9-14 during the Randomised Withdrawal Phase, Protocol Table 1).

The number and percentage of subjects who achieved a response (Yes, No, Missing) for each monthly visit will be summarised by randomised treatment group in the FAS.

The treatment effect concerns the overall Odds Ratio and will be analysed using a GEE model, with a binomial distribution family and a logit link and an exchangeable correlation matrix and tested using a two-sided alpha = 0.05. The dependent variable will be response (yes/no) at each visit. Fixed treatment effects will include randomised treatment, subject

recruitment country, a per visit indicator variable (e.g. visit 7, 8, 9, 10, 11, 12, 13 and 14) and open-label period cohort. The common odds ratio will be derived together with two-sided 95% confidence intervals.

Estimand Attributes

Endpoint:

- Being on spironolactone ≥ 25 mg daily at each visit

Population:

- Participants with symptomatic HFrEF who meet inclusion/exclusion criteria. Participants have either hyperkalaemia (sK+ 5.1-5.9 mEq/L) or normokalaemia (sK+ 3.5-5.0 mEq/L) who become hyperkalaemic during the first 3 weeks of the open-label period, and who maintain sK+ 3.5-5.0 when dosed with SZC, who are randomised and have one or more post randomisation central laboratory sK+ measurement available

Treatment:

- SZC or Placebo administered daily with spironolactone. Participants with sK+ ≥ 6.0 mEq/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 randomised-withdrawal period (Treatment policy strategy, i.e. regardless of the intercurrent event).
- Death prior to the EOT visit (Composite variable strategy, e.g. considered to be non-response).
- Participant lost to follow-up prior to the EOT visit (Composite variable strategy, e.g. considered to be non-response).

Population Level Summary:

- Common odds ratio of the occurrence of response in the SZC treatment group compared to the placebo group.

3. Time to first hyperkalaemia episode for subjects on SZC compared to placebo during the randomised-withdrawal period, with hyperkalaemia defined as sK+ >5.0 mEq/L as assessed by central laboratory.

This will be analysed using a cause-specific proportional hazard model with death and the use of rescue therapy treated as competing risk events, randomised treatment and subject recruitment country as independent factors and open-label period cohort as a stratification factor in the FAS. In practice, the use of the cause-specific proportional hazard model will treat subjects with a competing event as censored. Participants without hyperkalaemia will be censored at the date of the last available central laboratory measurement of sK+. The time to

first hyperkalaemia episode will be calculated as (date of serum potassium measurement – date of randomisation + 1).

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

The hazard ratio (SZC arm/placebo arm), adjusted for the stratification factor (HK vs NK at study entry) and its two-sided 95% confidence interval will be estimated using the Cox regression model. Kaplan-Meier survival curves (product-limit estimates) of time to first hyperkalaemia episode will be presented by randomised treatment group, together with a summary of associated statistics (median time to failure with the 25^{th} and 75^{th} percentiles and associated 95% CIs). The Kaplan-Meier figures will include the p-value from a log-rank test by randomised treatment group.

In addition, cumulative incidence survival curves will be presented by randomised treatment group with the estimated rate subjects develop hyperkalaemia at days 44, 88, 132 and 175 after the date of randomisation.

Estimand Attributes

Endpoint:

- Time of first hyperkalaemia episode with hyperkalaemia defined as sK+ >5.0 mEq/L as assessed by central laboratory.

Population:

- Participants with symptomatic HFrEF who meet inclusion/exclusion criteria. Participants have either hyperkalaemia (sK+ 5.1-5.9 mEq/L) or normokalaemia (sK+ 3.5-5.0 mEq/L) who become hyperkalaemic during the first 3 weeks of the open-label period, and who maintain sK+ 3.5-5.0 when dosed with SZC, who are randomised and have one or more post randomisation central laboratory sK+ measurement available

Treatment:

- SZC or Placebo administered daily with spironolactone. Participants with sK+ $\geq$ 6.0 mEq/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 randomised-withdrawal period (Hypothetical strategy, e.g. considered to be censored).
- Death prior to the EOT visit (Hypothetical strategy, e.g. considered to be censored).
- Participant lost to follow-up prior to the EOT visit (Hypothetical strategy, e.g. considered to be censored at the date of the last available central laboratory measurement of sK+ during the randomised-withdrawal period).

Population Level Summary:

- Kaplan-Meier estimates of the median time to first hyperkalaemia episode in the SZC treatment group compared to the placebo group.

Secondary Efficacy Endpoint Analysis – Sensitivity Analysis

As a sensitivity analysis a Cox regression model will be used with the same analysis approach where competing events in the previous model are treated as hyperkalaemia events. The following intercurrent event strategy will be used with all other components of the estimand as defined in the main analysis

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 randomised-withdrawal period (Composite variable strategy, e.g. considered to be event).
- Death prior to the EOT visit (Composite variable strategy, e.g. considered to be event).
- Participant lost to follow-up prior to the EOT visit (Hypothetical strategy, e.g. considered to be censored at the date of the last available central laboratory measurement of sK+ during the randomised-withdrawal period).

As an additional sensitivity analysis, subjects will be administratively censored at the earliest date of their visit 14 visit or last visit during the randomised-withdrawal period to investigate the impact of longer duration in the study for subjects enrolled prior to version 3 of the CSP.

A further sensitivity analysis will use the same analysis approach as the main analysis for this secondary endpoint but will define time of first hyperkalaemia episode using a definition for hyperkalaemia as sK+ >5.5 mEq/L as assessed by central laboratory.

4. Time to first instance of decrease of spironolactone dose due to hyperkalaemia for subjects on SZC compared to placebo during the randomised-withdrawal period.

