Clinical Study Protocol	
Study Intervention	Sodium Zirconium Cyclosilicate (SZC)
Study Code	D9480C00018
Version	4.0
Date	09Nov2023

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)

Sponsor Name: AstraZeneca AB

Legal Registered Address: 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s):

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: 4.0

Amendment Number: 3.0

EudraCT number: 2020-003312-27

Study Intervention: Sodium Zirconium Cyclosilicate (SZC)

Study Phase: 4

Acronym: REALIZE-K

PPD **Principal Investigator:** Mikhail Kosiborod

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	09-Nov-2023
Amendment 2	03-Aug-2022
Amendment 1	29-Jun-2021
Original Protocol	29-Sep-2020

Amendment 3, 09 November 2023

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment 3:

The overall rationale (one primary driver) for the changes implemented in the protocol amendment is the updated definition of primary endpoint to include additional datapoints during the maintenance phase. This will lead to a reduction in sample size.

Section # and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
1.1 Synopsis 3 Objectives and Endpoints 9.4.3.1 Primary Endpoint 9.4.3.2 Secondary Endpoints	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)".	Definition for primary endpoint amended to a longitudinal analysis which increases the power of study and allows for a reduced sample size.	Substantial
1.1 Synopsis 3 Objectives and Endpoints 9.4.3.1 Primary Endpoint 9.4.3.2 Secondary Endpoints	Added (a) "Response and Non-response definitions" (b) "each assessment visits" instead of "EOT visits" for patients who are lost to follow-up at the visit, including due to death.	(a) Updated for clarity (b) Updated non-response imputation rule for revision of primary and secondary endpoint definitions.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
1.1 Synopsis 5.1 Inclusion Criteria	Female participants should be willing to remain on the birth control "**7 days**" instead of 4 weeks after the last dose	Updated to align with Follow up period.	Non-substantial
1.1 Synopsis 9.2 Sample Size Determination	Decrease in number of participants who will be randomised and enter the 6-month randomised phase of the trial, from 260 to 166 patients.	Updated to align with the updated primary endpoint.	Substantial
1.1 Synopsis 9.2 Sample Size Determination	The expected correlation of response between scheduled visits was included to be 0.55.	Updated to align with the change in the sample size estimation calculation method for the revised primary endpoint.	Substantial
1.1 Synopsis 9.2 Sample Size Determination 9.4.3.1 Primary Endpoint 9.4.3.2 Secondary Endpoints	(a) GEE model for primary endpoint analyses and secondary efficacy endpoint analyses were added. (b) The logistic regression model was deleted.	Determined to be the appropriate statistical method for estimating responses at each time point and fixed treatment effect.	Substantial
1.1 Synopsis 3 Objectives and Endpoints 9.4.3.1 Primary Endpoint 9.4.3.2 Secondary Endpoints	Added "The treatment effect concerns the overall Odds Ratio".	Updated for clarity due to a new primary endpoint.	Substantial
1.1 Synopsis 3 Objectives and Endpoints 9.4.3.2 Secondary Endpoints	Added "SZC compared with placebo using HR" and deleted "for patients on SZC compared to placebo during the randomised-withdrawal phase".	Updated for clarity due to a new primary endpoint.	Substantial
1.1 Synopsis 3 Objectives and Endpoints 9.4.3.2 Secondary Endpoints	Added "SZC compared with placebo using difference in mean" and deleted "for	Updated for clarity due to a new primary endpoint.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
	patients on SZC compared to placebo".		
1.3 Schedule of Activities	Under "physical examination" procedure: deleted visit 6 and optional visits (6a and 6b) for cohort 1; deleted visit 6, 6.1, 6.2, and optional visits (6a and 6b) for cohort 2.	Clarifying edit.	Non-substantial
1.3 Schedule of Activities	Under "targeted physical examination, including for oedema" procedure: deleted visit number 1 (Screening) for Cohorts 1 and 2.	Clarifying edit.	Non-substantial
1.3 Schedule of Activities	Follow-up period was updated to 26 weeks in Randomised, Double-Blind, Withdrawal Phase and Post-EOT Follow-up table.	Clarifying edit.	Non-substantial
1.3 Schedule of Activities	ECG at visit 15 was added in Randomised, Double-Blind, Withdrawal Phase and Post-EOT Follow-up table.	Clarifying edit.	Non-substantial
1.3 Schedule of Activities	Added citation details for Study Intervention Administration in SoA.	Clarifying edit.	Non-substantial
8.1 Administrative Procedures	Added Section 8.1 header that was unintentionally omitted from previous CSP.	Formatting error.	Non-substantial
8.2.2 Patient-Reported Outcomes (PROs)	Added the use of paper PROs in addition to the electronic PROs.	Clarifying edit.	Non-substantial
8.4.8 Medication Error, Drug Abuse, and Drug Misuse	(a) Section name has been updated to "Medication Error, Drug Abuse, and Drug Misuse" (b) New sections have been added as follows "8.4.8.1	Updated to align with industry standards.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
	Timelines, 8.4.8.2 Medication Error, 8.4.8.3 Drug Abuse and 8.4.8.4 Drug Misuse".		
9.1. Statistical Hypotheses	Added the details of the primary hypothesis tested.	Updated for clarity due to a new primary endpoint.	Substantial
9.2 Sample Size Determination	A new statement "These assumed effect sizes for the original primary endpoint will be retained for the revised primary endpoint which will evaluate responses observed from weeks 5-25" has been added.	The original assumed effect size for SZC has been retained but applied to the new endpoint definition to increase the power of the study allowing for a reduced sample size.	Non-substantial
9.4.3.1 Primary Endpoints	A new statement "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" has been added	Updated to add a supplementary analysis for each dose option.	Non-substantial
9.4.3.3 Exploratory Endpoints	A new statement "• Patients who begin the double-blind intervention period receiving 5g every other day, 5g daily, or 10g daily" has been added	Updated to add a supplementary analysis for each dose option.	Non-substantial
Appendix A1: Regulatory and Ethical Considerations	"Regulatory Reporting Requirements for Serious Breaches" have been added.	Clarifying edit.	Non-substantial
Appendix A6: Dissemination of Clinical Study Data	A statement indicating that "any results both technical and lay summaries for this	Clarifying edit.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
	trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries" has been added.		
Appendix A7: Data Quality Assurance	(a) A statement indicating that "AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study" has been added (b) Records and documents retention has been updated to "25 years" instead of 15 years.	Clarifying edit.	Non-substantial
Appendix B4: Medication Error, Drug Abuse, and Drug Misuse	(a) Section name has been updated to "Medication Error, Drug Abuse, and Drug Misuse" (b) New sections have been added as follows "Drug Abuse, and Drug Misuse".	Clarifying edit.	Non-substantial
Appendix A8: Source Documents	Definition of the source documents has been provided	Clarifying edit.	Non-substantial
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarised.	Non-substantial

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: 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

Short Title: REALIZE-K

Rationale:

The American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and European Society of Cardiology (ESC) Heart Failure (HF) guidelines recommend renin-angiotensin-aldosterone system inhibitors (RAASi), including mineralocorticoid receptor antagonist (MRA) therapy, as a Class I recommendation for the treatment of symptomatic HF with reduced ejection fraction (HFrEF; level of evidence A). These patients often experience hyperkalaemia (HK) as an adverse event (AE), resulting in down-titration or discontinuation of therapy. Additionally, HK and subsequent suboptimal RAASi treatment is associated with increased morbidity and mortality in these patients. Sodium zirconium cyclosilicate (SZC) is a novel non-absorbed zirconium silicate that preferentially captures potassium (K+) in exchange for hydrogen and sodium and has been approved in the United States (US), European Union (EU), Canada, China, Japan, and Brazil for the treatment of HK in adult patients. The REALIZE-K Study is designed to be on-label for the US and will provide 6 months of double-blind, placebo-controlled, randomised-withdrawal data on the safety and efficacy of SZC treatment in rapidly optimizing and maintaining MRA in patients with symptomatic HFrEF.

Objectives and Endpoints:

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)	Per visit, response is 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 patients who are lost to follow-up at the visit, including due to death.

Objective	Endpoint (Outcome Variable)
	The monthly visits are used for response assessment from month 1 to month 6. 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 assistance of rescue therapy for hyperkalaemia (HK)	Per visit, response is 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 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 patients 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. The treatment effect concerns the overall Odds Ratio.
• To compare the SZC and placebo arms with respect to spironolactone dose	Per visit, response is defined by • Being on spironolactone ≥25 mg daily Response means bullet point holds. Non-response indicates bullet point does not hold. Additionally, for each assessment visit, non-response is indicated for patients 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. 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, with HK defined as sK+ >5.0 mEq/L as assessed by central laboratory. SZC compared with placebo using Hazard ratio (HR).
• 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. SZC compared with placebo using HR

Objective	Endpoint (Outcome Variable)
• To compare the SZC and placebo arms with respect to change from randomisation in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS)	• Change in KCCQ-CSS at the EOT visit (approximately 6 months post-randomisation) from randomisation. SZC compared with placebo using difference in mean.
Safety	
• To assess the safety and tolerability of SZC as compared to placebo in patients with HFrEF and HK, who are on RAASi treatment	• Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory, and electrocardiogram (ECG). Assessments related to AEs cover: o Occurrence/frequency o Relationship to SZC/placebo as assessed by investigator o Intensity o Seriousness o Death o AEs leading to discontinuation of SZC/placebo

Note: For Exploratory objectives and endpoints, see Section 3 of the clinical study protocol (CSP).

Overall Design:

This study is a parallel-group, placebo-controlled, multi-centre study with an open-label run-in phase. The population being studied is patients with symptomatic HFrEF who are taking no or low-dose spironolactone or eplerenone (<25 mg daily) at screening. Study sites are located in North and South America and Europe.

Total duration of study participation for each patient will be approximately 8 months. The study consists of 3 periods: 1) screening period, 2) treatment period comprised of an open-label run-in phase and a randomised double-blind withdrawal phase, and 3) follow-up period.

1. Screening period (up to 2 weeks)
    a. Patients receiving low-dose eplerenone will be switched to spironolactone 12.5 mg daily during the screening period.
    b. Cohort assignment is based on local lab sK+ on Visit 1.
    c. In patients with hyperkalaemia (HK) (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 phase (4-6 weeks)

i. **Cohort 1 (4 weeks): Patients who are HK at study entry:**

- HK Correction Phase: Patients 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:** Patients who do not achieve NK during the 48-hour correction phase will be discontinued from the study.
- sK+ Maintenance Phase: Patients who achieve NK will continue on SZC 10 g once 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: Patients will initiate or up-titrate spironolactone beginning on Day 2 or 3 when they become NK on SZC. Spironolactone will be systematically up-titrated to a target dose of 50 mg daily, as tolerated per protocol instructions. **NOTE:** Patients who develop HK on spironolactone 50 mg daily while receiving maximum dose SZC (15 g) but were NK on spironolactone 25 mg daily may remain in the open-label, run-in phase for up to 2 additional weeks in order to return to spironolactone 25 mg and become NK again.

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

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

iii. **NOTE**:

- Patients in Cohort 2 who do not develop HK during the first 4 weeks (and as a result do not meet the requirement to receive SZC) will be discontinued from the study during the run-in phase.
- Patients who develop HK on spironolactone 50 mg daily while receiving maximum dose SZC (15 g), but were NK on spironolactone 25 mg daily may remain in the open-label, run-in

phase for up to 2 additional weeks in order to return to spironolactone 25 mg and become NK again.

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

i. Patients who are NK on SZC and receiving spironolactone ≥25 mg daily at the end of the run-in phase 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.

- Instructions on how to manage patients who do not qualify for randomisation due to hyperkalaemia are detailed in Section 6.6.1.
- Complete information regarding SZC and spironolactone dosing is provided in 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).

Disclosure Statement: This is a parallel-group treatment study with 2 arms that is participant- and investigator-blinded.

Number of Participants:

Approximately 400 patients meeting the inclusion criteria will enter the open-label phase, and approximately 166 of these patients who are NK (3.5-5.0 mEq/L) on SZC and receiving spironolactone ≥25 mg daily at the end of the 4- to 6-week run-in phase will be randomised and enter the 6-month randomised phase of the trial.

Main Inclusion Criteria:

- Adults aged ≥18 years
- Potassium and estimated glomerular filtration rate (eGFR):
  - Cohort 1: sK+ 5.1-5.9 mEq/L at screening/study enrolment and eGFR ≥30 mL/min/1.73 m^2; **or**
  - Cohort 2: Normokalaemic (sK+ 3.5-5.0 mEq/L) at screening and 'at risk' of developing HK defined as **any of the following:**
    - Have a history of HK (sK+ >5.0 mEq/L) within the prior 36 months and eGFR ≥30 mL/min/1.73 m^2; **or**
    - sK+ 4.5-5.0 mEq/L and eGFR 30 to 60 mL/min/1.73 m^2; **or**
    - sK+ 4.5-5.0 mEq/L and age >75 years
- Documented diagnosis of symptomatic HFrEF (New York Heart Association [NYHA] class II-IV), which has been present for at least 3 months
- Left ventricular ejection fraction (LVEF) ≤40% (any measurement made within the past 24 months using echocardiography, multiple gate acquisition scan, computer

tomography scanning, magnetic resonance imaging, or ventricular angiography is acceptable, provided no subsequent measurement above 40%)

- Receiving angiotensin-converting enzyme inhibitor (ACEi), angiotensin II receptor blocker (ARB), or angiotensin receptor-Neprilysin inhibitor (ARNi; eg, Entresto® [sacubitril/valsartan])
- Not on, or on low-dose spironolactone or eplerenone (<25 mg daily).
- Receiving beta-blocker unless contraindicated.

Inclusion Criteria for Proceeding to the 6-month Randomised-Withdrawal Treatment Phase:

- NK (3.5-5.0 mEq/L) on SZC and receiving spironolactone ≥25 mg daily at the end of the run-in phase.

Sex

- Female:
    - Female participants of childbearing potential must have a negative pregnancy test (serum).
    - Female participants must be 1 year post-menopausal, surgically sterile, or using one highly effective form of birth control (defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly). They should have been stable on their chosen method of birth control for a minimum of 4 months before entering the study and willing to remain on the birth control until 7 days after the last dose.

Informed Consent

- Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this CSP
- Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative.

Main Exclusion Criteria:

- Heart failure (HF) due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy, or severe stenotic valve disease as a primary cause of HF
- Current inpatient hospitalisation with unstable HF, defined as any of the following:
    a. SBP <95 mmHg during the 6 hours prior to screening.
    b. Intravenous diuretic therapy during the 12 hours prior to screening.

c. Use of intravenous inotropic drugs during the 24 hours prior to screening.

d. Received mechanical circulatory support during the 48 hours prior to screening.

- Type 1 myocardial infarction (MI), unstable angina, or stroke within 12 weeks prior to enrolment
- Coronary revascularisation (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) or valvular repair/replacement within 12 weeks prior to enrolment or planned to undergo any of these procedures
- Implantation of a Cardiac Resynchronisation Therapy (CRT) device within 12 weeks prior to enrolment or intent to perform atrial fibrillation ablation or to implant a CRT device
- Previous cardiac transplantation or implantation of a ventricular assistance device (VAD) or similar device, or transplantation or implantation expected after randomisation
- Symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Subjects with atrial fibrillation controlled by medication are permitted.
- Clinically significant bradycardia, as per investigator's judgement, or second- or third-degree heart block without a pacemaker
- QTc(f) >550 msec
- History of QT prolongation associated with other medications that required discontinuation of that medication
- Congenital long QT syndrome
- Symptomatic hypotension or systolic blood pressure (SBP) <90 mmHg on 3 consecutive measurements
- Receiving dialysis or anticipated by the investigator to require dialysis therapy within 3 months
- >30% decline in eGFR within the past 30 days; if laboratory results are not available, then exclude if acute kidney injury (AKI) within past 30 days based on medical history or medical records
- Clinically significant hyponatraemia in the opinion of the investigator
- History of gynecomastia due to spironolactone therapy requiring down-titration or discontinuation of spironolactone, or switch to a different MRA
- Addison's disease
- Elevated potassium due to measurement in haemolysed sample (must repeat blood draw)

- Any condition outside the cardiovascular (CV) and renal disease area, such as, but not limited to, malignancy with a life expectancy of less than 1 year based on investigator's clinical judgement.

Prior/concomitant therapy:

- The following potassium-related prior/concomitant therapy:
    - Treatment with potassium-sparing diuretics other than spironolactone or eplerenone (eg, triamterene, amiloride) within 7 days prior to enrolment
    - Potassium-binding resins such as sodium polystyrene sulfonate (SPS; eg, Kayexalate®) or calcium polystyrene sulfonate (CPS; eg, Resonium®), the cation exchange polymer, patiromer sorbitex calcium (Veltassa®), or SZC within 7 days prior to enrolment
    - Potassium supplements within 7 days prior to enrolment.

Concurrent Clinical Study Experience

- Participation in another clinical study with an investigational product (IP) administered in the last month.[1]

Other Exclusions

- Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
- Judgement by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.
- Previous enrolment in the present study.
- For women only - breast-feeding or planning to become pregnant during the study.
- If the participant has evidence of Coronavirus disease 2019 (COVID-19) within 2 weeks prior to enrolment (see Appendix E), the participant cannot be enrolled in the study.

Intervention Groups and Duration:

Total duration of study participation for each patient will be approximately 8 months. The breakdown of duration by period/phase can be found in the Overall Design, Section 4.1, along with dosing at each phase.

Data Monitoring Committee (DMC): Yes.

The role of the independent DMC (iDMC) in this trial is to evaluate participant safety throughout the study and to ensure the integrity, validity, and scientific merit of the study. The

[1] Participants vaccinated with COVID-19 vaccine whilst still under Emergency Use Utilisation will not be excluded from the study.

roles and responsibilities of the iDMC are outlined in the respective Charter.

Statistical Methods:

Analyses will be further detailed in the Statistical Analysis Plan (SAP), which will be finalised prior to the unblinding and locking of the clinical database.

Primary Endpoint

Per visit, response is 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 patients 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.

- The treatment effect concerns the overall Odds Ratio and will be analysed using a Generalized 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 and tested using a two-sided alpha = 0.05. The odds ratio will be derived together with two-sided 95% confidence intervals. Sensitivity analyses will be pre-specified in the SAP and will determine the impact of treating deaths and lost to follow-up as a missing response. As a minimum, these will use the PPS population and will treat patients lost to follow-up and deaths as a missing response.

Secondary Efficacy Endpoints

Statistical analyses of the secondary endpoints will include strong controls for multiplicity. The details of this approach will be detailed in the SAP.

1.Per visit, response is 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*

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 patients 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.

The treatment effect concerns the overall Odds Ratio and will be analysed using a GEE model, with an estimate of response for each time point and fixed treatment effect, using a binomial distribution with exchangeable correlation matrix. Patients who are lost to follow-up, including due to death, prior to any specific assessment visits will be treated as non-response for those assessment visits. The common odds ratio will be derived together with two-sided 95% confidence intervals.

2. Per visit, response is defined by

- Being on spironolactone ≥25 mg daily

Response means bullet point holds. Non-response indicates bullet point does not hold.

Additionally, for each assessment visit,
non-response is indicated for patients 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.