This will be analysed using a cause-specific proportional hazard model with death treated as a competing risk event, randomised treatment and subject recruitment country as independent factors and open-label period cohort as a stratification factor in the FAS. In practice, the use of the cause-specific proportional hazard model will treat subjects with a competing event as censored. Participants without a decrease of spironolactone dose due to hyperkalaemia will be censored at the date of their last visit during the randomised-withdrawal period. To clarify, for

subjects who are enrolled in version 1.0 or 2.0 of the CSP this will be the date of visit 14b and for all other subjects this will be the date of visit 14. If these visits are not available, participants will be censored at the last available visit during the randomised-withdrawal period.

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

The hazard ratio (SZC arm/placebo arm), adjusted for the stratification factor (HK vs NK at study entry) and its two-sided 95% confidence interval will be estimated using the Cox regression model. Kaplan-Meier survival curves (product-limit estimates) of time to first hyperkalaemia episode will be presented by randomised treatment group, together with a summary of associated statistics (median time to failure with the 25^{th} and 75^{th} percentiles and associated 95% CIs). The Kaplan-Meier figures will include the p-value from a log-rank test by randomised treatment group.

In addition, cumulative incidence survival curves will be presented by randomised treatment group with the estimated rate subjects first decrease spironolactone dose at day 44, 88, 132 and 175 after the date of randomisation.

Estimand Attributes

Endpoint:

- Time to first instance of decrease of spironolactone dose due to hyperkalaemia during the randomised-withdrawal period.

Population:

- Participants with symptomatic HFrEF who meet inclusion/exclusion criteria. Participants have either hyperkalaemia (sK+ 5.1-5.9 mEq/L) or normokalaemia (sK+ 3.5-5.0 mEq/L) who become hyperkalaemic during the first 3 weeks of the open-label period, and who maintain sK+ 3.5-5.0 when dosed with SZC, who are randomised and have one or more post randomisation central laboratory sK+ measurement available.

Treatment:

- SZC or Placebo administered daily with spironolactone. Participants with sK+ $\geq$ 6.0 mEq/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 randomised-withdrawal period (Hypothetical strategy, e.g. considered to be censored).
- Death prior to the EOT visit (Hypothetical strategy, e.g. considered to be censored).
- Participant lost to follow-up prior to the EOT visit (Hypothetical strategy, e.g. considered to be censored at the date of their last visit during the randomised-withdrawal period).

Population Level Summary:

- Kaplan-Meier estimates of the median time to first hyperkalaemia episode in the SZC treatment group compared to the placebo group.

Secondary Efficacy Endpoint Analysis – Sensitivity Analysis

As a sensitivity analysis a Cox regression model will be used with the same analysis approach where competing events in the previous model are treated as spironolactone dose decrease events. The following intercurrent event strategy will be used with all other components of the estimand as defined in the main analysis

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 randomised-withdrawal period (Composite variable strategy, e.g. considered to be event).
- Death prior to the EOT visit (Composite variable strategy, e.g. considered to be event).
- Participant lost to follow-up prior to the EOT visit (Hypothetical strategy, e.g. considered to be censored at the date of their last visit during the randomised-withdrawal period).

As an additional sensitivity analysis, subjects will be administratively censored at the date of their visit 14 visit to investigate the impact of longer duration in the study for subjects enrolled prior to version 3 of the CSP.

5. Change in KCCQ-CSS at EOT visit (approximately 6 months post-randomisation) from randomisation baseline for subjects on SZC compared to placebo.

The KCCQ-CSS will be summarised and listed in the FAS using the visits of Visit 2 (Baseline), Visit 6 (Randomisation) and Visit 14 (EOT). Visit 14 results will include values from Visit 14b where results from Visit 14 are not available. The absolute values and change from baseline and randomisation in KCCQ-CSS will be summarised at each scheduled timepoint by randomised treatment group. Furthermore, the change from baseline and randomisation will be categorised as: <-5. -5 to +5, >5 - 10, >10 to 20, >20 and as: >=5, >=10,

>=15 and >=20 (responder analysis) and summarised at each visit by randomised treatment group using the FAS.

The change in KCCQ-CSS will be analysed with repeated measures analysis of covariance (ANCOVA) models where the dependent variable is post randomisation KCCQ-CSS and with fixed terms for randomised treatment group, KCCQ-CSS score at randomisation, stratification factor (HK vs NK at study entry) and subject recruitment country. The statistical model will be used to calculate the least squares mean (LSMean) treatment estimates, treatment difference (SZC – placebo) and 95% CI at EOT only. The p-value from the statistical model for the comparison of randomised treatment group will be presented.

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 EOT KCCQ-CSS and the independent variables are randomised treatment group, baseline KCCQ-CSS and an interaction term between randomised treatment group and baseline KCCQ-CSS. If $p>0.05$ for the interaction term, then we will accept the homogeneity of the treatment slopes.

Estimand Attributes

Endpoint:

- Change in KCCQ-CSS at EOT visit from randomisation baseline

Population:

- Participants with symptomatic HFrEF who meet inclusion/exclusion criteria. Participants have either hyperkalaemia (sK+ 5.1-5.9 mEq/L) or normokalaemia (sK+ 3.5-5.0 mEq/L) who become hyperkalaemic during the first 3 weeks of the open-label period, and who maintain sK+ 3.5-5.0 when dosed with SZC, who are randomised and have one or more post randomisation central laboratory sK+ measurement available

Treatment:

- SZC or Placebo administered daily with spironolactone. Participants with sK+ $\geq$ 6.0 mEq/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 randomised-withdrawal period (Treatment policy strategy, i.e. regardless of the intercurrent event).
- Death prior to the EOT visit (While on treatment strategy, i.e. the endpoint is only evaluable in subjects who remain alive and complete the KCCQ at EOT visit).
- Participant lost to follow-up prior to the EOT visit (While on treatment strategy, i.e. the endpoint is only evaluable in subjects who complete the KCCQ at EOT visit).

Population Level Summary:

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

Secondary Efficacy Endpoint Analysis – Sensitivity Analysis

As a sensitivity analysis, subjects will be administratively censored at the date of their visit 14 visit to investigate the impact of longer duration in the study for subjects enrolled prior to version 3 of the CSP.