3. The treatment effect concerns the overall Odds Ratio and will be analysed using a GEE model, with an estimate of response for each time point and fixed treatment effect, using a binomial distribution with exchangeable correlation matrix. Patients who are lost to follow-up, including due to death, prior to any specific assessment visits will be treated as non-response for those assessment visits. The common odds ratio will be derived together with two-sided 95% confidence intervals.
4. *Time to first HK episode with HK defined as sK+ >5.0 mEq/L as assessed by central laboratory* SZC compared with placebo using HR and will be analysed using a cause-specific proportional hazards model with death treated as a competing risk, randomised treatment as an independent factor, and open-label phase cohort as a stratification factor. The hazard ratio and two-sided 95% confidence interval will be presented. Graphically, the treatment difference will be displayed using cumulative incidence competing risk curves.
5. *Time to first instance of decrease or discontinuation of spironolactone dose due to HK* SZC compared with placebo using HR and will be analysed using a cause-specific proportional hazards regression model with death treated as a competing risk, randomised treatment as an independent factor, and open-label phase cohort as a stratification factor. The hazard ratio and two-sided 95% confidence interval will be presented. Graphically, the treatment difference will be displayed using cumulative incidence competing risk curves.
6. *Change in KCCQ-CSS at the EOT visit (approximately 6 months post-randomisation) from randomisation* SZC compared with placebo using difference in mean and will be analysed with repeated measures analysis of covariance (ANCOVA) models with fixed terms for treatment, KCCQ-CSS at randomisation, open-label phase cohort, visit, and treatment by visit interaction.

Safety Endpoints

Safety endpoints will be analysed using descriptive methods.

Sample Size:

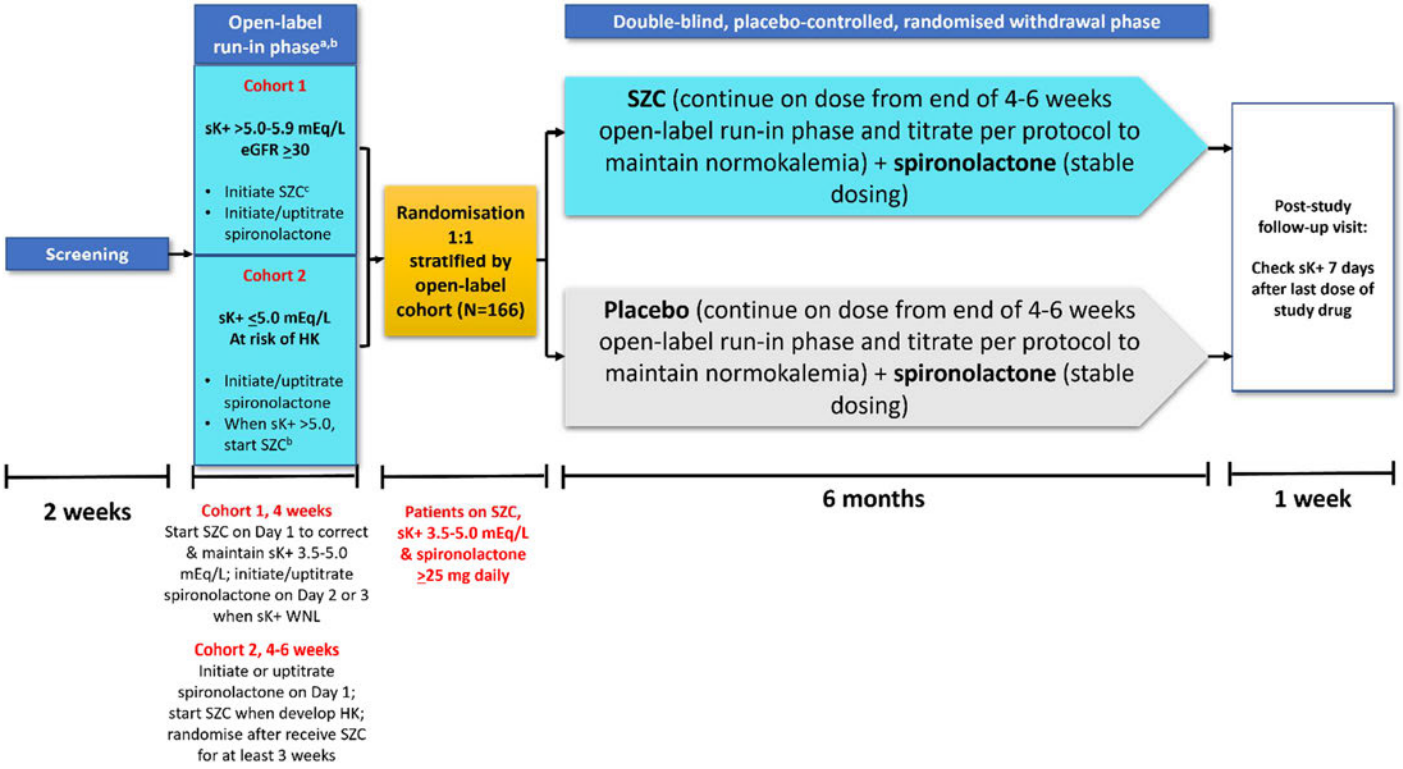
Sample size determination is based on the primary objective, ie, To evaluate the efficacy of SZC as compared with placebo in keeping potassium levels within the normal range (3.5-5.0 mEq/L) while on spironolactone ≥25 mg daily without assistance of rescue therapy for HK. Assuming that the probability 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 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 patients to be randomised. Clinical data suggests a death rate of 10 per 100 person years; therefore, approximately 8 deaths are expected. To ensure n=158 in the main sensitivity analysis for the primary endpoint, the sample size will be increased to approximately 166 randomised patients.

Analysis Populations:

- **Screened Set:** all patients who were screened for inclusion into the study.
- **Safety Set Open (SSO):** all patients who enter the open-label phase and receive at least one dose of SZC**.**
- **Safety Set Randomised (SSR):** all randomised patients who received at least one dose of either SZC or placebo. Safety analyses will be analysed using the SSO and SSR populations**.**
- **Full Analysis Set (FAS):** all randomised patients, irrespective of treatment and any protocol deviations, who have one or more post randomisation central laboratory sK+ measurements available. The FAS will be used as the primary population for the primary and secondary efficacy endpoints**.**
- **Per Protocol Set (PPS):** FAS patients without any important protocol deviations leading to exclusion from the PPS.

1.2 Schema

Figure 1 Study design



[a] Cohort assignment is based on local lab sK+ on Visit 1.
[b] Patients who develop HK on spironolactone 50 mg daily while receiving maximum dose SZC (15 g), but were NK on spironolactone 25 mg daily may remain in the open-label, run-in phase for up to 2 additional weeks in order to return to spironolactone 25 mg and become NK again.
[c] SZC 10 g three times daily for up to 48 h, then SZC 10g once daily, titrate if needed per protocol to maintain sK+ 3.5-5.0 mEq/L (range: 5 g every other day to 15 g daily.

Abbreviations: eGFR = estimated glomerular filtration rate; HK = hyperkalaemia; sK+ = serum potassium; SZC = sodium zirconium cyclosilicate; WNL = within normal limits.

1.3 Schedule of Activities

Table 1 Schedule of Activities (SoA)

Screening and Open-Label Run-in Phase – Cohort 1

Procedure	Screening	Open-Label Intervention Period (4 weeks)									Details in CSP section
Visit[a]	**1**	**2**	**2.1 (optional)[b]**	**2.2[c]**	**3**	**4**	**5**	**6[h]**	**6a (optional)[i]**	**6b (optional)[i]**	
Week	**-2 to 1**	**1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Treatment Day (Visit Window)	**-14 to 1**	**1**	**2**	**3**	**7 (±2)**	**14 (±3)**	**21 (±2)**	**28 (±3)**	**35 (±3)**	**42 (±3)**	
Informed consent	X										Section 5.1
Inclusion and exclusion criteria	X							X	X	X	Sections 5.1 and 5.2
Routine Clinical Procedures											
Demography	X										
Physical examination	X										Section 8.3.1
Targeted physical examination, including for oedema								X	X	X	Section 8.3.1
Medical history and comorbidities	X										Section 5.2
Concomitant medication (including diuretic use)	X	X	X	X	X	X	X	X	X	X	Section 6.5
Vital signs (including BP)	X	X	X	X	X	X	X	X	X	X	Section 8.3.2
Height	X										Section 8.3.1
Weight	X	X	X	X	X	X	X	X	X	X	Section 8.3.1
ECG including QTc(f)	X							X	X	X	Section 8.3.3
Routine Safety Measurements											
Adverse events (AEs)		X	X	X	X	X	X	X	X	X	Section 8.4

Serum pregnancy test (WOCBP only)	X										Section 5.1

Urine pregnancy test (pre-dose)		X									Section 8.3.4
Clinical safety laboratory assessments (including sK+ and sCr)[d]	X	X	X	X	X	X	X	X	X	X	Section 8.3.4
Biomarker Analyses											
Biomarker blood and urine collection	X							X	X	X	Section 8.7
First morning spot urine (3 consecutive days)[e]		X						X	X	X	Section 8.2.5
Genomics Initiative optional, exploratory genetic sample											
Blood sample		X									Section 8.8
Study Specific Assessments[f]											
KCCQ		X						X	X	X	Section 8.2.2
PGIS		X						X	X	X	Section 8.2.2
Study Intervention Administration											
Study intervention dispensation (open-label SZC)[g]		X			X	X	X		X		Section 6.6.1
Spironolactone[h]		X	X	X	X	X	X	X	X	X	Sections 6.6.1 and 6.6.2
Randomisation (1:1 SZC or placebo)[j]								X	X	X	Section 6.6.2
Study intervention dispensation (double-blind SZC or placebo)								X	X	X	Section 6.6.2

Abbreviations: BP = blood pressure; CSP = clinical study protocol; ECG = electrocardiogram; HK = hyperkalaemia; KCCQ = Kansas City Cardiomyopathy Questionnaire; NK = normokalaemic; PGIS = Patient Global Impression of Severity; sCr = serum creatinine; sK+ = serum potassium (3.5-5.0 mEq/L); SZC = sodium zirconium cyclosilicate; WOCBP = women of childbearing potential.

a Unscheduled visits can occur for patients who have a spontaneous AE report, are not feeling well for any reason, or if they have hypo- or hyperkalaemia that requires follow-up prior to the next scheduled visit.

b Visit 2.1 is optional for investigator's who would like to check the patient's serum K+ level 24 hours after starting SZC 10 g TID corrective dosing.

c For patients who complete the optional 2.1 visit, only those patients who are hyperkalaemic at this visit have to return for visit 2.2 to have their serum K+ level rechecked.

d Local laboratory for Chem 7 panel (eg, sCr and sK+; cohort assignment is based on local lab sK+ on Visit 1), and urinalysis (dipstick); central laboratory for chemistry, metabolic, renal panels, and biomarkers for the data analyses.

e Urine collection kits will be handed out at the visit before the visit when urine is to be collected to allow the subject to collect urine on the 3 consecutive mornings immediately preceding the visit. In the event that a subject forgets to collect any of the 3 first morning voids, the samples can instead be collected on the consecutive 3 mornings immediately following the visit, and delivered to the study site.

f Both KCCQ and PGIS will be administered in paper or using a site-based electronic device. It is preferred that patient-reported outcome (PRO) questionnaires are completed prior to any other study procedures and before discussion of disease progression to avoid biasing the patient's responses to the questions.

g HK Correction Phase: Start on Day 1, SZC 10 g three times daily for up to 48 hours until NK.
Maintenance Phase: Patients continue on SZC 10 g daily and then titrate between 5 g every other day and 5-15 g daily to maintain NK.

h The assessments unique to Visit 6 (namely the targeted physical exams, biomarker analyses, and the KCCQ & PGIS) will only occur once independently if the patient attends all optional visits (6a and 6b).

i Patients will initiate or up-titrate spironolactone beginning on Day 2 or 3 when they become NK. Spironolactone will be systematically up-titrated to a target dose of 50 mg daily as detailed in Section 6.6.1. Patients who develop HK on spironolactone 50 mg daily while receiving maximum dose SZC (15 g), but were NK on spironolactone 25 mg daily may remain in the open-label, run-in phase for up to 2 additional weeks in order to return to spironolactone 25 mg and become NK again.

j At end of run-in phase, patients who are NK on SZC and receiving spironolactone ≥25 mg daily will be randomised 1:1 to SZC or placebo on dose they were taking at end of run-in phase.

Screening and Open-Label Run-in Phase – Cohort 2

Procedure	Screening	Open-Label Intervention Period (4-6 weeks)															Details in CSP section
Visit[a]	1	2	3	3.1[b] optional	3.2	4	4.1[b] optional	4.2	5	5.1[b] optional	5.2	6[j,k]	6.1[j,k]	6.2[j,k]	6a (optional)[i]	6b (optional)[i]	
Week	-2 to 1	1	2	2	2	3	3	3	4	4	4	5	6	7	8	9	
Treatment Day (Visit Window)	-14 to 1	1	7 (±2)	8	9	14 (±3)	15	16	21 (±2)	22	23	28 (±3)	35 (±3)	42 (±3)	49 (±3)	56 (±3)	
Informed consent	X																Section 5.1
Inclusion and exclusion criteria	X											X	X	X	X	X	Sections 5.1 and 5.2
Routine Clinical Procedures																	
Demography	X																
Physical examination	X																Section 8.3.1
Targeted physical examination, including for oedema												X	X	X	X	X	Section 8.3.1
Medical history and comorbidities	X																Section 5.2
Concomitant medication (including diuretic use)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
Vital signs (including BP)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3.2
Height	X																Section 8.3.1
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3.1
ECG including QTc(f)	X											X	X	X	X	X	Section 8.3.3
Routine Safety Measurements																	
Adverse events (AEs)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.4

Serum pregnancy test (WOCBP only)	X																Section 5.1
Procedure	**Screening**	**Open-Label Intervention Period (4-6 weeks)**															**Details in CSP section**
Visit[a]	**1**	**2**	**3**	**3.1[b] optional**	**3.2**	**4**	**4.1[b] optional**	**4.2**	**5**	**5.1[b] optional**	**5.2**	**6[j,k]**	**6.1[j,k]**	**6.2[j,k]**	**6a (optional)[i]**	**6b (optional)[i]**	
Week	**-2 to 1**	**1**	**2**	**2**	**2**	**3**	**3**	**3**	**4**	**4**	**4**	**5**	**6**	**7**	**8**	**9**	
Treatment Day (Visit Window)	**-14 to 1**	**1**	**7 (±2)**	**8**	**9**	**14 (±3)**	**15**	**16**	**21 (±2)**	**22**	**23**	**28 (±3)**	**35 (±3)**	**42 (±3)**	**49 (±3)**	**56 (±3)**	
Urine pregnancy test (pre-dose)		X															Section 8.3.4
Clinical safety laboratory assessments (including sK+ and sCr)[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3.4
Biomarker Analyses																	
Biomarker blood and urine sample collection	X											X	X	X	X	X	Section 8.7
First morning spot urine (3 consecutive days)[d]		X										X	X	X	X	X	Section 8.2.5
Genomics Initiative optional, exploratory genetic sample																	
Blood sample		X															Section 8.8
Study Specific Assessments[e]																	
KCCQ		X										X	X	X	X	X	Section 8.2.2
PGIS		X										X	X	X	X	X	Section 8.2.2
Study Intervention Administration																	
Study intervention dispensation (open-label SZC)[f, g]			X[f]			X[f]			X[f]			X[f]	X	X	X		Section 6.6.1
Spironolactone[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Sections 6.6.1 and 6.6.2
Randomisation (1:1 SZC or placebo)[i]												X[j]	X[j]	X[j]	X[i]	X[j]	Section 6.6.2

Study intervention dispensation (double-blind SZC or placebo)												X	X	X	X	X	Section 6.6.2

Abbreviations: BP = blood pressure; CSP = clinical study protocol; ECG = electrocardiogram; HK = hyperkalaemia; KCCQ = Kansas City Cardiomyopathy Questionnaire; NK = normokalaemic; PGIS = Patient Global Impression of Severity; sCr = serum creatinine; sK+ = serum potassium (3.5-5.0 mEq/L); SZC = sodium zirconium cyclosilicate; WOCBP = women of childbearing potential.

a Unscheduled visits can occur for patients who have a spontaneous AE report, are not feeling well for any reason, or if they have hypo- or hyperkalaemia that requires follow-up prior to the next scheduled visit.

b For patients who become hyperkalaemic and start SZC 10 g TID corrective therapy for up to 48 hours, Visit X.1 (eg, Visit 3.1, 4.1 or 5.1) is optional for investigators who would like to check the patient's serum K^+ level 24 hours after starting SZC. For patients who complete the optional visit, only those who are hyperkalaemic at this visit have to return for visit X.2 (eg, Visit 3.2, 4.2 or 5.2) to have their serum K^+ level rechecked.

c Local laboratory for Chem 7 panel (eg, sCr and sK+), and urinalysis (dipstick); central laboratory for chemistry, metabolic, renal panels, and biomarkers for the data analyses.

d Urine collection kits will be handed out at the visit before the visit when urine is to be collected to allow the subject to collect urine on the 3 consecutive mornings immediately preceding the visit. In the event that a subject forgets to collect any of the 3 first morning voids, the samples can instead be collected on the consecutive 3 mornings immediately following the visit, and delivered to the study site.

e Both KCCQ and PGIS will be administered in paper or using a site-based electronic device. It is preferred that patient-reported outcome (PRO) questionnaires are completed prior to any other study procedures and before discussion of disease progression to avoid biasing the patient's responses to the questions.

f SZC dispensation if patient became HK.

g HK Correction Phase: Patients who develop HK during the first 4 weeks will begin SZC 10 g three times daily for up to 48 hours until NK.
Maintenance Phase (both cohorts): Patients continue on SZC 10 g daily and then titrate between 5 g every other day and 5-15 g daily to maintain NK.

h Initiate or up-titrate spironolactone beginning on Day 1. Up-titrate spironolactone to max dose of 50 mg daily as detailed in Section 6.6.1. Patients who do not develop HK by Visit 5 will be discontinued from the study during the run-in phase.

i Patients in Cohort 2 should receive at least 3 weeks of SZC before they can be considered for randomisation. Patients who develop HK on spironolactone 50 mg daily while receiving maximum dose SZC (15 g), but were NK on spironolactone 25 mg daily may remain in the open-label, run-in phase for up to 2 additional weeks in order to return to spironolactone 25 mg and become NK again.

j At end of run-in phase, patients who are NK on SZC and receiving spironolactone ≥25 mg daily will be randomised 1:1 to SZC or placebo on dose they were taking at end of run-in phase.

k The assessments unique to Visit 6 (or 6.1, 6.2) (namely the targeted physical exams, biomarker analyses, and the KCCQ & PGIS) will only occur once independently if the patient attends all optional visits (6a and 6b). Refer to Appendix K for the scenario when randomisation can happen for Cohort 2.

Randomised, Double-Blind, Withdrawal Phase and Post-EOT Follow-Up

Procedure	Double-Blind Intervention Period (6 months)								Follow-up Period	Details in CSP section
Visit[a]	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**EOT[b] 14**	**15**	
Week	**1**	**2**	**5**	**9**	**13**	**17**	**21**	**25**	**26**	
Treatment Day (Visit Window)	**3 days post-R (±2)**	**7 days post-R (±3)**	**1 mo post-R (±7)**	**2 mo post-R (±7)**	**3 mo post-R (±7)**	**4 mo post-R (±7)**	**5 mo post-R (±7)**	**6 mo post-R (±7)**	**7 days post-EOT(±3)**	
Targeted physical examination, including for oedema			X			X		X		Section 8.3.1
Concomitant medication (including diuretic use)	X	X	X	X	X	X	X	X	X	Section 6.5
Vital signs (including BP)	X	X	X	X	X	X	X	X	X	Section 8.3.2
Weight	X	X	X	X	X	X	X	X	X	Section 8.3.1
ECG including QTc(f)								X	X	Section 8.3.3
• **Routine Safety Measurements**										
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	Section 8.4
Clinical safety laboratory assessments (including sK+ and sCr)	X	X	X	X	X	X	X	X	X	Section 8.3.4
Biomarker Analyses										
Biomarker blood and urine sample collection			X			X[c]		X		Section 8.7
First morning spot urine (3 consecutive days)[d]			X					X		Section 8.2.5

Procedure	Double-Blind Intervention Period (6 months)								Follow-up Period	Details in CSP section
Visit[a]	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**EOT**[b] **14**	**15**	
Week	**1**	**2**	**5**	**9**	**13**	**17**	**21**	**25**	**26**	
Treatment Day (Visit Window)	**3 days post-R (±2)**	**7 days post-R (±3)**	**1 mo post-R (±7)**	**2 mo post-R (±7)**	**3 mo post-R (±7)**	**4 mo post-R (±7)**	**5 mo post-R (±7)**	**6 mo post-R (±7)**	**7 days post-EOT(±3)**	
Study Specific Assessment										
CV events (CV death and HF worsening)	X	X	X	X	X	X	X	X		Sections 8.2.4.1 and 8.2.4.2
KCCQ[e]								X		Section 8.2.2
PGIS[e]								X		Section 8.2.2
Study Intervention Administration										
Study intervention dispensation (double-blind SZC or placebo)[f]			X	X	X	X	X			Section 6.6.2
Spironolactone[g]	X	X	X	X	X	X	X	X	X	Section 6.6.2

Abbreviations: BP = blood pressure; CSP = clinical study protocol; CV = cardiovascular; ECG = electrocardiogram; EOT = end of treatment; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; NK = normokalaemic; PGIS = Patient Global Impression of Severity; R = randomisation; sCr = serum creatinine; sK+ = serum potassium; SZC = sodium zirconium cyclosilicate.

a Unscheduled visits can occur for patients who have a spontaneous AE report, are not feeling well for any reason, or if they have hypo- or hyperkalaemia that requires follow-up prior to the next scheduled visit, or for additional drug dispensation in case of dose titration.

b Patients who prematurely discontinue from the study during the randomised phase, including patients who prematurely discontinue study intervention and refuse to continue study visits for the duration of the randomised phase, should receive all EOT assessments at their last study visit.

c Only N-terminal pro-B-type natriuretic peptide (NT-proBNP) is collected at 4 months post-randomisation.

d Urine collection kits will be handed out at the visit before the visit when urine is to be collected to allow the subject to collect urine on the 3 consecutive mornings immediately preceding the visit. In the event that a subject forgets to collect any of the 3 first morning voids, the samples can instead be collected on the consecutive 3 mornings immediately following the visit, and delivered to the study site.

e Both KCCQ and PGIS will be administered in paper or using a site-based electronic device. It is preferred that patient-reported outcome (PRO) questionnaires are completed prior to any other study procedures and before discussion of disease progression to avoid biasing the patient's responses to the questions.

f Initial SZC/placebo dose at randomisation will continue with the same dose of SZC administered at end of run-in. SZC/placebo dose will then be adjusted between 5 g every other day and 5-15 g daily to maintain NK.

g Initial spironolactone dose at randomisation will continue with the same dose administered at end of run-in. Spironolactone dose will then be adjusted, if needed, as detailed in Section 6.6.2 and Table 9. Spironolactone dose will be adjusted, if needed, following study completion as detailed in Section 6.7.

1.4 Synopsis References

1. Epstein M, et al. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care*. 2015;21(Suppl 11):S212–S220.

2. Thomsen RW, et al. Elevated potassium levels in patients with congestive heart failure: occurrence, risk factors, and clinical outcomes. A Danish population-based cohort study. *J Am Heart Assoc*. 2018;7:e008912.

3. LOKELMA® (sodium zirconium cyclosilicate) for oral suspension. United States Prescribing Information (USPI). AstraZeneca Pharmaceuticals LP, Wilmington, DE. April 2020.

4. Lokelma powder for oral suspension. Summary of Product Characteristics (SmPC). https://www.ema.europa.eu/en/documents/product-information/lokelma-epar-product-information_en.pdf. Accessed 6 Feb 2020.

5. LOKELMA® (sodium zirconium cyclosilicate) powder for oral suspension. Product Monograph (PM). AstraZeneca Canada, Inc. August 2020.

2 INTRODUCTION

Sodium zirconium cyclosilicate (SZC) is a novel non-absorbed zirconium silicate that preferentially captures potassium in exchange for hydrogen and sodium that is being developed for the treatment of hyperkalaemia (HK) in adult patients. SZC (brand name LOKELMA®) is approved in the United States (US), European Union (EU), Canada, Japan, China, and Brazil.

2.1 Study Rationale

The purpose of REALIZE-K, a phase IV, double-blind, placebo-controlled, randomised-withdrawal trial, is to evaluate the long-term efficacy and safety of SZC compared with placebo in keeping potassium levels within the normal range (3.5-5.0 mEq/L) in patients with heart failure with reduced ejection fraction (HFrEF) while on spironolactone ≥25 mg daily without assistance of rescue therapy for HK.

Data from REALIZE-K will provide 6 months of double-blind, placebo-controlled, randomised-withdrawal safety and efficacy data as well as mineralocorticoid receptor antagonist (MRA) persistence data in the HFrEF population.

- In ZS-003, ZS-004, and ZS-005, only 10% to 15% of patients had HF as defined by AstraZeneca based on validated and standardised lists of preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA) narrow standardised MedDRA queries (SMQs) (USPI 2020; Data on file).

- In ZS-004E, only 13.2% of patients had HF (Roger et al. 2019). Additionally, while the study provides 11-months efficacy and safety data, the open-label single-arm study design significantly limits interpretation of the data, especially the safety data.

- In ZS-005, only 15% of patients had HF (Spinowitz et al. 2019). Additionally, while the study provides 12 months of efficacy and safety data, as well as renin-angiotensin-aldosterone system inhibitor (RAASi) persistence data, the open-label, single-arm study design significantly limits interpretation of the data, especially the safety data.

- While PRIORITIZE-HF will provide safety and efficacy, as well as RAASi optimisation data in HFrEF patients, the study duration is only 3 months (AstraZeneca 2020). Clinicians are requiring longer term data for SZC due to its sodium content and potential risk of oedema, especially in this patient population that is prone to fluid overload.

2.2 Background

The American College of Cardiology Foundation (ACCF), American Heart Association (AHA), and European Society of Cardiology (ESC) Heart Failure (HF) guidelines

recommend RAASi, including MRA therapy, as a Class I recommendation for the treatment of symptomatic HFrEF (level of evidence A). Specifically, the ACCF/AHA practice guidelines recommend MRA in all patients with chronic HFrEF (left ventricular ejection fraction [LVEF] ≤35%) and New York Heart Association (NYHA) class II–IV symptoms in the absence of contraindications (Yancy et al. 2013). The ESC HF guidelines similarly recommend MRA therapy in patients with HFrEF who remain symptomatic despite treatment with an angiotensin-converting enzyme inhibitor (ACEi)/angiotensin II receptor blocker (ARB)/angiotensin receptor-Neprilysin inhibitor (ARNi) and a β-blocker to reduce the risk of HF hospitalisation and death (Ponikowski et al. 2016).

While RAASi is a Class I recommendation in patients with HFrEF, these patients often experience HK as an adverse event (AE), resulting in down-titration or discontinuation of therapy (Epstein et al. 2015). Hyperkalaemia and subsequent suboptimal RAASi treatment is associated with increased morbidity and mortality in these patients (Epstein et al. 2015; Thomsen et al. 2018).

The 2022 AHA/ACC/HFSA HF Guideline recommends (Class 2b) patiromer or SZC for the management of hyperkalaemia (serum $K^+ \geq 5.5$ mEq/L) in patients with heart failure, but states that the effectiveness of these medications to improve outcomes by facilitating continuation of RAASi therapy is uncertain (Heidenreich, et al. 2022). While, not given a graded recommendation, the 2021 ESC HF guideline states that the administration of the K^+-lowering agents, patiromer or SZC, can be considered for the management of hyperkalaemia to potentially allow the initiation or uptitration of RAASi (McDonagh et al. 2021).

SZC is a novel non-absorbed zirconium silicate that preferentially captures potassium in exchange for hydrogen and sodium. SZC is approved in the US, EU, Canada, Japan, China, and Brazil for the treatment of HK in adult patients (United States Prescribing [USPI] 2020; Summary of Product Characteristics [SmPC] 2020; Product Monograph [PM] 2020).

A detailed description of the chemistry, pharmacology, efficacy, and safety of SZC is provided in the Investigator's Brochure (IB).

2.3 Benefit/Risk Assessment

This study will recruit subjects who either have mild-to-moderate HK or are at high risk of developing HK during MRA treatment. All subjects will receive spironolactone which has the potential to increase serum potassium (sK+), putting them at risk of developing HK. Additionally, there is a risk of HK in those subjects who are randomised to placebo in the treatment withdrawal phase. Hence, HK is the major medical risk for subjects participating in this trial. Additionally, up-titration of spironolactone during the run-in phase may result in decreased renal function, as assessed by serum creatinine (sCr). The following study design features were included to minimise the risk to subjects:

- Local laboratories will be used by sites to allow dose adjustments to occur rapidly at each visit by providing investigators with up-to-date sK+ and creatinine measurements.

- SZC and spironolactone dose titration and stopping rules based on local laboratory sK+ monitoring is included in this CSP to minimise the risk of HK due to spironolactone.

- The risk of HK upon randomisation to placebo will be mitigated with intensive monitoring of sK+ at the beginning of the randomised-withdrawal treatment phase.

- The risk of HK after the end of treatment (EOT) visit will be mitigated by careful monitoring of sK+ 7 days after the last study treatment dose.

- Hypokalaemia has been reported with SZC. SZC dose titration and stopping rules based on local laboratory sK+ monitoring is included in this CSP to minimise the risk of hypokalaemia in subjects receiving SZC.

- Spironolactone dose titration and stopping rules based on local laboratory sCr monitoring is included in this CSP to minimise the risk of decreased renal function due to spironolactone.

- Oedema-related events (grouped terms include preferred terms of oedema, oedema peripheral, generalised oedema, fluid retention, hypervolemia, localised oedema, and peripheral swelling) have been reported by patients treated with SZC, in particular at higher doses. Patients with HF have a high likelihood of experiencing oedema. Physical examinations to assess oedema will be performed and the subject will be weighed at prespecified visits to ensure development of oedema will be detected early and appropriately managed (see Section 8.3.1).

- Similar to PRIORITIZE-HF, there is a risk that investigators will not adhere to the protocolised up-titration of spironolactone during the run-in phase. To mitigate this risk, similar to PRIORITIZE-HF, all investigators will be required to document why spironolactone was not increased when parameters such as blood pressure and potassium were normal and renal function was stable.

More detailed information about the known and expected benefits and potential risks of SZC may be found in the IB.

2.3.1 Risk Assessment

Table 2 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention		
Common (≥1/100 to <1/10) adverse drug reaction (ADR) observed in SZC clinical studies: oedema-related events	Oedema-related events have only been observed in the maintenance phase of SZC clinical studies; they were reported by 5.7% of SZC subjects; 2.7%, 5.2%, 14.3%, and 1.7% of subjects randomised to SZC 5 g, 10 g, 15 g, and placebo, respectively. Grouped terms include preferred terms of Oedema, Oedema peripheral, Generalized oedema, Fluid retention, Hypervolemia, Localised oedema, and Peripheral swelling. (Refer to IB Section 5.4-5.5 and 6.4.)	Of the oedema-related events, 53% were managed with initiating diuretic treatment or adjusting the diuretic dose, while the remainder did not require treatment.
Common (≥1/100 to <1/10) ADR observed in SZC clinical studies: Hypokalaemia	Hypokalaemia (sK+ <3.5 mmol/L), a result of the pharmacological action of the drug, was observed in 4.1% of subjects treated with SZC.	Resolved with dose adjustment or discontinuation of SZC treatment.

2.3.2 Benefit Assessment

Clinical studies in patients with HK have demonstrated the efficacy of SZC in the correction of HK and maintenance of normokalaemia (NK).

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to participants participating in this study, the potential risks identified in association with SZC are justified by the anticipated benefits that may be afforded to participants with HK.

SZC has proven to effectively correct HK to the normal sK+ range and maintain NK for up to 12 months in a broad patient population with HK, including those on haemodialysis. Unfavourable effects were limited, and the adverse drug reactions (ADRs) of oedema-related events and hypokalaemia were generally mild and easily managed. Dose titration during maintenance treatment allows individualised treatment to maintain NK. Based on the available clinical data, the benefit-risk assessment is favourable for correction of HK with SZC 10 g three times daily for up to 2 days, and for maintenance treatment of patients with HK across

the dose range 5 g every other day to 5 to 15 g once daily. Data from these studies demonstrate that the majority of subjects can be adequately maintained on the 5 g daily or 10 g daily dose.

3 OBJECTIVES AND ENDPOINTS

Table 3 Objectives and Endpoints

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)	Per visit, response is 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 patients 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. 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	Per visit, response is 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 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 patients 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. The treatment effect concerns the overall Odds Ratio.

Objective	Endpoint (Outcome Variable)
• To compare the SZC and placebo arms with respect to spironolactone dose	Per visit, response is defined by • Being on spironolactone ≥25 mg daily Response means bullet point holds. Non-response indicates bullet point does not hold. Additionally, for each assessment visit, non-response is indicated for patients 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. 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 with HK defined as sK+ >5.0 mEq/L as assessed by central laboratory. SZC compared with placebo using HR.
• 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. SZC compared with placebo using HR.
• To compare the SZC and placebo arms with respect to change from randomisation in Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS)	• Change in KCCQ-CSS at EOT visit (approximately 6 months post-randomisation) from randomisation. SZC compared with placebo using difference in mean.
Safety	
• To assess the safety and tolerability of SZC as compared to placebo in patients with HFrEF and HK, who are on RAASi treatment	• Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory, and electrocardiogram (ECG) Assessments related to AEs cover: o Occurrence/frequency o Relationship to SZC/placebo as assessed by investigator o Intensity o Seriousness o Death o 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 (eg, 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

Objective	Endpoint (Outcome Variable)
• To explore the potential occurrence of cardiovascular (CV) death, worsening of HF (defined as HF Hospitalisations or Urgent HF visits regardless of intravenous [IV] loop diuretic use), and the individual components in the SZC and placebo arms during the randomised phase	• Time to first event of 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 phase: o CV Death o Worsening HF (HF hospitalisations or urgent HF visits regardless of IV loop diuretic use) o HF Hospitalisations o Urgent HF Visits
• To explore the potential change in mean urine albumin-to-creatinine ratio (UACR) in the SZC and placebo arms	• Change in mean UACR in SZC group compared with placebo group at: o Screening compared to EOT o Randomisation compared to EOT o Screening compared to randomisation
• To explore the change from randomisation 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
• To explore the relationship between aldosterone levels and PGIC and KCCQ scores, with particular attention to intrapatient consistency, between the SZC and placebo arms at the EOT visit compared to randomisation	• Change in PGIC and KCCQ scores with aldosterone levels at EOT compared with randomisation
• To explore the potential difference in N-terminal pro-B-type natriuretic peptide (NT-proBNP) between SZC and placebo arms (mean difference as compared to randomisation, as well as the likelihood of an increase, decrease, and stability)	• Change in NT-proBNP measurements at EOT (approximately 6 months post randomisation) compared with randomisation
• 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 phase

4 STUDY DESIGN

4.1 Overall Design

This study is a parallel-group, placebo-controlled, multi-centre study with an open-label run-in phase. The population being studied is patients with symptomatic HFrEF who are taking no or low-dose spironolactone or eplerenone (<25 mg daily) at screening. Study sites will be located in North and South America and Europe.

Total duration of study participation for each patient will be approximately 8 months. The study consists of 3 periods: 1) screening period, 2) treatment period comprised of an open-label run-in phase and a randomised double-blind withdrawal phase, and 3) follow-up period.

1. Screening period (up to 2 weeks)
   a) Patients receiving low-dose eplerenone will be switched to spironolactone 12.5 mg daily during the screening period.

   b) Cohort assignment is based on local lab sK+ on Visit 1

   c) In patients 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 phase (4-6 weeks)
      i. Cohort 1 (4 weeks): Patients who are HK at study entry:
         - HK Correction Phase: Patients 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:** Patients who do not achieve NK during the 48-hour correction phase will be discontinued from the study.
         - sK+ Maintenance Phase: Patients 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: Patients will initiate or up-titrate spironolactone beginning on Day 2 or 3 when they become NK on SZC. Spironolactone will be systematically up-titrated to a target dose of 50 mg daily, as tolerated per protocol instructions. **NOTE:** Patients who develop HK on spironolactone 50 mg daily while receiving maximum dose SZC (15 g) but were NK on spironolactone 25 mg daily may remain in the open-label, run-in phase for up to 2 additional weeks in order to return to spironolactone 25 mg and become NK again.

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

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

iii. **NOTE**:

- Patients in Cohort 2 who do not develop HK during the first 4 weeks (and as a result do not meet the requirement to receive SZC) will be discontinued from the study during the run-in phase.
- Patients who develop HK on spironolactone 50 mg daily while receiving maximum dose SZC (15 g), but were NK on spironolactone 25 mg daily may remain in the open-label, run-in phase for up to 2 additional weeks in order to return to spironolactone 25 mg and become NK again.

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

- Patients who are NK on SZC and receiving spironolactone ≥25 mg daily at the end of the run-in phase 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.
- Instructions on how to manage patients who do not qualify for randomisation due to hyperkalaemia are details in Section 6.6.1.
- Complete information regarding SZC and spironolactone dosing is provided in 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). Patients who are discontinued from the study during the run-in phase due to hyperkaleamia:

- Return spironolactone to the dose the patient was receiving (ie, no, or low-dose) prior to study enrolment. If the patient's dose was stopped during the run-in phase, do not restart it.
- Use clinical judgement to determine if the patient should/can be continued on commercially available SZC to manage their hyperkalaemia.

- Refer the patient to their HF treating clinician within 1 week of study discharge for follow-up and to determine their course of treatment moving forward.

4.2 Scientific Rationale for Study Design

The study was designed with 2 cohorts of patients in the open-label period (one with HK patients at screening and one with NK patients at screening) to increase the number of eligible patients and provide more clinically relevant data.

Inclusion criterion #2: By not capping the allowable eGFR but instead making it 30 mL/min/1.73 m^2 or greater, the number of eligible patients will increase as it captures patients with HF and comorbid conditions other than stage 3 chronic kidney disease (CKD) that increase the risk of HK.

Exclusion Criterion #2: Allows for the inclusion of hemodynamically stable patients who are either currently or recently hospitalised. These patients are often receiving suboptimal MRA and have challenging HK issues.

4.3 Justification for Dose

Clinical studies in subjects with HK consistently demonstrated that initial treatment with SZC 10 g three times daily for 24 hours up to 72 hours resulted in clinically meaningful sK+ reduction with a majority of subjects achieving NK within 24 to 48 hours. Moreover, subjects with higher baseline sK+ levels had greater reductions in sK+ levels. Onset of efficacy was rapid with sK+ reduction observed as early as 1 hour after dose intake.

After correction of HK, continued maintenance treatment for 28 days with SZC 5 g, 10 g, or 15 g daily resulted in continued effective control of sK+ within the NK range. The proportion of subjects who remained NK at the EOT with SZC 5 g, 10 g, and 15 g daily increased dose-dependently (range: 71% to 85%) and was superior to placebo. In addition, long-term maintenance treatment of up to 12 months with SZC utilising a dose titration scheme with the starting dose of 5 g daily or 10 g daily, titrated to a maximum of 15 g daily or a minimum of 5 g every other day was effective in maintaining NK in the majority of subjects.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 Participant must be ≥18 years of age, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 Potassium and estimated glomerular filtration rate (eGFR):

(a) Cohort 1: sK+ 5.1-5.9 mEq/L at screening/study enrolment and eGFR ≥30 mL/min/1.73 m^2; **or**

(b) Cohort 2: Normokalaemic (sK+ 3.5-5.0 mEq/L) at screening and 'at risk' of developing HK defined as **any of the following**:

i. Have a history of HK (sK+ >5.0 mEq/L) within the prior 36 months and eGFR ≥30 mL/min/1.73 m^2; **or**

ii. sK+ **4.5-5.0** mEq/L and eGFR 30 to 60 mL/min/1.73 m^2; **or**

iii. sK+ **4.5-5.0** mEq/L, and age >75 years

3 Documented diagnosis of symptomatic HFrEF (NYHA class II-IV), which has been present for at least 3 months

4 Left ventricular ejection fraction (LVEF) ≤40% (any measurement made within the past 24 months using echocardiography, multiple gate acquisition scan, computer tomography scanning, magnetic resonance imaging, or ventricular angiography is acceptable, provided no subsequent measurement above 40%)

5 Receiving ACEi, ARB, or ARNi (eg, Entresto® [sacubitril/valsartan])

6 Not on or on low-dose spironolactone or eplerenone, (<25 mg daily)

7 Receiving beta-blocker unless contraindicated.

Inclusion Criteria for Proceeding to the 6-month Randomised-Withdrawal Treatment Phase:

8 NK (3.5-5.0 mEq/L) on SZC and receiving spironolactone ≥25 mg daily at the end of the run-in phase.

Sex

9 Inclusion Criteria for the Females:

(a) Female participants of childbearing potential must have a negative pregnancy test (serum).