Secondary Efficacy Endpoint Analysis – Supplementary Analysis

Using the repeated measures ANCOVA model and ANCOVA homogeneity of slopes tests described for the 'change in KCCQ-CSS at EOT visit from randomisation baseline' the 'change in KCCQ-CSS at EOT visit from screening baseline' will also be analysed with a fixed term for KCCQ-CSS score at screening baseline replacing the fixed term for KCCQ-CSS score at randomisation in the models.

4.2.7.3 Subgroup Analysis

Exploratory analyses of the primary endpoint will be performed for the following subgroups. In the case of a low number of subjects within a subgroup level (<5 subjects), levels will be pooled when meaningful. If a subgroup analysis is presented by a variable used in the statistical model then this term will be removed from the model.

- Participant recruitment region (North America, South America, Europe)
- Participant stratification factor (HK vs NK at study entry)
- Participant age (<median, ≥median)
- Participant age (<75, ≥75)
- Participant sex (Male, Female)
- Participant race (White, Black or African American, Other: Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Other)
- Participants with and without diabetes at screening
- Participants with and without atrial fibrillation at screening
- Participants with LVEF > median and ≤median at screening
- Participants with NT-proBNP > median and ≤median at screening

- Participants with eGFR<45, ≥45ml/min at screening
- Participants with sK+ > median and ≤ median at screening
- Participants currently receiving or not receiving sodium-glucose cotransporter 2 inhibitor (SGLT2i) therapy at screening
- Participants currently receiving or not receiving low-dose mineralocorticoid receptor antagonist (MRA) at screening
- Participants currently receiving ACE inhibitor therapy at screening
- Participants currently receiving ARB therapy at screening
- Participants currently receiving ARNi therapy at screening
- Participants currently receiving ACE inhibitor or ARB therapy at screening
- Participants with and without recent hospitalisation for heart failure prior to randomisation (recent hospitalisation defined as a subject admitted to the hospital with a length-of-stay in hospital exceeding at least 24 hours during the 12 months prior to baseline).

4.2.7.4 Exploratory Efficacy Analyses

4.2.7.4.1 Exploratory Exposure Analyses

- SZC/placebo dose assigned at each visit during the study (e.g. 5 g every other day; 5, 10, 15 g once daily).

- The spironolactone dose assigned at each visit during the study

Furthermore, at each study visit during the open-label and randomised-withdrawal 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) and spironolactone (e.g. 12.5mg daily, 25mg daily, 50mg daily) without any inferential test statistics.

4.2.7.4.2 Exploratory Cardiovascular Analyses

- *Time to first event of cardiovascular (CV) death or worsening HF (defined as HF Hospitalisations or Urgent HF visits regardless of IV loop diuretic use), and the individual components during the randomised-withdrawal period:*
  - *CV Death*
  - *Worsening HF (HF hospitalisations or urgent HF visits regardless of IV loop diuretic use)*
- *Total events of CV death and worsening HF during the randomised period*

  All deaths reported post-randomisation, except for subjects who withdraw consent, will be adjudicated by the Clinical Events Committee. Deaths will be sub-classified by the CEC as either CV, non-CV primary cause or an undetermined cause of death. Participants without a date of death or worsening HF will be censored at their end of

treatment date. To clarify, for subjects who are enrolled in version 1.0 or 2.0 of the CSP this will be the date of visit 14b and for all other subjects this will be the date of visit 14. If these visits are not available, participants will be censored at the last available visit during the randomised-withdrawal period. The time to first cardiovascular event (days) will be defined as (Date of death/worsening HF/last follow-up visit – date of randomisation + 1). The time to first cardiovascular event, time to CV death and time to worsening HF will be presented graphically using Kaplan-Meier curves for each treatment group using the FAS. Additionally, tabular summaries will be provided of Kaplan-Meier survival probabilities with 95% CIs at day 44, 88, 132 and 175 after the after the date of randomisation, detailing the cumulative counts of subjects at risk, with events, and censored. Furthermore, the estimated median time to each event and 95% CI will be presented for each treatment group. The Kaplan-Meier figures will include the p-value from a log-rank test by randomised treatment group.

To assess for the proportionality of hazards the –log(-log(estimated survival function)) will be plotted compared to log(days) for each randomised treatment group and visually inspected to determine if the curves are approximately parallel. To assess for the impact of censoring, and the duration of follow-up, a reverse Kaplan-Meier figure will be produced where the status indicators are reversed such that the censor becomes the event and the composite event of interest as the censor. These will be presented by randomised treatment group, together with a summary of associated statistics (median time, 25th and 75th percentiles and associated 95% CIs).

- *Mean daily furosemide equivalent loop diuretic dose over time in the SZC group compared with the placebo group during the randomised-withdrawal period.*
The mean daily furosemide equivalent loop diuretic dose per subject during the randomised-withdrawal period is defined as the total cumulative dose of daily furosemide equivalent loop diuretic dose during the randomised-withdrawal period divided by the number of days of follow-up during the randomised-withdrawal period. The mean daily furosemide equivalent loop diuretic dose will be summarised by treatment group using descriptive continuous statistics in the FAS without any inferential test statistics. Change in mean daily furosemide equivalent loop diuretic dose during the randomised-withdrawal period will be summarised by treatment group using descriptive continuous statistics in the FAS without any inferential test statistics. The change daily furosemide equivalent loop diuretic dose during the randomised-withdrawal period will be analysed using an ANCOVA analysis with dependent variable of daily furosemide equivalent loop diuretic dose at EOT visit and independent variables of randomised treatment group and randomisation baseline value of daily furosemide equivalent loop diuretic dose. The statistical model will be used to calculate the LSMean treatment estimates, treatment difference (SZC –

placebo) and 95% CI at EOT only. The p-value from the statistical model for randomised treatment group will be presented.

- *Difference in NT-proBNP at the EOT visit compared to randomisation in the SZC and placebo arms*

  NT-proBNP will be summarised using the visits of: Randomisation, Visit 9, Visit 12 and Visit 14. Visit 14 results will include values from Visit 14b where Visit 14 results are not available. Absolute values, change from randomisation and change from randomisation in natural log-transformed NT-proBNP will be summarised by treatment group as continuous data using the FAS. The change in log-transformed NTproBNP during the randomised-withdrawal period will be analysed using an ANCOVA analysis with dependent variable of NTproBNP at EOT visit and independent variables of randomised treatment group and randomisation baseline value of NTproBNP. The statistical model will be used to calculate the LSMean treatment estimates, treatment difference (SZC – placebo) and 95% CI at EOT only. The p-value from the statistical model for randomised treatment group will be presented.

  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 EOT natural log-transformed NT-proBNP and the independent variables are randomised treatment group, natural log-transformed randomisation NT-proBNP and an interaction term between randomised treatment group and natural log-transformed randomisation NT-proBNP. If $p>0.05$ for the interaction term, then we will accept the homogeneity of the treatment slopes.

4.2.7.4.3 Exploratory Subject-Reported Outcome Analyses

- *To explore the difference in KCCQ-TSS, KCCQ-OSS, and other KCCQ subdomains (including KCCQ physical limitation score) between the SZC and placebo arms at the EOT visit compared to baseline*

The following KCCQ domains will be summarised using the visits of Baseline (Visit 2), Randomisation (Visit 6) and Visit 14: Visit 14 results will include values from Visit 14b where results from Visit 14 are not available. Physical Limitation Score, Symptom Stability Score, Symptom Frequency Score, Symptom Burden Score, Self Efficacy Score, Quality of

Life Score, Social Limitation Score, KCCQ-TSS and KCCQ-OSS. The absolute values and change from baseline and randomisation will be summarised by randomised treatment groups as continuous data using the FAS without any inferential test statistics. Furthermore, the change from baseline will be categorised as: <-5. -5 to +5, > 5 - 10, > 10 to 20, >20 and as: >=5, >=10, >=15 and >=20 (responder analysis) summarised at each visit by randomised treatment group using the FAS.

- *An anchor-based assessment to determine the minimally important difference (MID)*

  The PGIS will be used as an anchor to determine the MID for the change in KCCQ-CSS from randomisation to Visit 14. Visit 14 results will include values from Visit 14b where results from Visit 14 are not available. The PGIS will be coded with 1 representing "no symptoms" and 6 "very severe" and a linear regression approach [Angst et al 2017] will be used. The change in PGIS from randomisation to EOT will be calculated, values of 0 will be coded as "No change" = 0, values of +1 will be coded as "small negative change" = 1 and values of -1 will be coded as "small positive change"=1. Two separate linear regression models will be fitted for improving or deteriorating scores. The outcome variable will be KCCQ-CSS and the covariate the binary anchor variable. The resulting βs (i.e. the slope parameter of the model) correspond to the MID for improvement and deterioration respectively.

- *Change in PGIS and KCCQ scores from screening to the end of open-label, screening to the EOT and randomisation to EOT adjusted for change in aldosterone levels during the same period.*

  The change in aldosterone from screening to the end of open-label will be summarised and the change in aldosterone from, screening to visit 14, and randomisation to visit 14 will be summarised by randomised treatment group as continuous data using the FAS. Visit 14 results will include values from Visit 14b where results from Visit 14 are not available. The change from screening to the end of open-label, change from screening to visit 14, and change from randomisation to visit 14 in KCCQ-TSS, KCCQ-CSS, KCCQ-OSS and PGIS will be analysed using linear regression models in the FAS with the score at visit 14 as the dependent variable and the independent variables of change in natural log aldosterone over the same period, baseline KCCQ/PGIS score, baseline natural log aldosterone, randomised treatment group (excluding change from screening to the end of open-label), stratification group and interaction terms between natural log aldosterone change and baseline KCCQ/PGIS score, baseline natural log aldosterone and randomised treatment group. Baseline will indicate either screening value or value at randomisation depending upon the period being analysed. Change in natural log aldosterone, baseline KCCQ/PGIS score and baseline natural log aldosterone will be

included in the model using 3-knot natural splines, where knots are equally spaced between the extreme of the data, to allow for a non-linear association with EOT KCCQ/PGIS score. To avoid over-fitting a backward selection method will be used to select a parsimonious set of independent variables where for each model fit the highest p-value greater than 0.05 is removed.

As an example, the change in KCCQ-TSS from screening baseline to the visit 14 will be analysed with dependent variables of: natural log aldosterone change from screening to the visit 14, screening KCCQ-TSS, screening natural log aldosterone, randomised treatment group, aldosterone change from screening to visit 14*screening KCCQ-TSS, natural log aldosterone change from screening to visit 14*screening natural log aldosterone and natural log aldosterone change from screening to visit 14*randomised treatment group.

4.2.7.4.4 Exploratory Renal Analyses

- *Change in mean UACR*

  UACR will be summarised using the visits of Screening (Visit 1), Randomisation (Visit 6), Visit 9 and visit 14 (EOT). Visit 14 results will include values from Visit 14b where results from Visit 14 are not available. The absolute value and change from screening baseline and randomisation baseline will be summarised by randomised treatment groups as continuous data using the FAS without any inferential test statistics. In addition, a subgroup analysis will be conducted using the same method with baseline UACR strata (<30 mg/g; 31–300 mg/g; >300 mg/g).

- *Change in eGFR*

  eGFR will be summarised using the visits of Screening (Visit 1), Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Randomisation (Visit 7), Visit 8, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13, Visit 14, Visit 14a, Visit 14b, Visit 15 and Visit 15a. The absolute value and change from screening baseline (Visit 1) and randomisation baseline (Visit 6) will be summarised by randomised treatment group as continuous data using the FAS.