(b) Female participants must be 1 year post-menopausal, surgically sterile, or using one highly effective form of birth control (defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly). They should have been stable on their chosen method of birth control for a minimum of 4 months before entering the study and willing to remain on the birth control until 7 days after the last dose.

Informed Consent

10 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this CSP

11 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy, or severe stenotic valve disease as a primary cause of HF.

2 Current inpatient hospitalisation with unstable HF, defined as any of the following:
   (a) SBP <95 mmHg during the 6 hours prior to screening.
   (b) Intravenous diuretic therapy during the 12 hours prior to screening.
   (c) Use of intravenous inotropic drugs during the 24 hours prior to screening.
   (d) Received mechanical circulatory support during the 48 hours prior to screening.

3 Type 1 myocardial infarction (MI), unstable angina, or stroke within 12 weeks prior to enrolment

4 Coronary revascularisation (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) or valvular repair/replacement within 12 weeks prior to enrolment or planned to undergo any of these procedures

5 Implantation of a Cardiac Resynchronisation Therapy (CRT) device within 12 weeks prior to enrolment or intent to perform atrial fibrillation ablation or to implant a CRT device

6 Previous cardiac transplantation or implantation of a ventricular assistance device (VAD) or similar device, or transplantation or implantation expected after randomisation

7 Symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Subjects with atrial fibrillation controlled by medication are permitted.

8 Clinically significant bradycardia, as per investigator's judgement, or second- or third-degree heart block without a pacemaker

9 QTc(f) >550 msec

10 History of QT prolongation associated with other medications that required discontinuation of that medication

11 Congenital long QT syndrome

12 Symptomatic hypotension or systolic blood pressure (SBP) <90 mmHg on 3 consecutive measurements

13 Receiving dialysis or anticipated by the investigator to require dialysis therapy within 3 months

14 >30% decline in eGFR within the past 30 days; if laboratory results are not available, then exclude if acute kidney injury (AKI) within past 30 days based on medical history or medical records

15 Clinically significant hyponatraemia in the opinion of the investigator

16 History of gynecomastia due to spironolactone therapy requiring down-titration or discontinuation of spironolactone, or switch to a different MRA.

17 Addison's disease

18 Elevated potassium due to measurement in haemolysed sample (must repeat blood draw)

19 Any condition outside the cardiovascular (CV) and renal disease area, such as, but not limited to, malignancy with a life expectancy of less than 1 year based on investigator's clinical judgement

20 Participants with a known hypersensitivity to SZC or any of the excipients of the product.

Prior/Concomitant Therapy

21 The following potassium-related prior/concomitant therapy:

(a) Treatment with potassium-sparing diuretics other than spironolactone or eplerenone (eg, triamterene, amiloride) within 7 days prior to enrolment

(b) Potassium-binding resins such as sodium polystyrene sulfonate (SPS; eg, Kayexalate®) or calcium polystyrene sulfonate (CPS; eg, Resonium®), the cation exchange polymer, patiromer sorbitex calcium (Veltassa®), or SZC within 7 days prior to enrolment.

(c) Potassium supplements within 7 days prior to enrolment.

Prior/Concurrent Clinical Study Experience

22 Participation in another clinical study with an investigational product (IP) administered in the last month.[2]

Other Exclusions

23 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

24 Judgement by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.

25 Previous enrolment in the present study.

26 For women only - breast-feeding or planning to become pregnant during the study.

27 If the participant has evidence of Coronavirus disease 2019 (COVID-19) within 2 weeks prior to enrolment (see Appendix E), the participant cannot be enrolled in the study.

5.3 Lifestyle Considerations

No additional lifestyle restrictions are required by this study. Study sites are encouraged to instruct participants to adhere to any lifestyle restrictions that apply for similar patients not participating in a trial.

5.3.1 Meals and Dietary Restrictions

No additional dietary restrictions are required by this study. Study sites are encouraged to instruct participants to adhere to any dietary restrictions that apply for similar patients not participating in a trial.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

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,

[2] Participants vaccinated with COVID-19 vaccine whilst still under Emergency Use Utilisation will not be excluded from the study.

- Screening procedures cannot be completed within the 2-week period,
- Technical issues encountered at enrolment site visit

Patients who are rescreened should be assigned the same participant number as for the initial screening.

These subjects should have the reason for screen failure recorded in the electronic Case Report Form (eCRF).

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to or medical device(s) utilised by a study participant according to the CSP.

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 4 Investigational Products

Intervention Name	SZC	Placebo	Spironolactone
Dose Formulation/ Unit Dose Strength	White to grey crystalline powder for oral suspension in 5 g and 10 g sachets	Powder for oral suspension in a sachet	Commercially available tablet: 25 mg and 50 mg tablets
Dosage Level(s)	10 g three times daily; then titrate between 5 g every other day and 5 g daily to 15 g daily	Titrate between 5 g every other day and 5 g daily to 15 g daily	• Patients not on spironolactone at screening: 12.5 to 50 mg daily during the run-in phase (start at 12.5 mg daily and titrate to 25 mg daily at Week 2, then 50 mg daily at Week 3*). • Patients on low-dose spironolactone at screening: 25 to 50 mg daily during the run-in phase (increase to 25 mg daily at Week 1, increase to 50 mg daily at Week 2, and continue at 50 mg at Week 3*). • Patients on low-dose eplerenone at screening: switch to spironolactone

			12.5 mg daily during screening and then follow titration instructions for the low-dose spironolactone group. * Doses should be titrated as tolerated per protocol instructions. Spironolactone maximum daily dose is 50 mg.
Route of Administration	oral	oral	oral
Use	Investigational product	Placebo comparator	Background intervention
IMP and NIMP	IMP	IMP	NIMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Commercially available product
Packaging and Labelling	Study intervention will be provided in sachets packed in a box. Each sachet and box will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.	Placebo will be provided in sachets packed in a box. Each sachet and box will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.	Commercially available product

Abbreviations: IMP = investigational medicinal product; GMP = Good Manufacturing Practice; NIMP = non-IMP; SZC = sodium zirconium cyclosilicate.

6.2 Preparation/Handling/Storage/Accountability

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 Further guidance and information for the final disposition of unused study interventions will depend on local regulations in a given study country.

6.3 Measures to Minimise Bias: Randomisation and Blinding

This study begins with an open-label run-in phase, followed by a double-blind, randomised treatment period.

All participants entering the double-blind, randomised treatment period will be centrally assigned to randomised study intervention using an Interactive Response Technology/Randomisation and Trial Supply Management (IRT/RTSM). Randomisation will be stratified by the sK+ cohort determined by central laboratory at the start of the open-label phase (Day 1). Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site.

Study intervention will be dispensed at the study visits summarised in the Schedule of Activities (SoA, Table 1).

Returned study intervention should not be re-dispensed to the participants.

The IRT/RTSM will provide to the investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit.

Routines for this will be described in the IRT/RTSM user manual that will be provided to each centre.

The IRT/RTSM will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (e.g., antidote available), the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF.

The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of sachets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the eCRF.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency.

The study physician should be contacted if there are any questions regarding concomitant or prior therapy.

Table 5 Restricted Medications

Use Category	Type of Medication/Treatment	Timeline/Instructions
Prohibited	Potassium-sparing diuretics other than spironolactone and eplerenone (eg, triamterene, amiloride)	Not permitted
Restricted	Potassium binders including sodium polystyrene sulfonate (SPS), calcium polystyrene sulfonate (CPS), Patiromer Sorbitex Calcium (Veltassa®)	Only permitted to be used as rescue therapy to treat severe HK (sK+ >6.0 mEq/L) after IMP has been discontinued
	Potassium supplements or other drugs administered to raise sK+ (eg, potassium chloride)	Except if used to treat hypokalaemia (sK+ <3.5 mEq/L) according to medical judgement

Use Category	Type of Medication/Treatment	Timeline/Instructions
	Drugs with pH-dependent absorption	SZC can transiently increase gastric pH by absorbing hydrogen ions that can lead to changes in solubility and absorption kinetics for co-administrated drugs with pH-dependent bioavailability. Therefore, SZC should be administered at least 2 hours before or 2 hours after oral medications with clinically meaningful gastric pH dependent bioavailability such as azole antifungals (ketoconazole, itraconazole, and posaconazole), anti-HIV drugs (atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir, and rilpivirine), tyrosine kinase inhibitors (erlotinib, dasatinib, and nilotinib), and tacrolimus. SZC can be co-administered without spacing of dosing times with oral medications that do not exhibit pH-dependent bioavailability (LOKELMA CDS, 2022).
	Nonsteroidal anti-inflammatory drugs (NSAIDs)	Not permitted unless there is a compelling medical reason
Permitted	Daily multivitamins	Potassium content is not significant (~100 mg)
	Sodium-glucose transport protein 2 inhibitor (SGLT2i) therapy	
	Low dose acetylsalicylic acid (ASA)	

6.5.1 Rescue Medicine

Rescue therapy is defined as any therapeutic intervention considered necessary in accordance to local practice patterns to reduce sK+ in the setting of severe HK. This may include insulin/glucose, beta adrenergic agonists, sodium bicarbonate, potassium binders, as well as dialysis or other forms of renal replacement treatments given with the goal of controlling the HK. Rescue therapy should be followed by a study drug dose adjustment if appropriate and proper documentation of the event.

6.6 Dose Modification

6.6.1 Open-label Run-in Phase:

Open-label visit flow diagrams are provided for reference in Table 6.

Table 6 Dosing and Titration Schema: Open-Label Run-in Phase (4-6 Weeks[a])

Cohort 1 (Patients who are HK at study entry)	Cohort 2[b] (Patients who are NK at study entry)
Study Day 1: HK Correction Phase ❑ All patients will start SZC 10 g three times daily for up to 48 hours until sK+ 3.5-5.0 mEq/L	**Study Day 1: Spironolactone** ❑ All patients will initiate or up-titrate spironolactone. ❑ Spironolactone will be systematically up-titrated to a target dose of 50 mg daily, as tolerated per protocol instructions.
Study Day 2 or 3: sK+ Maintenance Phase ❑ Once NK, patients will begin SZC 10 g once daily. ❑ SZC will then be titrated between 5 g every other day and 5 to 15 g once daily to maintain sK+ 3.5-5.0 mEq/L per protocol instructions.	**HK Correction Phase** ❑ Patients who develop HK during the first 4 weeks of the run-in phase will begin SZC 10 g three times daily for up to 48 hours until sK+ 3.5-5.0 mEq/L. ❑ Patients who do not develop HK during the first 4 weeks of the run-in phase will be discontinued from the study.
Study Day 2 or 3: Spironolactone ❑ Once NK, patients will initiate or up-titrate spironolactone. ❑ Spironolactone will be systematically up-titrated to a target dose of 50 mg daily, as tolerated per protocol instructions.	**sK+ Maintenance Phase** ❑ Once NK, patients will begin SZC 10 g once daily. ❑ SZC will then be titrated between 5 g every other day and 5 to 15 g once daily to maintain sK+ 3.5-5.0 mEq/L per protocol instructions.

HK, hyperkalaemic; NK, normokalaemic; sK+, serum potassium; SZC, sodium zirconium cyclosilicate.
[a] Patients in either Cohort who develop HK on spironolactone 50 mg daily while receiving maximum dose SZC (15 g), but were NK on spironolactone 25 mg daily may remain in the open-label, run-in phase for up to 2 additional weeks in order to return to spironolactone 25 mg and become NK again.
[b]Patients in Cohort 2 could potentially develop hyperkalaemia at Week 2 (Visit 3), Week 3 (Visit 4), or Week 4 (Visit 5). If and when they develop hyperkalaemia, they will begin SZC. Patients in Cohort 2 who do not develop hyperkalaemia by Week 4 will be discontinued from the study.

Patients Receiving low-dose Eplerenone at Screening:

- Switch patients receiving low-dose eplerenone at screening to spironolactone 12.5 mg daily.

Spironolactone Dosing:

- During the run-in phase, spironolactone will be systematically initiated and/or up-titrated, as tolerated, based on dose at screening (e.g., no or low-dose), as well as potassium level, sCr level, and SBP as detailed in Table 7 and Table 8.
- Patients in Cohort 1 (HK at study entry) will initiate or up-titrate spironolactone when NK is achieved with SZC 10 g three times daily correction treatment (study Day 2 or 3).
- Patients in Cohort 2 (NK at study entry) will initiate or up-titrate spironolactone on Day 1. Patients who develop HK on spironolactone will start SZC 10 g three times daily for up to 48 hours and stay on their current dose of spironolactone (at the time they develop HK). Patients who do not develop HK during the first 4 weeks of the run-in phase will be discontinued from the study.
- Patients in either Cohort who develop HK on spironolactone 50 mg and maximal dose SZC (15 g), but were NK on spironolactone 25 mg daily may remain in the open-label,

run-in phase for up to 2 additional weeks in order to return to spironolactone 25 mg and become NK again.

Table 7 Spironolactone Dose Titration During the 4- to 6-Week[a], Open-label, Run-in Phase

Week #	Spironolactone Dose in Cohort 1 (HK at study entry)		Spironolactone Dose in Cohort 2[b] (NK at study entry)	
	Not on spironolactone at screening	Low-dose spironolactone or eplenerone at screening	Not on spironolactone at screening	Low-dose spironolactone or eplerenone at screening
1	When NK (Day 2 or 3): □ Initiate 12.5 mg daily	When NK (Day 2 or 3): □ Increase dose to 25 mg daily	Day 1: □ Initiate 12.5 mg daily	Day 1: □ Increase dose to 25 mg daily
2	□ Increase dose to 25 mg daily	□ Increase dose to 50 mg daily	□ Increase dose to 25 mg daily	□ Increase dose to 50 mg daily
3	□ Increase dose to 50 mg daily	□ Continue 50 mg daily	□ Increase dose to 50 mg daily	□ Continue 50 mg daily

Note: Spironolactone dose should be up-titrated as tolerated, based on potassium level, serum creatinine level, and systolic blood pressure (SBP) as detailed in Table 8.
[a] Patients in either cohort who develop HK on spironolactone 50 mg daily while receiving maximum dose SZC (15 g), but were NK on spironolactone 25 mg daily may remain in the open-label, run-in phase for up to 2 additional weeks in order to return to spironolactone 25 mg and become NK again.
[b] Patients in Cohort 2 who do not develop HK during the first 4 weeks of the run-in phase will be discontinued from the study.

SZC Dosing:

HK Correction Phase:

- Cohort 1 (HK at study enrolment): Patients 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).
- Cohort 2 (NK at study enrolment): Patients will not receive SZC until they develop HK on spironolactone. Patients who develop HK during the first 4 weeks of the run-in phase will begin SZC 10 g three times daily for up to 48 hours until sK+ 3.5-5.0 mEq/L. Patients who do not develop HK during the first 4 weeks of the run-in phase will be discontinued from the study.
- Patients in either cohort who achieve NK during the 48-hour correction phase while on SZC will proceed to the sK+ maintenance phase.
- Patients in either cohort who do not achieve NK during the 48-hour correction phase will be discontinued from the study.

sK+ Maintenance Phase:

- Patients in Cohort 1 and Cohort 2 who achieved NK during the correction phase will then receive SZC 10 g daily to maintain sK+ between 3.5-5.0 mEq/L. The SZC dose will be adjusted between 5 g every other day and 5 to 15 g daily during the remainder of the run-in phase to maintain NK as described in Table 8. SZC dosing instructions for patients with sK+ <3.5 mEq/L or ≥6.0 mEq/L are also detailed in Table 8.
- Patients in either cohort who develop HK on spironolactone 50 mg daily and maximum dose SZC (15 g daily), but were NK on spironolactone 25 mg daily may remain in the open-label, run-in phase for up to 2 additional weeks in order to return to spironolactone 25 mg and become NK again.

Table 8 SZC and Spironolactone Dosing Based on Serum Potassium (sK+), Serum Creatinine (sCr), and Systolic Blood Pressure Status During the Open-label, Run-in Phase

sK^+ Level	SZC action	Spironolactone Action	Other Actions	Follow-up Actions
sK^+ <3.0 mEq/L	❑ **Hold SZC**	❑ If receiving spironolactone 12.5 mg daily, **increase** dose to 25 mg daily ❑ If receiving spironolactone 25 mg daily, **increase** dose to 50 mg daily ❑ If receiving spironolactone 50 mg daily, **maintain** dose	❑ Confirm sK^+ by taking a 2nd measurement.	❑ **Permanently discontinue** SZC if 2nd sK^+ measurement is <3.0 mEq/L and check ECG. ❑ Treat hypokalaemia according to medical judgement based on sK+ level and ECG results.
sK^+ <3.5 mEq/L	❑ **Hold SZC**		❑ Treat hypokalaemia according to medical judgement based on sK^+ level.	❑ The decision if and when SZC can be re-started should be made after careful clinical and laboratory monitoring. ❑ **If SZC is restarted when sK^+ >3.5 mEq/L:** ❑ **Decrease** the daily dose by 5 g daily. ❑ **Permanently discontinue** SZC if patient was on 5 g every other day.
sK^+ 3.5-5.0 mEq/L	❑ **Maintain** current SZC dose			
sK^+ 5.1-5.9 mEq/L	**If receiving SZC 5 g every other day – 10 g daily**			
	❑ **Increase** SZC dose by 5 g daily	❑ **Maintain** spironolactone dose.		
	If receiving SZC 15 g daily			
	❑ **Maintain** SZC dose	❑ **Decrease** spironolactone dose by 12.5 mg daily; ❑ **Discontinue** spironolactone if on 12.5 mg every other day		
sK^+ ≥6.0 mEq/L	If receiving SZC 5 g every other day – 10 g daily: ❑ **Increase** SZC dose by 5 g daily	❑ **Temporarily hold** spironolactone.	❑ Consider checking ECG in patients with sK^+ >6.0 mEq/L, depending on the individual patient's clinical picture. ❑ Treat severe HK according to medical judgement until sK^+ <6.0 mEq/L	❑ **Restart** spironolactone at 50% of the prior dose when sK+ <6.0 mEq/L; ❑ **Discontinue** spironolactone if dose was 12.5 mg every other day.
	If receiving SZC 15 g daily: ❑ **Maintain** SZC dose			

*In Cohort 2, SZC should not be started until the study subject develops hyperkalaemia (HK correction with SZC 10 g 3 times daily x 2-3 days, then maintenance of normokalaemia starts with SZC 10 g once daily.
ECG, electrocardiogram; sK^+, serum potassium; SZC, sodium zirconium cyclosilicate.

sCr and SBP Status	Other Actions	Follow-up Actions
SBP ≤90 mmHg or clinically relevant signs/ symptoms of hypotension	❑ Review and reduce other antihypertensives that are not disease modifying (eg, calcium channel blockers, diuretics).	
>50% increase in sCr	❑ First evaluate for volume depletion, hypotension, intercurrent medical problems (including UTI, urinary obstruction), and concomitant drugs (eg, diuretics, ACEi/ARB/ARNi, NSAIDs, trimethoprim) that may increase sCr and make adjustments as appropriate for the patient.	❑ Recheck sCr in 3–5 days ❑ If sCr remains elevated, reduce spironolactone dose by 50%; discontinue therapy if current dose is 12.5 mg every other day.

Discontinuation from the study during the open-label phase:

- **Patients who are discontinued from the study during the run-in phase due to hyperkalaemia:**
  - Return spironolactone to the dose the patient was receiving (ie, no, or low-dose) prior to study enrolment. If the patient's dose was stopped during the run-in phase, do not restart it.
  - Use clinical judgement to determine if the patient should/can be continued on commercially available SZC to manage their hyperkalaemia.
  - Refer the patient to their HF treating clinician within 1 week of study discharge for follow-up and to determine their course of treatment moving forward.
- **Patients in Cohort 2 who are discontinued from the study during the run-in phase because they did not develop HK on spironolactone:**
  - The investigator should refer the patient to their cardiologist within 1 week of study discharge to determine whether or not to continue spironolactone therapy. If spironolactone is continued the patient should be monitored by their clinician as per standard of care.
- **Patients who qualify for randomisation but decide to discontinue from the study during the run-in phase and do not continue on commercially available SZC** should have their spironolactone returned to the dose they were receiving prior to study enrolment (eg, no spironolactone or <25 mg/day) and be managed as per standard of care.

6.6.2 Double-blind, Placebo-controlled, Randomised-withdrawal Phase

As stated previously, patients who maintain NK while receiving spironolactone ≥25 mg daily and SZC at the end of the open-label, run-in phase will be randomised 1:1 to receive either SZC or placebo in the 6-month, double-blind, placebo-controlled, randomised-withdrawal phase. Randomisation will be stratified according to the presence of HK/NK at study entry.

Monitoring of Serum Potassium Following Randomisation to SZC or Placebo (Discontinuation of SZC):

sK+ levels will be monitored as described in Section 8.2 to quickly identify patients who may develop HK following randomisation to placebo (discontinuation of SZC).

SZC/Placebo Dosing:

In this study phase, SZC/placebo will continue with the same dose of SZC administered at the end of the open-label, run-in phase. Dose titration instructions to maintain NK (sK+ 3.5-5.0 mEq/L) are detailed in Table 8.

If SZC/placebo is temporarily held due to sK+ 3.0 to <3.5 mEq/L, it may be restarted as detailed in Table 9.

SZC/placebo should be permanently discontinued if sK+ <3.0 mEq/L (sK+ confirmed by a second reading).

Spironolactone Dosing:

Spironolactone dose at the end of the open-label run-in phase should be maintained in the 6-month randomised-withdrawal phase. Spironolactone dose should not be increased further however, it's allowed to be decreased in patients with HK as detailed in Table 9. The dose of spironolactone may also be decreased due to other AEs such as hypotension, elevated sCr, and gynaecomastia.

Table 9 SZC/Placebo and Spironolactone Dosing Based on Serum Potassium (sK+) Levels During the 6-Month Double-blind, Placebo-controlled, Randomised-withdrawal Phase

sK^+ Level	SZC/Placebo Action	Spironolactone Action	Other Actions	Follow-up Actions
<3.0 mEq/L	❑ **Hold SZC/Placebo** ❑ Refer to 'Follow-up Actions' column	❑ **Maintain** spironolactone dose	❑ Confirm sK^+ by taking a 2nd measurement.	❑ If 2nd sK^+ measurement is <3.0 mEq/L, **permanently discontinue** SZC/Placebo **and** check ECG. ❑ Treat hypokalaemia according to medical judgement based on sK^+ level and ECG results.
<3.5 mEq/L	❑ **Hold SZC/Placebo** ❑ Refer to 'Follow-up Actions' column	❑ **Maintain** spironolactone dose	❑ Treat hypokalaemia according to medical judgement based on sK^+ level.	❑ The decision if and when SZC/Placebo can be re-started should be made after careful clinical and laboratory monitoring. ❑ **If SZC/Placebo is restarted when sK^+ >3.5 mEq/L:** ❑ **Decrease** the daily dose by 5 g daily. ❑ **Permanently discontinue** SZC/Placebo if patient was on 5 g every other day. ❑ Monitor sK^+ in 7 (±2) days if SZC/Placebo is restarted
3.5-5.0 mEq/L	❑ **Maintain** current SZC/Placebo dose	❑ **Maintain** spironolactone dose		
5.1-5.9 mEq/L	**If receiving SZC/Placebo 5 g every other day – 10 g daily** ❑ **Increase** SZC/Placebo dose by 5 g daily	❑ **Maintain** spironolactone dose.		❑ Monitor sK^+ in 7 (±2) days if SZC/placebo or spironolactone dose changed
	If receiving SZC/Placebo 15 g daily ❑ **Maintain** SZC/Placebo dose	❑ **Decrease** spironolactone dose by 12.5 mg daily; ❑ **Discontinue** spironolactone if on 12.5 mg every other day		
≥6.0 mEq/L	**If receiving SZC/Placebo 5 g every other day – 10 g daily** ❑ **Increase** SZC/Placebo dose by 5 g daily	❑ **Temporarily hold** spironolactone ❑ Refer to 'Follow-up Actions' column	❑ Consider checking ECG in patients with sK^+ >6.0 mEq/L, depending on the individual patient's clinical picture. ❑ Treat severe HK according to medical judgement until sK^+ <5.0 mEq/L ❑ Monitor sK^+ until ≤5.5 mEq/L	❑ **If 2nd occurrence, discontinue from study** ❑ **If 1st occurrence:** ❑ When sK^+ ≤5.5 mEq/L; **restart spironolactone** at **50% lower dose.** ❑ Patients on **spironolactone** 12.5 mg every other day should **discontinue** treatment permanently.
	If receiving SZC/Placebo 15 g daily ❑ **Maintain** SZC/Placebo dose			

ECG, electrocardiogram; sK^+, serum potassium; SZC, sodium zirconium cyclosilicate.

Rescue Therapy:

Patients with sK+ ≥6.0 mEq/L will be managed with rescue therapy based on the investigator's clinical judgement, employing local standard of care and monitored more intensely until local lab-K has been confirmed to be between 3.5 and 5.5 mEq/L inclusive. Rescue therapy is defined as treatments which reduce sK+, such as insulin/glucose, beta-adrenergic agonists, sodium bicarbonate, potassium binders, and dialysis or other forms of

renal replacement treatments given with the goal of controlling the HK. Rescue therapy does not include reduction in spironolactone dose or discontinuation of spironolactone therapy, nor dose reduction or discontinuation of concomitant medications that are known to elevate sK+ (including, but not limited to, ACEi, ARB, ARNi, beta-blockers, NSAID, trimethoprim). Additional study visits may occur at any time at the investigator's discretion to ensure safety and protocol adherence.

Patients with local laboratory sK+ <3.0 mEq/L will be managed with rescue therapy based on the investigator's clinical judgement, employing local standard of care should be treated according to the investigator's medical judgement using standard of care and monitored more intensely until local lab-K has been confirmed to be between 3.5 and 5.5 mEq/L inclusive. Potassium supplements may be administered at the investigator's discretion and as medically appropriate. Additional study visits may occur at any time at the investigator's discretion to ensure safety and protocol adherence.

6.7 Intervention after the End of the Study

Upon study completion, patients who will not continue on commercially available SZC after study completion, should be returned to their original spironolactone dose prior to study enrolment and managed by their physician per standard of care. In instances in which the investigator had down-titrated or stopped spironolactone, the patient should not be returned to their original dose and should be given the lowest spironolactone dose administered during the randomised-withdrawal period.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is permanently discontinued, the participant will remain in the study and will be excluded from the PPS population. See the SoA (Table 1) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

For patients discontinuing from the study during the run-in phase, please refer to Section 6.6.1, for guidance on treatment management.

Patients who discontinue the study early during the randomised phase should have their EOT visit as soon as possible after their last dose of study drug (assuming they discontinue the drug while at home and not at a study visit).

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from

the study.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed

For discontinuation pertaining to COVID-19, please see Appendix E.

7.1.1 Temporary Discontinuation

Please refer to Table 9.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Study Intervention Discontinuation visit should be conducted, as shown in the SoA (Table 1). See the SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Efforts to reach the subject should continue until the end of the study. Should the subject be unreachable at the end of the study the subject should be considered to be lost to follow up with unknown vital status at end of study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Administrative Procedures

- Study procedures and their timing are summarised in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- For management of study procedures during the COVID-19 pandemic, please see Appendix E.
- An open-label visit flowchart is provided for reference in Appendix K.

8.2 Efficacy Assessments

8.2.1 Potassium

Serum samples will be analysed locally using local laboratory to generate local lab-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 analysis of sK+ for use in analysis of applicable efficacy endpoints.

All serum samples should be examined and any overtly haemolysed samples must be redrawn.

See the laboratory manual for details on drawing, preparation, and analysis of blood samples.

8.2.2 Patient-Reported Outcomes (PROs)

PROs is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become important endpoints for regulatory and reimbursement authorities when evaluating effectiveness of treatments in clinical trials.

Patients will either complete the PRO assessments in paper or using an electronic tablet during clinic visits at the time points indicated in the SoA (Table 1). Patients will have the option to decide if they prefer to use paper or the electronic device to provide answers.

If the subject is unable to read the questionnaire (eg, is blind or illiterate), the subject will be exempted from completing the PRO questionnaires and may still participate in the study.

Each site must allocate the responsibility for the administration of the PROs to a specific site personnel and, if possible, assign a backup person to cover if that individual is absent. A key aspect of study success is to have high PRO compliance. Therefore, it is essential that site personnel follow the SoA (Table 1) and ensure that the paper PRO questionnaires are available and/or the device is charged and set up properly before the first patient comes for PRO visits (baseline [Day 1 of open-label phase], randomisation visit, and EOT visit), in order to minimise missing data.

If patients have any medical problems, they should discuss them with their doctor or research nurse separately from the PRO assessment.

The research nurse or appointed site staff must remind patients there are no right or wrong answers and that the value and relevance of PRO data is to hear directly from patients, without interpretation from health care professionals or others, how they function and feel.

The following best practice guidelines should be followed:

- The PRO questionnaires must be completed before any other study procedures are conducted, including being seen by the investigator.

- The appointed site personnel must show patients how to use the electronic PRO device (if applicable), in accordance with the instructions provided.
- To avoid bias patients must not receive help from relatives, friends, or site staff to answer or to clarify the PRO questionnaires.
- The PRO questionnaires must be completed by the patient in privacy.
- The patient should be given enough time to complete the PRO questionnaires at his or her own speed.
- On completion of the questionnaires the paper/tablet should be handed back to the designated responsible person, who should check that all questionnaires, relevant for the specific visit (Table 1), were completed. If any PRO questionnaire was not completed the site personnel must document the reason why a patient could not complete assessments in the REVPRDI module in the eCRF.

The following PROs will be used in this study: KCCQ and PGIS.

8.2.2.1 Kansas City Cardiomyopathy Questionnaire (KCCQ)

Patients with HF experience debilitating symptoms that substantially impact daily functioning, physical capacity and quality of life. For these reasons, it is important to measure the impact of new HF therapies on the HF patient's symptoms and functioning (Zannad et al. 2013).

The KCCQ instrument quantifies both the frequency of 4 cardinal HF-symptoms (fatigue, peripheral oedema, dyspnoea, and orthopnoea) and how bothersome 3 of the cardinal HF symptoms (fatigue, peripheral oedema, and dyspnoea) are to patients, as well as HF-related physical limitations, social limitations, self-efficacy, and health-related quality of life. First developed in 1996 (Green et al. 2000; Spertus et al. 2005) over the following 2 decades the experience with the KCCQ has grown in industry-sponsored and academic studies and it is now the most common disease PRO instrument collected in HF studies.

The KCCQ consists of 23 items measuring, from the patients' perspectives, their HF-related symptoms, physical limitations, social limitations, self-efficacy, and health-related quality of life over the prior 2 weeks (see Appendix F).

8.2.2.2 Patient Global Impression of Severity (PGIS)

The PGIS is a 1-item question assessing patient perception of his or her severity of HF symptoms the last 2 weeks. The item is used to enable anchor-based assessments of within-patient clinically meaningful change. Patients will choose from 6 response options, ranging from 'no symptoms' to 'very severe' (see Appendix G).

8.2.3 New York Heart Association (NYHA) Class

The investigator will evaluate NYHA class according to the NYHA Functional Classification as included in Appendix H. Assessment will be recorded in the eCRF.

8.2.4 Endpoint reporting overview

The following potential endpoints will be reported and source documents submitted for central adjudication by the Clinical Events Committee (CEC) during the randomised phase at each study visit, including any additional unscheduled visits:

- All deaths
- All HF events (hospitalisations for HF or urgent HF visits).

8.2.4.1 Classification of Death

All AEs with a fatal outcome should be recorded as SAEs and on a separate page in the eCRF; all deaths will be submitted to the CEC for adjudication. The CEC members will adjudicate and classify all deaths based on definitions described in Appendix I. The investigator will record the classification of death as CV, non-CV, or undetermined cause of death in the eCRF. Both the investigator and CEC will assess the events, but only CV deaths that occur during the randomised-withdrawal phase that are CEC-adjudicated will be included in the efficacy analysis.

8.2.4.2 Heart Failure Events

Worsening HF events (ie, hospitalisations defined as HF hospitalisations or urgent HF visits regardless of intravenous [IV] loop diuretic use) that occur during the randomised-withdrawal phase will be included in the efficacy analysis and should be recorded in the eCRF. All worsening HF events that meet SAE/AE criteria should be recorded as an SAE/AE and as potential CV endpoints. All worsening HF events will be submitted to the CEC for adjudication based on the definitions specified in Appendix I. The definition of Heart failure event is according to CDISC definition (Hicks et al. 2015) which is currently the latest version. CDISC may be updated during the course of the study.

8.2.5 Urine Analysis

Three consecutive first morning void spot urine samples will be collected at the time points indicated in the SoA (Table 1). Urinary albumin and creatinine will be measured at the central laboratory and reported, and mean urine albumin-to-creatinine ratio (UACR) will be calculated based on the measured urinary albumin and creatinine and reported.

Urine collection kits will be handed out at the visit before the visit when urine is to be collected to allow the subject to collect urine on the 3 consecutive mornings immediately preceding the visit. Hence, 3 urine samples will be collected for each time point.

In the event that a subject forgets to collect any of the 3 first morning voids, the samples can instead be collected on the consecutive 3 mornings immediately following the visit, and delivered to the study site.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.3.1 Physical Examinations

A complete physical examination will be performed at screening as indicated in the SoA (Table 1) and will include an assessment of general appearance, respiratory system, CV system (including signs of fluid overload), abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid gland, musculo-skeletal system (including spine and extremities), and neurological system.

A targeted physical examination, including oedema assessment, will be performed at the time points indicated in the SoA and will include an assessment of general appearance and the musculo-skeletal system (lower extremities), respiratory system, CV system, and abdomen.

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.

Investigators should pay special attention to clinical signs related to underlying medical conditions (including HF, renal impairment, signs of fluid overload, and diabetes). Patients can be assessed as needed throughout the study if they show signs of worsening HF or report they are feeling unwell. New or worsening abnormalities may qualify as AEs, see Section 8.4 for details.

Height will be assessed at screening using locally available tools without the subject wearing shoes, and recorded in the eCRF.

Weight will be assessed using the same scale, properly maintained and calibrated at each visit, and with the subject wearing similar amount of clothes (eg, underwear only or light indoor clothing only) at each visit.

8.3.2 Vital Signs

Vital signs will be performed at time points as specified in the SoA (Table 1).

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones).

Systolic and diastolic blood pressure will be measured by an adequately trained health care

professional. Measurements with a calibrated sphygmomanometer are preferred. If not available, another device calibrated carefully in proportion to a mercury sphygmomanometer is preferred. Use of aneroid manometers should be avoided. Appropriate cuff size must be used to ensure accurate measurement.

The disappearance of sound (Korotkov phase V) should be used for the diastolic reading. Three (3) readings separated by 2 minutes should be averaged, and the average result will be recorded in the eCRF. If the first 2 readings of systolic blood pressure (SBP) differ by more than 5 mmHg, additional readings should be obtained.

Blood pressure should be measured in either the supine or sitting position. No shift from one position to another should be made during the study. Supine or sitting posture should be adopted for at least 5 minutes before measurement. The subject should be relaxed and with the arm outstretched and supported.

Blood pressure should be measured under standardised conditions, as nearly as possible at the same time each visit, on the same arm (preferably the dominant arm), by the same personnel, and with the same apparatus.

8.3.3 Electrocardiograms (ECGs)

An ECG will be performed at screening, randomisation, end of treatment, and follow-up (as specified in the SoA [Table 1]), and according to clinical judgement in connection with severe hypokalaemia (sK+ <3.0 mEq/L), severe HK (sK+>6.0), or any symptoms or clinical events suggesting cardiac arrhythmia.

Study subjects with pacemakers:

- All ECG variables, including QT/QTc(f), should be read manually and be recorded in the eCRF.
- If not fulfilling the inclusion/exclusion criteria or fulfilling the discontinuation criteria, pacemaker patients should be managed as recommended by protocol (without exceptions).

8.3.4 Clinical Safety Laboratory Assessments

Table 10 lists the clinical safety laboratory tests to be performed and the SoA (Table 1) includes the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA.

The routine clinical chemistry and haematology will be performed at a central laboratory, with the exception of potassium and creatinine measurements performed both locally using local laboratory and at the central laboratory at each visit, and pregnancy tests performed only locally. Urinalysis (dipstick) will be analysed at the local laboratory. Samples for sK+ and

creatinine analysis using local laboratories should be collected according to sample collection and processing requirements for these parameters. Potassium and creatinine measured locally will be used for subject management and for study inclusion and will be reported in the eCRF, but samples collected at the same time and analysed at the central laboratory will be used for the main statistical analyses.

Sites are encouraged to use local laboratories that can provide potassium and creatinine results as rapidly as possible. If the site can obtain the results in a reasonable time (as determined by the investigator and the subject), the samples for the local laboratories can be drawn at the beginning of each visit, and then the patient medications titrated and/or IP dispensed before the patient leaves the clinic.

The maximum amount of time between local laboratory sample collection and obtainment of data results should be 1 day. If blood samples for local laboratory testing are taken at the study visit and the results are not known prior to the subject leaving the visit, the investigator may call the subjects or bring them back the following day for instructions regarding concomitant medication titration and IP dosing. Alternatively, if more feasible for the subject and investigator, blood samples for the local laboratory tests may be collected 1 day before study procedure in cases when the local laboratory sample analysis time is expected to be longer than the duration of the subject's clinic visit.

The results of potassium and creatinine levels performed locally using local laboratories will be provided to the investigator the same day and analysed before assessment against the inclusion criteria and randomisation. It is recommended to perform the local laboratory assessment of creatinine and potassium before other assessments, with the exception of the KCCQ questionnaire, as the local laboratory assessment is likely to trigger the most screening failures.

Additional safety samples may be collected ('unscheduled') if clinically indicated at the discretion of the investigator. The date, time of collection, and results (values, units and reference ranges) will be recorded on the appropriate eCRF. If additional safety analyses of potassium or creatinine are conducted (with or without subsequent calculation of eGFR), then local laboratories should be used to perform the analysis of the additional safety samples.

Estimated glomerular filtration rate (eGFR) will be calculated using the non-race-based chronic kidney disease epidemiology (CKD-EPI) collaboration equation formula for each time point when creatinine is analysed.