  Three mixed effect models will be calculated using the FAS to determine the impact of SZC on eGFR:

  - The dependent variable will be eGFR during the open-label period. The independent fixed effect variables will include days from screening assessment, eGFR at screening, stratification factor, subject recruitment country and an interaction between randomised treatment group and days from screening.
  - The dependent variable will be eGFR during the randomised-withdrawal period. The independent fixed effect variables will include randomised treatment group, days from screening assessment, eGFR at randomisation, stratification factor, subject recruitment country and an interaction between randomised treatment group and days from screening.

- The dependent variable will be eGFR during the open-label and randomised-withdrawal periods. The independent fixed effect variables will include randomised treatment group, days from screening assessment, eGFR at screening, stratification factor, subject recruitment country and an interaction between randomised treatment group and days from screening.

Post model parameter estimates for the eGFR slope for each treatment group, 95% CI and p-value for the interaction term will be reported from each model. The estimate for the difference in eGFR between treatment groups, 95% CI and p-value will be presented for each model.

- *Change in Natriuretic response*

  Natriuretic response will be analysed using the fractional excretion of Na+ using the visits of Screening (Visit 1), Randomisation (Visit 6), Visit 9 and Visit 14 (EOT). Visit 14 (EOT) results will include values from Visit 14b where results from Visit 14 (EOT) are not available. The absolute value and change from screening baseline (Visit 1) and randomisation baseline (Visit 6) will be summarised by randomised treatment group as continuous data using the FAS without any inferential test statistics.

4.2.7.4.5 Exploratory Hyperkalaemia Analyses

- *Time to first instance of use of rescue therapy for hyperkalaemia during the randomised withdrawal period*

  The time (days) to the first use of rescue for hyperkalaemia during the randomised-withdrawal period is defined as the date of first use of rescue therapy – date of randomisation +1. Participants who do not require rescue therapy will be censored at the date of their last visit during the randomised-withdrawal period. To clarify, for subjects who are enrolled in version 1.0 or 2.0 of the CSP this will be the date of visit 14b and for all other subjects this will be the date of visit 14. If these visits are not available, participants will be censored at the last available visit during the randomised-withdrawal period. The time to first use of rescue therapy for hyperkalaemia will be presented graphically using Kaplan-Meier curves for each treatment group using the FAS. Additionally, tabular summaries will be provided of Kaplan-Meier survival probabilities with 95% CIs at days 44, 88, 132 and 175 after the date of randomisation, detailing the cumulative counts of subjects at risk, with events, and censored. Furthermore, the estimated median time to each event and 95% CI will be presented for each treatment group. The Kaplan-Meier figures will include the p-value from a log-rank test by randomised treatment group.

  To assess for the proportionality of hazards the –log(-log(estimated survival function)) will be plotted compared to log(days) for each randomised treatment group and visually inspected to determine if the curves are approximately parallel. To assess for the impact of censoring, and the duration of follow-up, a reverse Kaplan-Meier figure will be produced where the status indicators are reversed such that the censor becomes the event

and the composite event of interest as the censor. These will be presented by randomised treatment group, together with a summary of associated statistics (median time, 25th and 75th percentiles and associated 95% CIs).

- *Number of hyperkalaemia episodes per treatment group*

  The overall number of hyperkalaemia episodes during the open-label period, randomised-withdrawal period and overall, including subjects with one or more instance of hyperkalaemia and multiple instances of hyperkalaemia per subject will be summarised by treatment group using the FAS without any inferential test statistics.

- *Worst sK+ during randomised-withdrawal phase*

  The worst (highest) sK+ during the randomised-withdrawal per subject will be presented with the number and percentage of subjects in the following ranges per randomised treatment group using the FAS without any inferential test statistics: 5.1-5.4 mEq/L; 5.5-5.9 mEq/L, 6.0-6.4 mEq/L, ≥6.5mEq/L

- *Number of emergency department visits for hyperkalaemia in the SZC and placebo arms*

  The overall number of emergency department visits during the open-label period, randomised withdrawal period and overall, including subjects with one or more emergency department visits and multiple emergency department visits per subject will be summarised by treatment group using the FAS without any inferential test statistics.

- *Number of hospitalizations with diagnosis code for hyperkalaemia in the SZC and placebo arms*

  The overall number of hospitalizations during the open-label period, randomised withdrawal period and overall, including subjects with one or more emergency department visits and multiple emergency department visits per subject will be summarised by treatment group using the FAS without any inferential test statistics.

- *Persistence of RAASi medication*

  Based on the original RAASi (ACEi/ARB/ARNi) being received at enrolment in the open-label period the following number and percentage of subjects will be presented without any inferential test statistics:

  - Remaining on original dose from randomisation
  - With dose decrease from randomisation
  - With dose increase from randomisation
  - Discontinued original RAASi from randomisation
  - Missing

- *Initiation of ARNi*

  Participants who are classified as not receiving ARNi at enrolment at randomisation will have the number and percentage of subjects who initiate ARNi during the randomised withdrawal period presented by treatment group.

- *Change in sK+ at 7 days post EOT compared with EOT*

sK+ will be summarised using the visits of EOT, Visit 15 (7 days post EOT) and Visit 15a (21 days post EOT). The absolute value and change from EOT will be summarised by randomised treatment group as continuous data using the FAS.

A mixed effect models will be calculated using the FAS to determine the impact of SZC on sK+ post EOT:

- The dependent variable will be sK+ during the follow-up period. The independent fixed effect variables will include days from EOT, sK+ at EOT, stratification factor, subject recruitment country and an interaction between randomised treatment group and days from EOT.

Post model parameter estimates for the eGFR slope for each treatment group, 95% CI and p-value for the interaction term will be reported from the model.