Table 10 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 CO_2)
B-Platelet count	S-Chloride (Cl-)
B-Haematocrit (Hct)	S-Glucose
	S-Creatinine
	S-Blood Urea Nitrogen (BUN)
	Urea (BUN)/Creatinine Ratio
	Estimated glomerular filtration rate (eGFR) using the non-race-based CKD-EPI formula
Urinalysis (dipstick)	Anion gap
U-Hb/Erythrocytes/Blood	S-Albumin
U-Protein/Albumin	S-Total Protein
U-Glucose	S-Calcium (Ca++)
	S-Magnesium (Mg++)
	S-Phosphate (PO_4)
	S-Bilirubin, total
	S-Alkaline phosphatase (ALP)
	S-Alanine amino transferase (ALT)
	S-Aspartate amino transferase (AST)

8.4 Adverse Events and Serious Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

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

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

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

AEs will be collected from the start of the open-label run-in phase, throughout the treatment period, and during the follow-up period.

SAEs will be recorded from the time of signing of ICF.

If the investigator becomes aware of an SAE with a suspected causal relationship to the

investigational medicinal product that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.4.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the follow-up visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum AE intensity (mild, moderate, severe)
- Whether the AE is serious or not
- Investigator causality rating against the study intervention (yes or no)
- Action taken with regard to IP
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication.

8.4.3 Causality Collection

The investigator will assess causal relationship between IP and each AE, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may

have been caused by the IP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.4.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.4.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol (CSP) mandated laboratory tests and vital signs will be summarised in the Clinical Study Report (CSR).

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

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the screening assessment will be reported as an AE unless unequivocally related to the disease under study.

8.4.6 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the

study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

For further guidance on the definition of an SAE, see Appendix B.

8.4.7 Pregnancy

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

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

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

8.4.7.1 Maternal Exposure

Women of childbearing potential are not allowed to be included in this study unless using acceptable methods of contraception (see Section 5.1). Should a pregnancy still occur, the IP should be discontinued immediately, and the pregnancy reported to AstraZeneca

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) should be followed up and documented even if the participant

was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.7) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

8.4.7.2 Paternal Exposure

There is no restriction on fathering children or donating sperm during the study.

8.4.8 Medication Error, Drug Abuse, and Drug Misuse

8.4.8.1 Timelines

If a medication error, drug abuse, **or** drug misuse occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error, drug abuse, or misuse (see Sections 8.4.8.2, 8.4.8.3, and 8.4.8.4) and within 30 days for all other events.

The definition of a medication error can be found in Appendix B.

8.4.8.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix B 4.

8.4.8.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.4.8.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.5 Overdose

During the HK correction phase any SZC dose greater than 30 g within 1 day, or continuation of the correction dose (10 g three times daily) for more than 72 hours will be considered an overdose.

During the maintenance period, a dose higher than 15 g per day will be considered an overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for overdoses associated with an SAE (see Section 8.4.6) and within 30 days for all other overdoses.

8.6 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples, see Appendix C.

8.6.1 Pharmacokinetics

PK parameters are not evaluated in this study.

8.6.2 Immunogenicity Assessments

Immunogenicity will not be assessed in this study.

8.6.3 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.7 Human Biological Sample Biomarkers

Blood samples for the following CV and renal biomarkers will be collected to evaluate how they are affected by the addition of SZC and optimal doses of spironolactone:

- Plasma/serum: NT-pro-BNP, serum aldosterone*

  * Patients need to be either standing or seated upright for at least 2 hours before sample collection for aldosterone.

In addition, blood and urine samples will be collected and analysis may be performed on additional biomarkers thought to play a role in HF, CKD, or potassium homeostasis to evaluate their association with observed clinical responses to SZC or the effect of SZC on the biomarkers. Samples may also be used for research to develop methods, assays, prognostics and/or companion diagnostics related to SZC, HF, CKD, HK, and/or other diseases.

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

8.8 Optional Genomics Initiative Sample

Approximately 6 mL blood sample for deoxyribonucleic acid (DNA) isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the subject. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix D for information regarding Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendix or in the Laboratory Manual.

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples may be stored for a maximum of 15 years or as per local regulations from the date of the Last Subject's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organisations working with the DNA.

For storage and destruction of genetic samples, see Appendix D.

8.9 Health Economics

Health economics parameters are not applicable in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Patients assigned to the SZC are expected to have a larger likelihood of being NK, receiving spironolactone ≥25 mg daily and not having received rescue therapy for HK compared to patients receiving placebo.

The primary hypothesis tested is that of no difference between SZC and Placebo

H0: OR = 1

vs

H1: OR ≠ 1

Assuming that the OR is constant over the maintenance period from month 1 to month 6.

9.2 Sample Size Determination

Sample size determination is based on the primary objective, ie,

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).

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 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 patients to be randomised. Clinical data suggests that the rate of death in this patient population is approximately 10 deaths per 100 person-years. With 79 patient-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 approximately166 randomised patients to ensure n=158 in the main sensitivity analysis for the primary endpoint. Patients will be entered into the open-label phase until the required number of randomised patients is reached, at which point the recruitment will stop. Tentatively, it is expected that approximately 400 patients will enter the open label phase in order to achieve the goal of 166 randomised patients.

Under the original primary endpoint which was to be evaluated at EOT, results from the DIAMOND study suggest that a similar effect size between SZC and placebo should be observed if the duration of the double-blind randomised phase is reduced from 8 months to 6 months due to the early separation of Kaplan-Meier curves between placebo and active treatment. In the DIAMOND study, at 25 and 33 weeks, the KM failure estimate for first HK event (serum K+ > 5.5 mEq/L) are approximately 0.18 and 0.22 in the placebo arm compared to 0.12 and 0.155 in the active arm. If it's assumed a probability of response of 0.75 in the SZC group and 0.56 in the placebo group then a two group chi-square test with a 5% two-sided significance level and 124 patients per treatment group will have a power of 87.93%. If it's assumed a probability of response of 0.75 in the SZC group and 0.58 in the placebo group then a two group chi-square test with a 5% two-sided significance level and 124 patients per treatment group will have a power of 81.34%. These assumed effect sizes for the original primary endpoint will be retained for the revised primary endpoint which will evaluate responses observed from weeks 5-25.

9.3 Populations for Analyses

Table 11 Populations for Analysis

Population/Analysis Set	Description	Treatment Assignment
Screened Set	All patients who were screened for inclusion into the study.	Not applicable
Safety Set Open (SSO)	All patients who enter the open-label phase and receive at least one dose of SZC.	Not applicable
Safety Set Randomised (SSR)	All randomised patients who received at least 1 dose of either SZC or placebo. Safety analyses will be analysed using the SSO and SSR populations.	According to treatment actually received

Population/Analysis Set	Description	Treatment Assignment
Full Analysis Set (FAS)	All randomised patients, irrespective of treatment and any protocol deviations, who have 1 or more post randomisation central laboratory sK+ measurements available. The FAS will be used as the primary population for the primary, secondary, and exploratory efficacy endpoints.	According to randomised treatment
Per Protocol Set (PPS)	FAS patients without any important protocol deviations leading to exclusion from the PPS.	According to randomised treatment

The number of patients in each analysis set, and the number excluded and associated reasons will be summarised by treatment group and overall. In addition, the following periods will be defined for the purpose of reporting.

Table 12 Analysis Periods

Period	Description
Screening	Screening refers to the period from informed consent to the first dose of open-label study intervention or screen failure.
Open-label	The open-label period refers to the period from the date of first dose of open-label study intervention to the earliest date of randomisation, withdrawal of consent, last contact with the patient, or death.
Randomised-withdrawal	The randomised-withdrawal period refers to the period from the date of randomisation to the earliest date of last assessment during the follow-up period, withdrawal of consent, last contact with the patient, or death.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalised prior to the unblinding and locking of the clinical database and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

Intercurrent events, such as death, are handled as outlined within each section for the primary and secondary endpoints below. Screening baseline is defined as the last available assessment prior to the date of first dose of open-label treatment. Measurements made on the same date as the first dose of open-label treatment will not be considered unless the measurement is confirmed to be pre-dose by the times the measurement and dose are recorded. Randomisation baseline is defined as the last available assessment prior to or on the date of the randomisation visit for all patients, unless otherwise specified.

Continuous data will be summarised by treatment group using the number of observations available (n), mean, standard deviation (SD), minimum, quartile 1, median, quartile 3, and maximum. Categorical data will be summarised by treatment group using the count of patients and percentage.

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

The open-label phase cohort (Cohort 1 or 2) is used as a stratification factor for this study. In the event of a difference between the stratified group and the collected eCRF value at randomisation, the stratified group used to randomise the patient will be included in statistical modelling, unless otherwise specified.

9.4.2 COVID-19 Considerations

It is anticipated that additional sensitivity and supplementary analyses will be required to determine the impact of the COVID-19 pandemic on this trial and its endpoints. Planned sensitivity analyses will distinguish between pandemic and non-pandemic-related intercurrent events in terms of the approach taken for sensitivity analyses. For instance, in the pre-planned tipping point sensitivity analysis for the primary endpoint, 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. (See Section E 4, Modified Visits, in Appendix E.)

9.4.3 Efficacy

All primary and secondary efficacy endpoints and exploratory endpoints will be analysed using the FAS.

9.4.3.1 Primary Endpoint

Per visit, response is 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 patients 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.

- The treatment effect concerns the overall Odds Ratio and will be analysed using a GEE model, with an estimate of response for each time point and fixed treatment effect, using a binomial distribution with exchangeable correlation matrix and tested using a two-sided alpha = 0.05. The complete model, including the complete list of covariate adjustments will be described in the SAP. Patients who are lost to follow-up, *including due to death,* prior to any specific assessment visits will be treated as non-response for those assessment visits for the purpose of the primary analysis. The common odds ratio will be derived together with two-sided 95% confidence intervals. Sensitivity analyses will be prespecified in full in the SAP and will determine the impact of treating deaths and patients lost to follow-up as a non-response. As a minimum, these will use the PPS population and will treat deaths as a missing observation. 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.

9.4.3.2 Secondary Endpoints

Statistical analyses of the secondary endpoints will include strong controls for multiplicity. The details of this approach will be detailed in the SAP.

1. Per visit, response is 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

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 patients 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.

The treatment effect concerns the overall Odds Ratio and will be analysed using a GEE model, with an estimate of response for each time point and fixed treatment effect, using a binomial distribution with exchangeable correlation matrix. Patients who are lost to follow-up, *including due to death,* prior to any specific assessment visits will be treated as non-response for those assessment visits. The common odds ratio will be derived together with two-sided 95% confidence intervals.

2. Per visit, response is defined by

- Being on spironolactone ≥25 mg daily

Response means bullet point holds. Non-response indicates bullet point does not hold.

Additionally, for each assessment visit,
non-response is indicated for patients 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.

The treatment effect concerns the overall Odds Ratio and will be analysed using a GEE model, with an estimate of response for each time point and fixed treatment effect, using a binomial distribution with exchangeable correlation matrix. Patients who are lost to follow-up, *including due to death,* prior to any specific assessment visits will be treated as non-response for those assessment visits. The common odds ratio will be derived together with two-sided 95% confidence intervals.

3. *Time to first HK episode with HK defined as sK+ >5.0 mEq/L as assessed by central laboratory.* SZC compared with placebo using HR and will be analysed using a cause-specific proportional hazard model with death treated as a competing risk, randomised treatment as an independent factor and open-label phase cohort as a stratification factor. The hazard ratio and two-sided 95% confidence interval will be presented. Graphically, the treatment difference will be displayed using cumulative incidence competing risk curves.
4. *Time to first instance of decrease or discontinuation of spironolactone dose due to HK* SZC compared with placebo using HR and will be analysed using a cause-specific proportional hazard model with death treated as a competing risk, randomised treatment as an independent factor, and open-label phase cohort as a stratification factor. The hazard ratio and two-sided 95% confidence interval will be presented. Graphically, the treatment difference will be displayed using cumulative incidence function competing risk curves.
5. *Change in KCCQ-CSS at EOT visit (approximately 6 months post-randomisation) from randomisation.* SZC compared with placebo using difference in mean and will be analysed with repeated measures analysis of covariance (ANCOVA) models with fixed terms for treatment, KCCQ-CSS at randomisation, open-label phase cohort, visit, and treatment by visit interaction.

9.4.3.3 Exploratory Endpoints

All exploratory endpoints will be analysed using the FAS.

Heart Failure

- Key Cardiovascular Exploratory Endpoint:
  - Time to first event of 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 phase:
    - CV Death
    - Worsening HF (HF hospitalisations or urgent HF visits regardless of IV loop diuretic use)
- Other CV Exploratory Endpoints/pre-specified analyses:

- Total events of CV death and worsening HF (as defined above) during the randomised phase
- Mean daily furosemide equivalent loop diuretic dose over time in the SZC group compared with the placebo group during the randomised phase
- Change in NT-proBNP at the EOT visit compared to randomisation in the SZC and placebo arms.

Patient-Reported Outcomes

- 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 randomisation.

- To explore the relationship between aldosterone levels and PGIC and KCCQ scores, with particular attention to intrapatient consistency, between the SZC and placebo arms at the EOT visit compared to randomisation.

Renal

- Key Renal Exploratory Endpoint:
  - Change in mean UACR* in the SZC group compared with placebo group at:
    - Screening compared to EOT
    - Randomisation compared to EOT
    - Screening compared to randomisation
- Other Renal Exploratory Endpoints/pre-specified analyses:
  - Change in mean UACR in SZC group compared with placebo group (as above), analysed by UACR strata at screening (<30 mg/g; 31–300 mg/g; >300 mg/g)
  - Absolute change in eGFR from randomisation to EOT in SZC group compared with placebo group
  - Change in eGFR slope in SZC group compared with placebo group (acute [screening to randomisation], chronic [randomisation to EOT], and total [screening to EOT] eGFR slope)
  - Natriuretic response over time in SZC vs placebo groups:
    - Fractional excretion of Na+ (blood to urine [same urine sample as for UACR; must collect urine sample prior to loop diuretic dose])
    - Monitor at screening; at randomisation; 1-month post-randomisation; EOT

* UACR measured as the mean of 3 consecutive 1st morning spot urine collections.

Other Exploratory Endpoints:

- Adherence to study drug (descriptive)
- SZC/placebo dose assigned at each visit during the study (eg, 5 g every other day; 5, 10, 15 g daily)
- Spironolactone dose assigned at each visit during the study in the SZC and placebo arms (eg, 0 mg/day; 12.5 mg/day or 25 mg every other day; 25 mg/day; 50 mg/day)

HK-related endpoints:

- Time to first instance of use of rescue therapy for HK during the randomised-withdrawal phase
- # of HK episodes per treatment group during the randomised-withdrawal phase
- % of patients per treatment group with a sK+ value in the following ranges during the 6-month randomised phase: sK+ 5.1-5.4 mEq/L; 5.5-5.9 mEq/L; 6.0-6.4 mEq/L; ≥6.5 mEq/L
- # of emergency department visits for HK in the SZC and placebo arms
- # of hospitalisations with diagnosis code for HK in the SZC and placebo arms.

Open-label Run-in Phase Descriptive Analyses:

- % of patients that are NK and receiving spironolactone ≥25 mg daily at the end of the open-label run-in phase (eg, % of patients receiving 25 mg, % receiving 50 mg)
- % of patients discontinued from study during the open-label run-in phase due to reasons other than HK:
  - % of patients with worsened renal function
  - % of patients with hypotension
  - % other

Subgroup analyses:

- Demographics (country, comorbid conditions, NTproBNP, etc)
- Patients with HK vs NK at screening (analysis for both study phases)
- Patients with/without diabetes
- Patients on sodium-glucose transport protein 2 inhibitor (SGLT2i)
- Patient on no vs low-dose MRA at screening (analysis for both phases)
- Patients on ACEi/ARB/ARNi; dosing/persistence throughout study in both treatment arms
- Patients enrolled during hospitalisation
- Patients with recent hospitalisation

- Patients who begin the double-blind intervention period receiving 5g every other day, 5g daily, or 10g daily.

Genetic Research

- To collect and store samples of plasma and serum for future exploratory biomarker and (optional) genetic research. Results to be reported outside of the CSR.

9.4.4 Safety

Safety will be assessed in terms of AEs, SAEs, AEs leading to treatment discontinuation, laboratory data, vital signs, ECG, and physical examinations during both the run-in and randomised-withdrawal study phases. These assessments will be collected for all patients.

Appropriate summaries of these data will be presented by treatment group. AEs will be classified using the MedDRA system of nomenclature system organ class (SOC) and preferred term (PT).

A treatment-emergent AE (TEAE) will be defined as an AE with the start date on or after the first dose date and up to (and including) 14 days after the last dose date. Similarly, the number of patients experiencing SAEs, AEs that led to withdrawal, AEs that led to death, and treatment-related AEs, and number of such events, will be summarised by treatment group.

An overview of oedema-related AEs and instances of sK+ <3.5 will be presented.

The identified risk of hypokalaemia is defined by laboratory values and not by specific MedDRA terms.

All AE data will be listed for all patients. In addition, SAEs and AEs that led to withdrawal or death, and treatment-related AEs will be listed.

Clinical safety laboratory assessments (including sK+ and sCr) will be summarised and listed. Shift tables will be provided for select tests, where shift from screening to the worst value within each part of the study and overall will be summarised. Laboratory data outside the reference ranges will be indicated in all listings.

All safety analyses will be performed on the Safety Sets. In general, safety assessments will be reported descriptively by treatment group and separately for the open-label and randomised-withdrawal phases. Full details on safety analyses will be provided in the SAP.

9.5 Interim Analyses

No interim analysis is planned for this study.

9.6 Independent Data Monitoring Committee

An iDMC that is independent of the sponsor will be utilised for this study. Appendix A, Section A 5, provides more details on the rationale for and the remit of the committee.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organisation (CRO) but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

A Steering Committee consisting of members independent of AstraZeneca has been established for the SZC development programme in HF. See the Steering Committee member contracts and/or charter for details. The Steering Committee designed significant aspects of this study protocol.

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with the Patient Safety function at AstraZeneca. Issues identified will be addressed, eg, by amending the CSP and letters to Investigators.

A data monitoring committee will be established to review emerging safety data at predefined intervals. The committee will include member(s) independent of the sponsor. See the independent data monitoring committee (iDMC) charter for details on the scope and membership. The iDMC may request unblinded data if needed to assess any emerging safety concerns. The iDMC can recommend the study to be amended if necessary for the protection of the subjects participating in the trial.

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and

monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan.
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).
- Study monitors will perform ongoing source data verification as per the Monitoring Plan to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Trial Master File and Investigator Site File. All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants. The study start date for this study will be December 2020.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of adverse events

An adverse event (AE) is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Life threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity rating scale:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process-related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of Investigational Medicinal Product (IMP) or AstraZeneca Non-IMP (NIMP) for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both

if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for donated biological samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A pathogens are eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900:

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN 3373 and IATA 650.

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the CSP and provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection
  - Healthy Volunteers and paediatric patient samples will not be collected for the Genomics Initiative.

Withdrawal of Consent for Genetic Research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the protocol.

Collection of Samples for Genetic Research

- The blood sample for this genetic research will be obtained from the participants at study entry. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an adverse event (AE). If for any reason the sample is not drawn at study entry, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

- The informed consent for the optional genomics initiative sample will be obtained at Visit 1.
- The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The Principal investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data Management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.
- Genetic data will be reported separately from the clinical study report.

Appendix E Management of Study Procedures During the COVID-19 Pandemic

E 1 Introduction

Safeguarding the health and wellbeing of our participants and ensuring the continued supply of our medicines to participants remains of paramount importance for AstraZeneca through the ongoing COVID-19 outbreak.

Management described in this appendix related to study visits and SARS-COV-2 testing should be implemented only during the COVID-19 pandemic and will apply until further notice, as communicated by the sponsor. Changes to study visits due to participants not wishing to or being unable to visit sites should only be implemented if allowable by local/regional guidelines and following agreement from the sponsor.

Changes that may affect the study participants' participation in the study should be communicated to the participant. It is the Principal Investigator's responsibility to inform the study participants of any change in the study conduct that may be implemented. The participants' assent and/or consent to any such change in study conduct should also be documented.