- *Response (yes/no) of subjects on SZC compared to placebo who, at the earliest visit of either EOT or visit 14 (approximately 6 months post-randomisation), have sK+ within 3.5-5.0 mEq/L, are on spironolactone≥25mg daily, and did not use rescue therapy for hyperkalaemia at any point during the randomisation-withdrawal period*

  Response (yes/no) will be compared between treatment groups in the FAS using a logistic regression model including response as the dependent variable, randomised treatment and subject recruitment country as independent factors and open-label period cohort as a stratification factor, and will be tested using a two-sided alpha = 0.05. Subjects who have not remained on spironolactone≥25mg daily at EOT visit or who have used rescue therapy for hyperkalaemia at any point during the randomised-withdrawal period are treated as non-response. Subjects who are lost to follow-up prior to the EOT visit will have response treated as missing. Subjects who die prior to the EOT visit will be treated as non-response for the purpose of the primary analysis. For subjects who are assigned a non-response value, a sub table will be provided to summarize the intercurrent events which led to this assignment by treatment group. The number and percentage of subjects who achieved a response (Yes, No, Missing) will be summarised by randomised treatment group in the FAS. The common odds ratio will be derived together with the two-sided 95% confidence interval.

4.2.7.4.6 Exploratory Open-label Period Analyses

- *Number and percentage of subjects that are normokalaemic (NK) and receiving spironolactone ≥25 mg daily at the end of the open-label run-in period*

  The overall number and percentage of subjects with 3.5 ≤ sK+ ≤5.0 mEq/L in the SSO at the date of randomisation will be summarised by the dose of spironolactone received at the date of randomisation (e.g. 12.5mg daily, 25mg daily, 50mg daily) without any inferential test statistics.

- *Number and percentage of subjects discontinued from study during the open-label run-in period due to reasons other than HK*

The overall number and percentage of subjects in the SSO who discontinued treatment during the open-label period will be summarised, without any inferential test statistics, including reasons for discontinuation which will include:

- Worsened renal function
- Hypotension
- Other

The overall number and percentage of subjects who entered the open label period and discontinued from study during the open-label run-in for the following reasons:

- Deaths
- AEs leading to treatment discontinuation
- Subjects in Cohort 1 (hyperkalaemic at entry) who remained hyperkalaemic at end of open-label phase
- Subjects in Cohort 2 (normokalaemic at entry) who never became hyperkalaemic
- Subjects in Cohort 2 (normokalaemic at entry) who became hyperkalaemic and remained hyperkalaemic at the end of the open-label phase
- Subjects with important protocol deviation indicating they were incorrectly enrolled after screening
- Subject who withdrew from the study

Subjects should be reported in a hierarchical fashion by the first category which applies in the order presented above.

- *Spironolactone dose among Cohort 2 subjects who never became hyperkalaemic*

  The maximum dose of spironolactone achieved among cohort 2 subjects in the SSE who never became hyperkalaemic will be summarised categorically by dose and summarised as continuous data.

- *Number and proportion of subjects achieving normokalaemia during the first 48 hours of the open-label run-in correction period*

  The overall number and percentage of subjects with $3.5 \leq sK+ \leq 5.0$ mEq/L in the SSE during the first 48 hours of the open-label run-in correction period will be summarised without any inferential test statistics.

- *Number and proportion of subjects who are normokalaemic by their last visit during the open-label run-in period*

  The overall number and percentage of subjects with $3.5 \leq sK+ \leq 5.0$ mEq/L in the SSE at the date of randomisation will be summarised without any inferential test statistics.

- *Number and proportion of subjects who do not have an episode of hyperkalaemia during the open-label run-in period*

  The overall number and percentage of subjects in the SSE who did not have an episode of *hyperkalaemia* during the open-label run-in period will be summarised without any inferential test statistics.

- *Number and proportion of subjects who achieve at least 25mg of spironolactone during open-label run-in period*

  The overall number and percentage of subjects in the SSE who achieve at least 25mg of spironolactone during the open-label run-in period will be summarised without any inferential test statistics.

4.2.7.4.7 Other Exploratory Analyses

Change in serum bicarbonate

Serum bicarbonate will be summarised using the visits of Screening (Visit 1), Randomisation (Visit 6), and Visit 14. Visit 14 (EOT) results will include values from Visit 14b where results from Visit 14 (EOT) are not available. The absolute value and change from screening baseline and randomisation baseline will be summarised by randomised treatment groups as continuous data using the FAS without any inferential test statistics.

4.2.7.4.8 Genomics Initiative

Optional genetic sample collection will be listed only using the SSO. Any further analyses of genomic samples will be provided in a separate analysis plan.

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 period and will be presented by open-label cohort and overall. Analyses using the SSR will include all AEs and will be presented by treatment group received during the randomised-withdrawal period and overall.

Any AE occurring within 14 days of the discontinuation of investigational product will be included in the AE summaries. Treatment emergent adverse events (TEAEs) occurring prior to first dose of investigational product (i.e. before study day 1) which subsequently worsen in severity following dosing will be presented in the summary tables. All other AEs occurring prior to first dose of investigational product (i.e. before study day 1) or more than 15 days after the discontinuation of investigational product will be listed separately, but not included in the summaries.

An overview table will summarize the number and percentage of subjects 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. For the overall summary of subjects with any AEs and SAEs, in the safety set randomised 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

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

- AEs 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, by 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;
- AEs assessed by investigator as possibly related to treatment leading to treatment interruption, by SOC and PT;
- AEs leading to dose reduction, by SOC and PT;
- AEs assessed by investigator as possibly related to treatment leading to dose reduction, 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;
- Oedema related events, by PT;
- Heart failure events (Heart failure events as classified by the central adjudication committee), by 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 period, study treatment at the time of event.

In addition, details collected on the peripheral oedema and heart failure event eCRF pages will be summarised using the SSO and SSR. Analyses using the SSO will be restricted to peripheral oedema and heart failure events which occurred during the open-label period and will be presented by open-label cohort and overall. Analyses using the SSR will include all incidences of peripheral oedema and heart failure events and will be presented by treatment group received during the randomised-withdrawal period and overall. The first instance of peripheral oedema or heart failure event per subject in the SSO and SSR analysis periods will be reported.

4.2.8.2 Deaths

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

- Cardiovascular/Non-cardiovascular/Undetermined cause of death
- Primary cause of cardiovascular deaths
- Primary cause of non-cardiovascular deaths
- Number of subjects with any AE with outcome = death

All deaths will be listed.

4.2.8.3 Laboratory Data

Laboratory data (clinical chemistry, haematology and urinalysis) will be summarised 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 summarised at each scheduled assessment time. Separate tables will be provided for the SSO, restricted to visits during the open-label period and presented by open-label cohort and for the SSR which will include all visits and be presented by treatment received during the randomised-withdrawal period.

Shift tables will be provided for select tests, where shift from baseline to the maximum value will be summarised. These will be provided separately for the SSO which will be limited to visits during the 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 presented by open-label cohort and the SSR which will summarize the worst CTC grade across all visits and be presented by treatment received during the randomised-withdrawal period.

The total number of subjects with events of hypokalaemia (<3.5, <3.0 and <2.5 mEq/L) and hyperkalaemia (>5.0, >5.5, >6.0 and >6.5 mEq/L) will be summarised, as well as the cumulative count for each category. Separate tables will be provided for the SSO, restricted to visits during the open-label period and presented by open-label cohort and for the SSR which will include all visits and be presented by treatment received during the randomised-withdrawal period.

In addition, the number and percentage of subjects with markedly abnormal clinical laboratory values will be summarised 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 by open-label cohort, and the SSR, which will summarize abnormal clinical laboratory values across all visits and be presented by treatment received during the randomised-withdrawal period.

4.2.8.4 Vital Signs

Vital sign values will be summarised and listed. Vital sign data absolute and change from baseline will be summarised at each scheduled timepoint. The continuous vital sign parameters will be summarised with descriptive statistics. If a 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 period and presented by open-label cohort, and the SSR which will include all visits with scheduled vital sign assessment and be presented by treatment received during the randomised-withdrawal period.

4.2.8.5 Electrocardiograms

ECG data will be summarised and listed. Absolute and change from baseline in ECG parameters will be summarised at each scheduled timepoint. The continuous ECG parameters will be summarised with descriptive statistics. If a 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 period and presented by open-label cohort, and the SSR which will include all visits with ECG assessments and be presented by treatment received during the randomised-withdrawal period.

The number and percentage of subjects with QTcF results exceeding ICH boundaries (>450, >480, >500) and with increases from baseline >30, >60, >90 will be presented for the SSO, limited to visits during the open-label period and presented by open-label cohort, and the SSR which will include all visits with scheduled ECG assessment and be presented by treatment

received during the randomised-withdrawal period. Participants are included based on maximum QTcF value and are counted in all applicable categories (e.g. a subject with a QTcF value of 510ms would be included in 450, 480 and 500 rows).

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 summarised over time by open-label cohort for the SSO, restricted to visits during the open-label period, and by treatment received during the randomised-withdrawal period using the SSR.

4.2.8.7 Heart Failure Events

For subjects who experience a heart failure event, reported as an AE, the following information will be listed: study day of AE, treatment group, IP dose at AE onset, age, gender, causality assessment, NYHA class at baseline, NYHA class at AE assessment, LVEF % at baseline, eGFR at AE assessment, MedDRA dictionary-derived and reported term for the heart failure adverse event, severity of HF event (hospitalised/urgent visit), action taken with IP (dose not changed, dose increased, dose reduced, dose interrupted, drug permanently discontinued), additional action taken (additional/increase in IV diuretic therapy, IV vasoactive therapy, initiation of augmentation of oral diuretic therapy) and adverse event outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal).

4.2.8.8 Oedema Assessment

Oedema assessments where a new or worsening abnormality is observed will be reported as an AE. For subjects who experience oedema, reported as an AE, the following information will be listed: study day of AE, treatment group, IP dose at AE onset, causality assessment, blood pressure (systolic/diastolic) at last available measurement prior to AE onset, eGFR, description of oedema (location & severity), action taken with IP (dose not changed, dose increased, dose reduced, dose interrupted, drug permanently discontinued), diuretic dose change (dose not changed, dose increased, dose reduced, dose interrupted, drug permanently discontinued), and adverse event outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal).

4.2.8.9 Exposure

Exposure (in days) to investigational product i.e. total amount of study drug will be summarised by open-label cohort for the SSO and treatment group for the SSR.

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

The dosage (g/day) will be calculated for the open-label period and randomised-withdrawal period respectively:

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

SZC/Placebo and Spironolactone dosage (g/day and mg/day, respectively) will be summarised by the following: range, mean, range of mean doses, median dose, interquartile range of dose. Total cumulative dose received (g and mg, respectively) will be summarised by mean and range. The range of the maximum dose received (g/day and mg/day, respectively) will be summarised.

For each study visit period (e.g. from visit 1 to visit 2, visit 2 to visit 3) the total number (%) of subjects who received dose will be presented and the prescribed daily dose. In order to determine the dose at study visit x, the latest exposure record where the start date of administration is less than or equal to the study visit date will be selected. If multiple exposure records exist for the same day, the record with the highest dose will be selected. For SZC/Placebo the IP dose at visit eCRF field will be presented and for Spironolactone the prescribed dose will be presented.

For the randomised-withdrawal period the total number of subjects with IP up-titrated at any time point, down-titrated at any point and with no registered change will be summarize by treatment group for the SSR.

4.2.8.10 Pregnancy Test

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

4.2.9 Biomarker Sample Collection

The collection of biomarker samples (NT-proBNP and serum aldosterone) will be listed using the SSO analysis set.