E 2 Risk Assessment for COVID-19 Pandemic

SZC is a potassium binder acting in the gastrointestinal tract and is not absorbed. No additional risk from COVID-19 is expected due to SZC. However, the risk of exposure to infected people cannot be completely excluded during study participation as the participants may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff).

Measures to mitigate the risks associated with COVID-19

- This study will start or resume enrolment only when the sponsor deems it is appropriate. In addition, the enrolment at a site level will only start or resume when local regulations and guidelines allow.
- National laws and local recommendations regarding the pandemic will be strictly adhered to.
- Site is encouraged to contact the participant within 1 day prior to a study visit, see next section. Study visits may be modified where appropriate and permitted by local practice, see Section E 4.

E 3 COVID-19 Assessment

In order to limit potential infection at the site, the site is encouraged to contact the participant within one day prior to any study visit to ask for signs and symptoms related to COVID-19.

COVID-19 symptoms include, but are not limited to: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhoea.

Recommended questions to determine risk of COVID-19 are included below for information:

1 Have you experienced unexplained fever, cough, shortness of breath, chills, muscle pain, headache, sore throat, and/or new loss of taste or smell within the past 14 days?
2 Have you been in contact with anyone who is sick or with symptoms in the last 14 days?
3 Note to site: probe on the same symptoms as Q1
4 Have you been exposed to someone diagnosed with COVID-19 in the last 14 days?
5 Have you been practicing social distancing over the last 14 days?
6 Note to site: please refer to region/city/country regulations
7 Have you travelled in the last 14 days, if so where?
8 Note to site: recent travel including to countries/regions with Centers for Disease Control and Prevention (CDC) Level 2 or higher travel warning or equivalent or known COVID-19 hot spots.
9 Have you been in isolation or quarantine for any reason in the past 14 days?
10 Have you been diagnosed with COVID-19 at any time, if so where and when?

The participant is also encouraged to contact the study site in case he/she develops any symptoms of or has a confirmed COVID-19 diagnosis.

COVID-19 prior to enrolment

It is important that participants with possible ongoing or not completely resolved COVID-19 infection are not to be enrolled in the study. If the participant has evidence of COVID-19 within 2 weeks prior to enrolment (eg, a positive COVID-19 test or a clinical risk that has not been satisfactorily excluded), the participant cannot be enrolled and will be treated according to standard of care.

Suspected COVID-19 after enrolment

Participant is severely ill or hospitalised.

If the participant becomes symptomatic after enrolment, and has suspected COVID-19 (regardless of any SARS-Cov-2 test results that may be available), and is severely ill and/or hospitalised the participant will permanently discontinue study intervention.

If possible, the participant is encouraged to attend the study visits according to schedule even if off treatment. Visits may be modified per guidance in Section E 4 and per local regulations and guidelines related to COVID-19.

Participant is NOT severely ill or hospitalised.

If the participant becomes symptomatic after enrolment, and has suspected COVID-19 (regardless of whether any SARS-Cov-2 test results are available or not), and is NOT severely ill and/or hospitalised the investigator should determine if continuation of treatment with IP is in the best interest of the patient.

Regardless if IP is continued or not, the participant is encouraged to attend the study visits according to schedule. Visits may be modified per guidance in Section E 4 and per local regulations and guidelines related to COVID-19.

E 4 Modified Visits

As a general rule, the sponsor's expectation is that as long as conditions permit, the participant should remain in the study and complete visits as per the schedule. Of note, when directly interacting with a participant within the boundaries set by this guidance document (eg, study visit of any kind) it is expected and assumed by the sponsor that it is done in accordance with 'social distancing' and protection requirements as set by local orders to manage the COVID-19 pandemic. The specifics of such conduct are not part of the scope of this document.

Visits may be modified if needed due to the COVID-19 pandemic, if an on-site visit is not possible due to participants not wishing to or being unable to visit sites. Modified visits can only replace a site visit if allowed by local/regional guidelines and regulations. Further, modified visits should also be agreed with the sponsor.

The sponsor should be notified of any deviation from the regular scheduled visits and planned study procedures, and of the alternative plan the site will implement. Any deviation from the protocol should be documented in the participant file with a comment explaining the relation to COVID-19. A modified visit may for example be a home visit. Regardless of the modified visit approach, every effort should be made to complete the full scope of the study visit activities and procedures (see Schedule of Activities [SoA], Table 1). If this is not possible, the minimum safety measurements should always include sK+ measurements and, where indicated, an ECG, in addition to collection of adverse events and concomitant medication.

If an in-person visit with the participant is not possible, the site may consider having a telemedicine visit. The term telemedicine visit refers to remote contact with the participants using telecommunications technology such as phone calls, virtual or video visits, and mobile health devices. Having a telemedicine contact with the participant will allow adverse events, concomitant medication and potentially review of the dosing card and diary to be reported and documented. At the earliest possibility, the minimum safety measurements including sK+ measurements and, where indicated, an ECG, must be done.

Appendix F Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KC Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	❑	❑	❑	❑	❑	❑
Showering/Bathing	❑	❑	❑	❑	❑	❑
Walking 1 block on level ground	❑	❑	❑	❑	❑	❑
Doing yardwork, housework or carrying groceries	❑	❑	❑	❑	❑	❑
Climbing a flight of stairs without stopping	❑	❑	❑	❑	❑	❑
Hurrying or jogging (as if to catch a bus)	❑	❑	❑	❑	❑	❑

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
❑	❑	❑	❑	❑	❑

Original US English

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
❑	❑	❑	❑	❑	❑

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
❑	❑	❑	❑	❑	❑

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑	❑	❑

Original US English

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
❑	❑	❑	❑	❑	❑

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
❑	❑	❑	❑	❑

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
❑	❑	❑	❑	❑

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
❑	❑	❑	❑	❑

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
❑	❑	❑	❑	❑

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
❑	❑	❑	❑	❑

Original US English

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
❑	❑	❑	❑	❑

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	❑	❑	❑	❑	❑	❑
Working or doing household chores	❑	❑	❑	❑	❑	❑
Visiting family or friends out of your home	❑	❑	❑	❑	❑	❑
Intimate relationships with loved ones	❑	❑	❑	❑	❑	❑

Original US English

Appendix G Patient Global Impression of Severity for Heart Failure Symptoms

Overall, how would you rate the severity of your heart failure symptoms over the past 2 weeks?

- ☐ No symptoms
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

Appendix H New York Heart Association (NYHA) Functional Classification

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Appendix I Endpoint Definitions

All cardiovascular endpoint definitions are modifications based on the draft Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials for CDISC (Hicks et al. 2015).

I 1 Classification of Death

Cardiovascular Death

Cardiovascular death includes the following categories:

1 **Death due to Acute Myocardial Infarction (MI):** refers to a death within 30 days after a myocardial infarction (MI) related to consequences seen immediately after the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or refractory arrhythmia. If these events occur after a "break" (eg, a CHF and arrhythmia free period), they should be designated by the immediate cause. The acute MI should be verified by the diagnostic criteria outlined for acute MI (including autopsy findings showing recent MI or recent coronary thrombus) and there should be no conclusive evidence of another cause of death.

Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood should be considered death due to acute myocardial infarction.

Death resulting from a procedure to treat myocardial ischemia or to treat a complication resulting from myocardial infarction should also be considered death due to acute MI.

If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence.

Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause.

2 **Sudden Cardiac Death:** refers to death that occurs unexpectedly and includes the following deaths:

a. Death witnessed and instantaneous without new or worsening symptoms
b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms

c. Death witnessed and attributed to an identified arrhythmia (eg, captured on an electrocardiographic (ECG) recording or witnessed on a monitor by either a medic or paramedic, or unwitnessed but found on implantable cardioverter-defibrillator review)

d. Death after unsuccessful resuscitation from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac etiology

e. Death >24 hours after a patient has been successfully resuscitated from cardiac arrest and without identification of a non-cardiovascular etiology

f. Unwitnessed death in a subject seen alive and clinically stable ≤24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available.

3 **Death due to Heart Failure or Cardiogenic Shock:** refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure not in the context of an acute MI and without evidence of another cause of death. New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:

a. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure.

b. Heart failure symptoms or signs requiring continuous intravenous drug therapy or oxygen administration

c. Confinement to bed predominantly due to heart failure symptoms

d. Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

e. Cardiogenic shock not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.

   Cardiogenic shock is defined as systolic blood pressure (SBP) <90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

   - Cool, clammy skin or
   - Oliguria (urine output <30 mL/hour) or
   - Altered sensorium or
   - Cardiac index <2.2 L/min/m^2

Cardiogenic shock can also be defined as SBP ≥90 mm Hg as a result of positive inotropic or vasopressor agents alone and/or with mechanical support in less than 1 hour.

This category will include sudden death occurring during an admission for worsening heart failure.

4 **Death due to Stroke:** refers to cerebrovascular event the sequelae of which lead to death, generally within 30 days. The cerebrovascular event should be verified by the diagnostic criteria outlined for cerebrovascular events (including autopsy findings) and there should be no conclusive evidence of another cause of death.

5 **Death due to Cardiovascular Procedures:** refers to death caused by the immediate complications of a cardiac procedure.

6 **Death due to Cardiovascular Haemorrhage:** refers to death related to haemorrhage such as a non-stroke intracranial haemorrhage, non-procedural or non-traumatic vascular rupture (eg, aortic aneurysm), or haemorrhage causing cardiac tamponade

7 **Death due to Other Cardiovascular Causes:** refers to a CV death not included in the above categories but with a specific, known cause (eg, pulmonary embolism or peripheral arteria disease).

Non-Cardiovascular Death

Non-cardiovascular death is defined as any death not covered by cardiovascular death and falling into one of the following categories:

- Pulmonary failure
- Renal*
- Gastrointestinal causes
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Inflammatory (eg, Systemic Inflammatory Response Syndrome (SIRS) / Immune (including autoimmune) (may include anaphylaxis from environmental (eg, food) allergies)
- Haemorrhage that is neither CV bleeding or stroke
- Non-CV procedure or surgery
- Trauma
- Suicide
- Non-prescription drug reaction or overdose

- Prescription drug reaction or overdose
- Neurological (non-cardiovascular)
- Malignancy
- Other, please specify.

*Renal death is defined as death due to ESRD but dialysis treatment was deliberately withheld (dialysis was not started or discontinued) for any reason, eg, patient refuses dialysis, treating physician considers the dialysis futile, or dialysis is not available. If death is related to other causes than ESRD, the death will NOT be adjudicated as renal cause of death. Renal death will be classified as a non-CV death.

Undetermined Cause of Death

Undetermined Cause of Death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (eg, the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, most deaths should be classifiable as CV or non-CV, and the use of this category of death, therefore, should be discouraged and should apply to few patients in well-run clinical trials.

I 2 Hospitalization for Heart Failure

A Heart Failure Hospitalization is defined as an event that meets ALL of the following criteria:

1 The patient is admitted to the hospital with a primary diagnosis of HF

2 The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)

3 The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following:

   a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
   b. Decreased exercise tolerance
   c. Fatigue
   d. Other symptoms of worsened end-organ perfusion or volume overload (as determined by the medical judgement of the investigator)

4 The patient has objective evidence of new or worsening HF, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion, including:

a. Physical examination findings considered to be due to heart failure, including new or worsened:
   i. Peripheral edema
   ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
   iii. Pulmonary rales/crackles/crepitations
   iv. Increased jugular venous pressure and/or hepatojugular reflux
   v. S3 gallop
   vi. Clinically significant or rapid weight gain thought to be related to fluid retention
b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
   i. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP >500 pg/mL or NT-proBNP >2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above screening baseline.
   ii. Radiological evidence of pulmonary congestion
   iii. Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' >15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TVI))

   OR

   iv. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mmHg, central venous pressure ≥12 mmHg, or a cardiac index <2.2 L/min/m^2

Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events.

5 The patient receives initiation or intensification of treatment specifically for HF, including at least ONE of the following:
   a. Augmentation in oral diuretic therapy

b. Intravenous diuretic or vasoactive agent (eg, inotrope, vasopressor, or vasodilator)
c. Mechanical or surgical intervention, including:
    i. Mechanical circulatory support (eg, intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)
    ii. Mechanical fluid removal (eg, ultrafiltration, hemofiltration, dialysis).

An Urgent Heart Failure Visit is defined as an event that meets all of the following:

1 The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization.
2 All signs and symptoms for HF hospitalization (ie, 3) symptoms, 4) physical examination findings/laboratory evidence of new or worsening HF, as indicated above).
3 The patient receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.

Appendix J Abbreviations

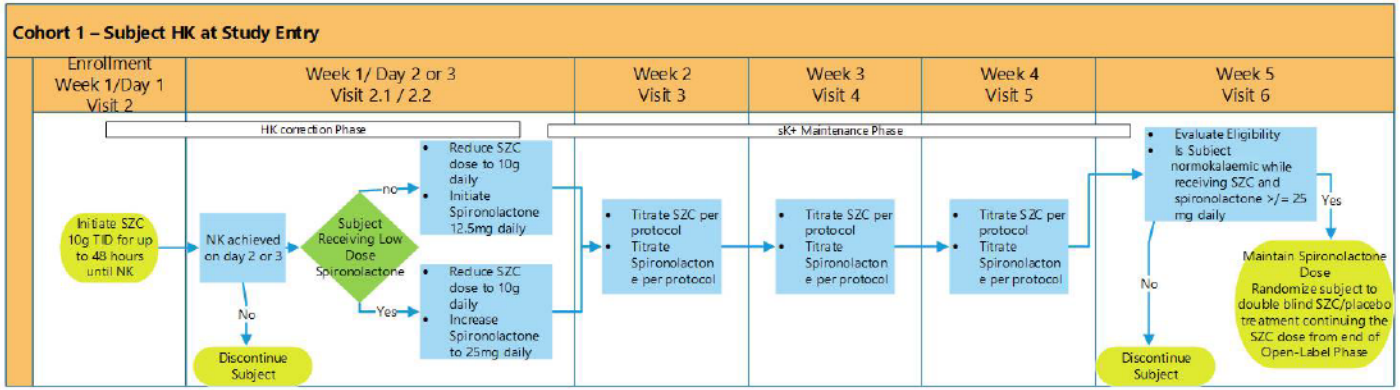
Abbreviation	Explanation
ACCF	American College of Cardiology Foundation
ACEi	angiotensin-converting enzyme inhibitor
ADR	adverse drug reaction
AE	adverse event
AHA	American Heart Association
AKI	acute kidney injury
ANCOVA	analysis of covariance
ARB	angiotensin II receptor blocker
ARNi	angiotensin receptor-Neprilysin inhibitor
BNP	B-type natriuretic peptide
CABG	coronary artery bypass grafting
CEC	Clinical Events Committee
CKD	chronic kidney disease
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CPS	calcium polystyrene sulfonate
CRO	Contract Research Organisation
CRT	Cardiac Resynchronisation Therapy
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTIS	Clinical Trial Information System
CV	cardiovascular
DES	Data Entry Site
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
ESC	European Society of Cardiology
FAS	Full Analysis Set
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation

Abbreviation	Explanation
GMP	Good Manufacturing Practice
GRAD	Global retention and Disposal
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HK	hyperkalaemia or hyperkalaemic
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
iDMC	independent data monitoring committee
IMP/NIMP	Investigational Medicinal Product/Non-IMP
IP	investigational product
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRT/RTSM	Interactive Response Technology/Randomisation and Trial Supply Management
IV	intravenous
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire Clinical Summary Score
KCCQ-OSS	Kansas City Cardiomyopathy Questionnaire Overall Symptom Score
KCCQ-TSS	Kansas City Cardiomyopathy Questionnaire Total Symptom Score
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRA	mineralocorticoid receptor antagonist
NK	normokalaemia or normokalaemic
NSAID	nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PGIS	Patient Global Impression of Severity
PPS	Per Protocol Set
PRO	patient reported outcome
RAASi	renin-angiotensin-aldosterone system inhibitor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
sCr	serum creatinine
sK+	serum potassium

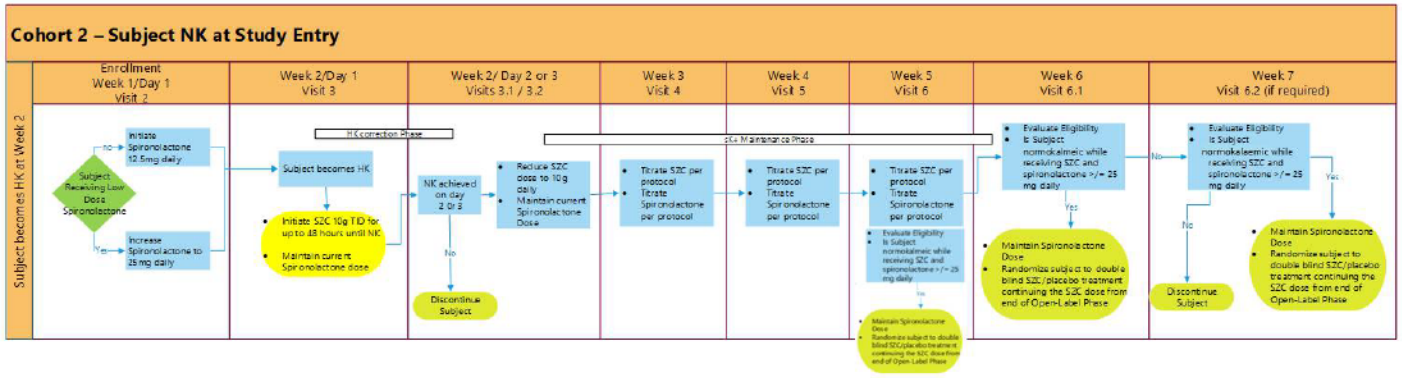
Abbreviation	Explanation
SmPC	Summary of Product Characteristics
SMQ	standardised MedDRA queries
SoA	Schedule of Activities
SOC	Standard of Care
SPS	sodium polystyrene sulfonate
SSO	Safety Set Open
SSR	Safety Set Randomised
SZC	sodium zirconium cyclosilicate
UACR	urine albumin-to-creatinine ratio
USPI	United States Prescribing Information
VAD	ventricular assistance device

Appendix K Open-Label Visit Flow Diagrams

Cohort 1 - Patient HK at Study Entry[a, b]



Cohort 2 - Patient NK at Study Entry; Becomes HK at Week 2[a, c, d]



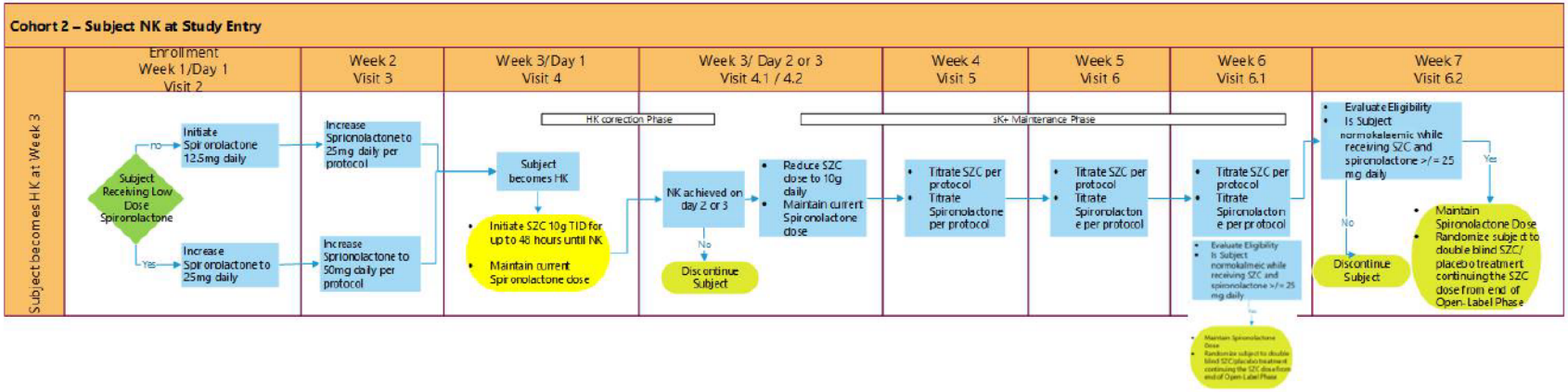
[a] Patients in either cohort who develop HK on spironolactone 50 mg daily while receiving maximum dose SZC (15 g), but were NK on spironolactone 25 mg daily may remain in the open-label, run-in phase for up to 2 additional weeks in order to return to spironolactone 25 mg and become NK again.