5 INTERIM ANALYSES

This study includes a DMC, unblinded to study treatment, who are responsible for safeguarding the interests of study subjects, assessing safety of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMC will be responsible for recommending whether to continue or terminate the trial, and for recommending whether amendments to the protocol or changes in study conduct are required.

DMC meetings are enrolment driven and are to occur at approximately:

- 10% subjects randomised
- 25% subjects randomised
- 50% subjects randomised
- 75% subjects randomised

DMC meeting will be held at least every six months. Full details of the composition and responsibilities of the committee are described in the DMC charter.

The DMC committee will not evaluate the efficacy results as part of their remit to safeguard the safety of trial subjects. Some efficacy tables may be included in the reports for DMC data review meetings to allow consideration of potential benefits in the assessment of safety risks. A subset of tables, listings and figures to be prepared for each DMC review is indicated in Appendix A. No formal interim analyses are planned for this study and no adjustment is required for the type I error rate.

6 CHANGES OF ANALYSIS FROM PROTOCOL

The definition of the safety set open was revised. The protocol states that the SSO is defined as "All participants who enter the open-label phase and receive at least one dose of SZC" This was revised to "All participants who meet inclusion/exclusion criteria and enter the open-label period of the study and receive at least one dose of SZC or Spironolactone."

The definition of the per protocol set was revised. The protocol states that the PPS is defined as "FAS participants without any important protocol deviations leading to exclusion from the PPS". The PPS is used for sensitivity analyses of efficacy endpoints only so was revised to "participants in the FAS who do not have any important protocol deviations considered to have a major effect on efficacy."

The protocol suggests that a "pre-planned tipping point sensitivity analysis" will be used for the primary endpoint and that "tipping point assumptions on response will vary for CV-related deaths and loss to follow-up but standard missing at random approaches such as multiple imputation will be used for COVID-19-related deaths or loss to follow-up." Multiple imputation is not being applied for the primary endpoint and an alternate intercurrent event strategy has been described to evaluate the impact of the COVID-19 pandemic on the primary estimand.

The protocol states that a "supplementary analysis will be conducted including an interaction term between treatment and a time dependent covariate of dose received (5g every other day, 5g daily, 10g daily, 15g daily) to allow for the effect of dose to be assessed." Per protocol, an increase in serum potassium should lead to increases in the dose of SZC and placebo. As such,

time-dependent dose acts as a mediator and confounder and will lead to biased estimates of treatment effect. This analysis has been updated to include dose received at baseline.

The protocol states that Change in PGIC and KCCQ scores with aldosterone levels at EOT compared with randomisation will be analysed. PGIS is collected in this study so will be investigated instead.

The addition of exploratory endpoint Change in sK+ at 7 days post EOT compared with EOT was added to the SAP and is not referenced in the protocol.

7 REFERENCES

Angst F, Aeschlimann A, Angst J. The minimal clinically important difference raised the significance of outcome effects above the statistical level, with methodological implications for future studies. J Clin Epidemiol 2017;82:128–36. 10.1016/j.jclinepi.2016.11.016.

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APPENDIX A: TFL SHELLS PRESENTED TO DMC

TFL Number, Title (Analysis Population)	DMC
Table 14.3.2.1: Number of subjects with adverse events in any category (Safety Set Open)	Y
Table 14.3.2.2: Number of subjects with adverse events in any category (Safety Set Randomised)	Y
Table 14.3.2.5: Number of subjects with adverse events, most common (frequency of >5%), by system organ class and preferred term (Safety Set Open)	Y
Table 14.3.2.6: Number of subjects with adverse events, most common (frequency of >5%), by system organ class and preferred term (Safety Set Randomised)	Y
Table 14.3.2.19: Number of serious adverse events, by system organ class and preferred term (Safety Set Open)	Y
Table 14.3.2.20: Number of serious adverse events, by system organ class and preferred term (Safety Set Randomised)	Y
Appendix 16.2.4.1: Demographic and baseline characteristics, Safety Set Open	Y
Appendix 16.2.4.2: Demographic and baseline characteristics, Safety Set Randomised	Y
Appendix 16.2.4.4: Concomitant medication on entry and during the study, Safety Set Open	Y
Appendix 16.2.5.1: Administration of investigational product, Safety Set Randomised	Y
Appendix 16.2.7.1: Adverse events prior to first dose of investigational product, Screened Set	Y
Appendix 16.2.7.2: Adverse events after discontinuation of investigational product, Screened Set	Y
Appendix 16.2.7.3: Adverse events, Screened Set	Y
Appendix 16.2.7.4: Heart Failure Adverse Events, Screened Set	Y
Appendix 16.2.7.5: Oedema-related Adverse Events, Screened Set	Y
Appendix 16.2.8.1: Individual laboratory measurement, Safety Set Open	Y
Appendix 16.2.9.1: Individual vital signs data, Safety Set Open	Y
Appendix 16.2.10.1: Electrocardiogram data, Safety Set Open	Y
Appendix 16.2.10.2: Abnormalities in electrocardiogram, Safety Set Open	Y
DMC Table 14.3.2.2.2: Number of subjects with adverse events in any category, presented by treatment and open-label cohort groups (Safety Set Randomised)	Y
DMC Table 14.3.2.6.2: Number of subjects with adverse events, most common (frequency of >5%), by system organ class and preferred term, presented by treatment and open-label cohort groups (Safety Set Randomised)	Y
DMC Table 14.3.2.20.2: Number of serious adverse events, by system organ class and preferred term, presented by treatment and open-label cohort groups (Safety Set Randomised)	Y
DMC Table 14.3.7.1.2.2: Haematology and clinical chemistry laboratory variables over time, presented by treatment and open-label cohort groups (Safety Set Randomised)	Y
DMC Table 14.3.8.1.4.2: ECG variables over time, presented by treatment and open-label cohort groups (Safety Set Randomised)	Y