[b] For Cohort 1, the randomisation will occur at Visit 6 or at one of the optional Visits 6a or 6b (depending on when the patient becomes NK).

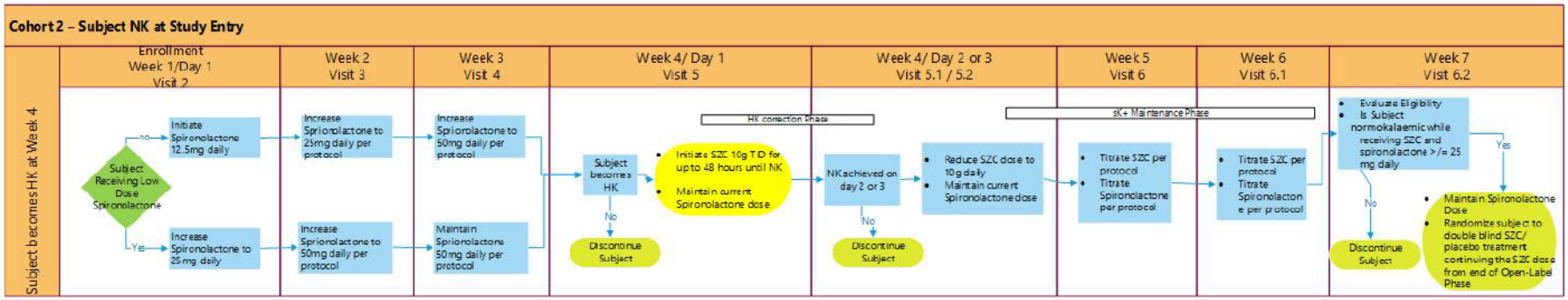
[c] Patients in Cohort 2 should receive at least 3 weeks of SZC before they can be considered for randomisation.

[d] The randomisation will occur at Visit 6, Visit 6.1, Visit 6.2 or at one of the optional Visits 6a or 6b (depending on when the patient becomes NK).

Cohort 2 - Patient NK at Study Entry; Becomes HK at Week 3[a, b, c]



Cohort 2 - Patient NK at Study Entry; Becomes HK at Week 4[a, b, d]



[a] Patients in either cohort who develop HK on spironolactone 50 mg daily while receiving maximum dose SZC (15 g), but were NK on spironolactone 25 mg daily may remain in the open-label, run-in phase for up to 2 additional weeks in order to return to spironolactone 25 mg and become NK again.
[b] Patients in Cohort 2 should receive at least 3 weeks of SZC before they can be considered for randomisation.
[c] The randomisation will occur at Visits 6.1, 6.2 or at optional Visits 6a or 6b (depending on when the patient becomes NK).
[d] The randomisation will occur at Visit 6.2 or at one of the optional Visits 6a or 6b (depending on when the patient becomes NK).

Appendix L Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 2, 03 August 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment 2:

The overall rationale (one primary driver) for the changes implemented in protocol amendment 2 is the shortening of the randomised, double-blind, withdrawal phase from 8 to 6 months. Based on recent results from a similar study (DIAMOND study), shortening the duration by 2 months will not impact the results and may alleviate the burden to the patients.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis 1.3 Schedule of Activities (randomised, double-blind withdrawal phase) 2.1 Study Rationale 3. Objectives and Endpoints 4.1 Overall Design 5.1 Inclusion Criteria 6.6.2 Double-blind, Placebo-controlled, Randomised-withdrawal Phase 9.1 Statistical Hypotheses 9.2 Sample Size Determination 9.4.3.1 Primary Endpoint 9.4.3.2 Secondary Endpoints	Decrease of the randomised, double-blind, withdrawal phase from 8 to 6 months	Ease patient visit burden	Non-substantial
1.1 Synopsis 4.1 Overall Design	Patients from Cohorts 1 and 2 in the HK Correction Phase who do not achieve NK within 48 hours will be discontinued from the study	Clarifying edit	Not substantial
1.1 Synopsis 4.2 Scientific Rationale for Study Design 5.2 Exclusion Criteria	Criterion #2: Clarify that patients currently hospitalised due to heart failure (HF) can be enrolled if HF is hemodynamically stable.	Enable patients with recent HF worsening to be enrolled as these patients often have HK and/or are on no or low-dose	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		mineralocorticoid receptor antagonist (MRA)	
1.1 Synopsis 5.1 Inclusion Criteria	Criterion #2 (b): added complementary definition of 'at risk of developing hyperkalaemia (HK)' for Cohort 2.	Clarifying edit	Non-substantial
1.1 Synopsis 5.1 Inclusion Criteria	Criterion #2 (b): Timeframe used to define history of HK has been extended from 24 to 36 months.	During the COVID-19 pandemic, not all patients have laboratory values recorded in the past 2 years. Extending the time frame by 1 year (pre-pandemic) may help capture these patients.	Substantial
1.1 Synopsis 5.1 Inclusion Criteria	Criterion #4: Timeframe used to define left ventricular ejection fraction has been extended from 12 to 24 months.	During the COVID-19 pandemic, some patients were hesitant to go to in-person visits for HF assessments, such as echocardiograms. Extending the time frame by 1 year may help capture these patients with less frequent assessments.	Substantial
1.1 Synopsis 5.1 Inclusion Criteria	Criterion #5: Removed restriction on stable dose duration for angiotensin-converting enzyme inhibitor (ACEi), angiotensin II receptor blocker (ARB), or angiotensin receptor-Neprilysin inhibitor (ARNi).	Enable patients with recent RAASi dose changes to be enrolled	Substantial
1.1 Synopsis 4.1 Overall Design 5.1 Inclusion Criteria 5.2 Exclusion Criteria	Criterion #6: Patients on low-dose (<25 mg daily) of eplerenone are now allowed to participate in the study. They	Enable patients on low-dose eplerenone to switch to low-dose spironolactone so they	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
6.1.1 Investigational Products 6.5 Concomitant therapy 6.6.1 Open-label Run-in Phase	will be switched to spironolactone 12.5 mg daily (1:1 dose conversion) at study screening once it's confirmed they meet the criteria for study entry.	may be enrolled, as these patients are on low-dose MRA due to HK.	
1.1 Synopsis 5.1 Inclusion Criteria	Criterion #7: Removed restriction on stable dose duration for beta-blockers.	Enable patients with recent beta-blocker dose changes to be enrolled	Substantial
1.1 Synopsis 5.1 Inclusion Criteria	Criteria #9 applies only for females Criterion #9 (b): time frame defined for birth control use before entering the study has been adjusted from 3 to 4 months, and from 12 to 4 weeks after the study's last dose.	Clarifying edit to align to PSSR version 8	Non-substantial
1.1 Synopsis 5.2 Exclusion Criteria	Criterion #4: clarification on coronary revascularization **or valvular repair/replacement** procedure	Clarifying edit	Non-substantial
1.1 Synopsis 5.2 Exclusion Criteria	Criterion #16: clarification on history of gynecomastia	Clarifying edit	Non-substantial
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities 4.1 Overall Design	Clarify that cohort assignment is based on local laboratory serum potassium (sK+) on Visit 1.	Clarifying edit	Non-substantial
1.1 Synopsis 1.3 Schedule of Activities (Follow-up) 2.3 Benefit/Risk Assessment 4.1 Overall Design	Change the duration of the follow-up period from 3 weeks to 1 week after end of treatment (EOT) Follow-up period after the EOT visit: sK+ will now be checked 7 days after last dose of study drug instead of 2 and 21 days.	Ease patient visit burden	Non-substantial
1.1 Synopsis 1.2 Schedule of Activities, Cohorts 1 and 2 4.1 Overall Design	Open-label run-in phase can be extended by 2 weeks.	Patients who develop HK on spironolactone 50 mg daily, but were NK on spironolactone	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
6.6.1. Open-label Run-in Phase Appendix K		25 mg daily are now allowed to remain in the open-label, run-in phase for up to 2 additional weeks in order to return to spironolactone 25 mg and become NK again and thus qualify for randomisation.	
1.1 Synopsis 4.1 Overall Design	In Cohort 1, Visit 2 may occur at the same time as, or shortly after Visit 1 (Screening), for patients with hyperkalaemia.	To expedite treatment with SZC	Non-substantial
1.2 Schema	Figure 1 has been updated to reflect the new number of patients in the open-label cohort (N=260) The text was updated as Cohort 2 should receive at least 3 weeks of SZC before they can be considered for randomisation.	Clarifying edit	Non-substantial
1.3 Schedule of Activities	Clarification has been added for urine collection.	Clarifying edit	Non-substantial
1.3 Schedule of Activities	For Cohort 1, the 24-hour visit (Visit 2.1) has been updated as optional during the SZC 10 g TID dosing phase.	Ease patient visit burden	Non-substantial
1.3 Schedule of Activities	For Cohort 2, the 24-hour visits (Visits 3.1, 4.1 and 5.1) have been updated as optional during the SZC 10 g TID dosing phase.	Ease patient visit burden	Non-substantial
1.3 Schedule of Activities	Added optional 2 visits (6a and 6b) for Cohorts 1 and 2 to be aligned with the footnote added in SoA (Patients who develop HK on spironolactone 50 mg daily while receiving maximum dose SZC (15 g), but were NK on spironolactone 25 mg daily may remain in the open-label,	To enable patients who can maintain normokalaemia on spironolactone 25 mg daily to remain on guideline-directed medical therapy and stay in the study	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	run-in phase for up to 2 additional weeks in order to return to spironolactone 25 mg and become NK again).		
1.3 Schedule of Activities	Additional information was added to ensure that for both cohorts the assessments unique to Visit 6 (or 6.1, 6.2) (namely the physical exams, biomarker analyses, and the KCCQ & PGIS) will only occur once independently if the patient attends all optional visits (6a and 6b).	Clarifying edit	Non-substantial
1.3 Schedule of Activities 8.2.4 Clinical Safety Laboratory Assessments	Local laboratory to be used instead of central laboratory for urinalysis (dipstick).	Clarifying edit	Non-substantial
2.2 Background	Additional information provided in the background.	Updated background section with new 2021 and 2022 HF Guidelines	Non-substantial
2.3 Benefit/ Risk Assessment	Removed fluid overload among oedema-related events	Fluid overload has been demoted to LLT and is included with PT hypervolaemia (according to MedDRA update version 24.1)	Non-substantial
4.1 Overall Design	Removed text about the possibility of a registry for a real-word observation of the HF management of patients who completed the study	No longer applicable	Non-substantial
5.4 Screen Failures	Conditions under which rescreening is allowed have been added. Also clarified that rescreening can happen twice.	Increase the number of patients eligible for enrolment	Non-substantial
6.6.2 Double-blind, Placebo-controlled, Randomised-withdrawal Phase	Spironolactone doses are allowed to be decreased in patients with HK during the randomised withdrawal phase	Clarifying edit	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
6.5 Concomitant Therapy	DDIs have been updated according to the CDS	Clarifying edit to be aligned to CDS 2022	Non-substantial
6.5 Concomitant Therapy	Additional restricted medication (tacrolimus) was added.	New data available showing the need to separate tacrolimus from SZC administration by 2 hours	Non-substantial
6.5 Concomitant Therapy	Additional permitted medication was added (low dose acetylsalicylic acid).	Clarifying edit to avoid confusion with the NSAID restriction	Non-substantial
6.6.1 Open-label Run-in Phase	Table 8 was replaced by the corresponding table from Appendix K and Appendix K was deleted. Table 8 was modified for clarification about the recommendation for spironolactone when sK^+ <3.0 mEq/L should be the same as for patients with sK^+ <3.5 – 5 mEq/L.	Enables patients with low potassium to remain on spironolactone and remain on guideline-directed medical therapy	Non-substantial
6.6.1 Open-label Run-in Phase	Text was added for clarification about study discontinuation during the open-label phase.	Clarifying edit	Non-substantial
6.6.2 Double-blind, Placebo-controlled, Randomised-withdrawal Phase	Table 9 was replaced by the corresponding table from Appendix L and Appendix L was deleted. Text was added in Table 9 for clarification about the recommendation to maintain spironolactone when sK^+ <3.0 mEq/L.	Enables patients with low potassium to remain on spironolactone and remain on guideline-directed medical therapy	Non-substantial
8.2.4 Clinical Safety Laboratory Assessments	Complementary information regarding the CKD-EPI formula to be used was added.	Clarifying edit	Non-substantial
8.3.7.2 Paternal Exposure	Text about the documentation of pregnancy of the participant's partner has been removed to be aligned to Lokelma PSSR.	Clarifying edit. AZ is not collecting data on pregnant partners to	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		males who participate in Lokelma studies	
9.4.3.3 Exploratory Endpoints	'Patients enrolled during hospitalisation' added as a sub-group analysis.	Hospitalised patients to be analyzed as a subgroup to keep the consistency of results across patient types	Non-substantial
Appendix K	The flowcharts were updated to clarify that: In Cohort 1 the randomisation occurs at Visit 6 or at one of the optional Visits 6a or 6b (depending on when the patient becomes NK). In Cohort 2, subjects should be receiving SZC for a minimum of 3 weeks prior to randomisation. Cohort 2 starts SZC at Visit 3 and the randomisation will occur at Visit 6, Visit 6.1, Visit 6.2, or at one of the optional Visits 6a or 6b (depending on when the patient becomes NK). Cohort 2 starts SZC at Visit 4 and the randomisation will occur at Visit 6.1, Visit 6.2 or at one of the optional Visits 6a or 6b (depending on when the patient becomes NK). Cohort 2 starts SZC at Visit 5 and the randomisation will occur at Visit 6.2 or at one of the optional Visits 6a or 6b (depending on when the patient becomes NK).	Clarifying edit	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
11 References	Added CDS 2022 as a reference as the SmPC has not yet been approved by the EMA. Added Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines [in press-corrected proof; posted online April 1, 2022]. J Am Coll Cardiol. 2022. doi:10.1016/j.jacc.2021.12.012. Added McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599-3726.	Clarifying edit	Non-substantial
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarised	Non-substantial

Amendment 1, 29 June 2021

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment 1:

The overall rationale (one primary driver) for the changes implemented in the protocol amendment was minor clarifications and further descriptions, below (e.g., changes to individual inclusion/exclusion criteria).

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis - Objectives and Endpoints; Statistical Methods; 3 Objectives and Endpoints; 9.4.3 Efficacy	Change of the word "proportion" to "occurrence" (yes/no) at all instances in the table Secondary endpoint sentence was changed as following – "Patients who are lost to follow-up, including due to death, prior to the EOT visit will be treated as non-response" Change in KCCQ from Total Symptom Score (TSS) to Clinical Summary Score (CSS)	Clarity of analysis	Non-substantial
3 Objectives and Endpoints	Secondary Objective and Endpoint - Change in KCCQ from TSS to CSS Exploratory Objective and Endpoint - Change in KCCQ from CSS to TSS	Change on emphasis of participants' physical limitation (CSS) rather than symptom frequency and symptom burden domains (TSS)	Non-substantial
1.1 Synopsis – Overall Design; 1.1 Schema; 4.1 Overall Design; 6.6 Dose Modification	Treatment Period - Cohort 2 – HK Correction Phase - change in study assessment / monitoring days of HK for 4 weeks instead of 3 weeks. Follow-up period after the EOT visit: sK+ will now be checked 2 and 21 days after last dose of study drug instead of 7 and 21 days.	Decreased the time to monitor for changes in sK+ following EOT visit	Non-substantial
1.3 Schedule of Activities (SoA), Table 1	Changes were made to reflect the changes in the text of the protocol and the Screening and Open-Label Run-in Phase Table was split into two – For Cohort 1 and for Cohort 2.	The SoA was updated for clarity purpose	Non-substantial
4.1 Overall Design; 6.6.1 4- to 6-Week Open-label Run-in Phase	Text was added: patients who do not qualify for randomisation due to hyperkalaemia should have a follow-up visit 2 days after their last dose of study drug.	Clarify for patient safety that patients not being randomised to double-blind due to HK are to have a follow-up visit within 2 days.	Non-substantial
5.2 Exclusion Criteria	Criteria # 22 added as a footnote about COVID-19 vaccinated patients to be included in the study	COVID vaccines are not approved – but will be allowed due to	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		the COVID-19 pandemic	
6.3 Measures to Minimise Bias: Randomisation and Blinding	Randomisation code blind-breaking instructions were detailed.	Clarity on randomisation code blind-breaking instructions	Non-substantial
6.6.1 4- to 6-Week Open-label Run-in Phase	Sentence about open-label titration guide as referenced in Appendix K was added. A new Table 6 was added on dosing and titration. Table 8 – If receiving SZC 15 g daily – sentence for "monitoring of sK+ in 7 (±2) days if SZC or spironolactone dose changed" was deleted	Clarity on titration guidance and patient safety	Non-substantial
6.6.2 8-Month Double-blind, Placebo-controlled, Randomised-withdrawal Phase	Sentence about open-label titration guide as referenced in Appendix L was added. Table 9 – If receiving SZC/placebo 15 g daily – sentence for "monitoring of sK+ in 7 (±2) days if SZC/placebo or spironolactone dose changed" was deleted. A footnote was added on the SZC/Placebo and Spironolactone Dose Adjustment – "Monitor sK+ in 7 +/-2 days if SZC/placebo or spironolactone dose changed"	Clarity on titration guidance and patient safety	Non-substantial
7.1 Discontinuation of Study Intervention	The following sentence was added – "Patients who discontinue the study early during the randomised phase should have their EOT visit as soon as possible after their last dose of study drug (assuming they discontinue the drug while at home and not at a study visit)."	Clarity that discontinued patients should have an EOT visit as soon as possible	Non-substantial
8 Study Assessments and Procedures	The following bullet point was added – "An open-label visit flowchart is provided for reference in Appendix M"	Reference to new Appendix M	Non-substantial
8.6 Human Biological Sample Biomarkers	Urine sample was deleted from CV and renal biomarkers including plasma renin activity (PRA)*, total renin, angiotensinogen, atrial natriuretic peptide (ANP), high sensitivity troponin I, Urine: angiotensinogen, total renin, ACE, ACE2. The words "blood and urine samples" were added to additional biomarkers.	Removed specific blood and urine parameters at this time but retaining the samples for potential future analyses.	Non-substantial
8.3.7 Pregnancy; 10. Appendix B-2	The word "abnormality" was changed to "anomaly"	Better clarity	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
3 Objectives and Endpoints; 9.4.3.3 Exploratory Endpoints	Endpoint regarding relationship between aldosterone levels and PGIC and KCCQ scores was added	To confer any association between aldosterone levels and the patient 'feeling better' and exploring potential reasons for the improvement in PGIC and KCCQ scores.	Non-substantial
10. Appendix A – A7 Data Quality Assurance	Records and documents retention time was changed to 15 years	To harmonize between ICF and sample storage	Non-substantial
10. Appendix K	Open-label run-in phase titration guidance added	Guidance added to clarify dosing guidance during the open-label run-in phase	Non-substantial
10. Appendix L	Double-blind titration guidance added	Guidance added to clarify dosing guidance during the double-blind phase	Non-substantial
10. Appendix M	Open-label flow diagrams were added for Cohorts 1 and 2	Patient flow diagrams added to clarify the patients' progression through the study	Non-substantial

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