Clinical Study Protocol	
Study Intervention	Sodium zirconium cyclosilicate
Study Code	D9480C00023
Version	4.0
Date	16 Oct 2023

An Open-Label, Randomised, Phase 4 Study of Continuing Sodium Zirconium Cyclosilicate (SZC) after Discharge in Participants with Chronic Kidney Disease treated for Hyperkalaemia

Sponsor Name: AstraZeneca AB

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Regulatory Agency Identifier Number(s): 2021-003527-14

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

Study Intervention: Sodium zirconium cyclosilicate (SZC); brand name LOKELMA®

Study Phase: 4

Short Title: Continuing Sodium Zirconium Cyclosilicate (SZC) after discharge study

Acronym: CONTINUITY

Study Physician Name and Contact Information will be provided separately.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	16 Oct 2023
Amendment 2	07 Jul 2022
Amendment 1	02 Aug 2021
Original Protocol	12 Jul 2021

Amendment 3.0: 16 October 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.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 2.1 Study Rationale Section 3 Objectives and Endpoints Section 4.2 Scientific Rationale for Study Design Section 8.1.2 Main Secondary Endpoints Section 9.1 Statistical Hypothesis 9.2 Sample Size Determination 9.2.2 Main Secondary Endpoint 9.4.3.2 Secondary Endpoints	In the definition of the first secondary objective and endpoint, "time to first occurrence of hospital admissions or ED visits with HK as a contributing factor" was changed to "occurrence of all-cause hospital admissions, or ED visits with HK as a contributing factor". In relation to this change, a sensitivity analysis with hospital admission with HK as a contributing factor has been added as well as 2 secondary objectives and endpoints.	To expand the definition of the main secondary endpoint to encompass a wider range of hospital admissions to facilitate a larger, clinically meaningful effect size for detection in order to reduce sample size.
Section 1.1 Synopsis Section 4.1 Overall Design Section 9.2.2 Main Secondary Endpoint Section 11 References	Sample size was re-calculated based on the new definition of the secondary endpoint.	To align with changes in the main secondary endpoint.
Section 1.1 Synopsis Section 5.1 Inclusion Criteria	Change in inclusion criterion #3 to allow enrolment of participants with any chronic kidney disease (CKD) stage or a higher estimated glomerular filtration rate (eGFR).	Although HK is less common in early stages of CKD, these patients may already have had HK episodes, have been using RAASI medications and are at high risk of HK recurrence.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 4.1 Overall Design	Guidance on sodium zirconium cyclosilicate (SZC) initiation at baseline have been modified.	At the time of enrolment, participants are being treated for HK & therefore switch to SZC is within label.
Section 1.1 Synopsis Section 1.2 Schema Section 1.3 Schedule of Activities	Clarifications on visit windows and other minor editorial changes.	Clarification edit.
Section 1.3 Schedule of Activities Section 2.1 Study Rationale	Renin-angiotensin-aldosterone system inhibitor dose changes/discontinuations has been added in the list of data to be collected on hospital admission and ED visit.	Clarification edit.
Section 1.3 Schedule of Activities	Added assessment of local laboratory K^+ at follow-up phase	Clarification edit.
Section 2.3.1 Risk Assessment	Constipation has been added as potential risk of clinical significance.	To align with updated SZC specific safety requirements.
Section 1.1 Synopsis Section 1.2 Schema Section 5.1 Inclusion Criteria Section 6.1 Screening and Inpatient Phase	Change in inclusion criterion #4 to clarify that patients treated for current episode of HK can be NK at time of enrolment	Clarification edit.
Section 5.2 Exclusion Criteria	Exclusion criterion #1 is simplified to exclude any participant with a hospitalisation for an acute cardiovascular event within 12 weeks prior to screening.	The rationale for this exclusion criteria is to avoid patients at high risk of re-admission for reasons unrelated to HK, therefore wording was simplified.
Section 5.2 Exclusion Criteria	Wording of exclusion criterion #5 is simplified.	Clarification edit.
Section 5.2 Exclusion Criteria	Exclusion criteria # 6 and 10 are pooled in a single exclusion criterion (#10).	Clarification edit.
Section 5.2 Exclusion Criteria	Exclusion criterion # 12 is deleted to avoid duplication with new exclusion criterion #5.	Clarification edit.
Section 1.1 Synopsis Section 1.2 Schema Section 4.2 Scientific Study Rationale	Exclusion criterion # 13 is modified to specify which K-binders are prohibited before current ED visit/hospitalisation preceding enrolment. It is also specified that	Clarification edit.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria	initiation of SZC or patiromer during the current ED visit/hospitalisation preceding enrolment is allowed.	
Section 5.2 Exclusion Criteria	Exclusion criterion # 14 is modified to allow emergency/unscheduled haemodialysis to treat HK during the current ED visit/hospitalisation preceding enrolment.	Clarification edit.
Section 5.2 Exclusion Criteria	Exclusion criterion #15 is modified to remove note regarding participants vaccinated with COVID-19 vaccine while still under emergency use utilization.	Consistency with current standards.
Section 5.2 Exclusion Criteria	Exclusion criterion #20 is updated to add the exclusion of WOCBP who are not stable on the contraceptive method for the last month and to clarify contraception must be used until 7 days after last dose	Clarification edit
Section 8.3.9 Medication Error, Drug Abuse, and Drug Misuse Appendix B 4	The whole section has been modified to include drug abuse and drug misuse sections.	Update required due to EU "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')" and Astra Zeneca corporate safety CAPA.
Section 9.4.4 Safety	Reduced time window of AE occurrence post-last dose from 14 days to 7 days for an event to be considered treatment emergent.	To correct an error in the protocol and to align with the follow-up visit 7 days after EOT.
Section 9.5 Interim Analyses	The planned interim analysis has been cancelled.	Due to decreased sample size, running an interim analysis is not justified.
Appendix A 1	Added sub-heading "Regulatory Reporting Requirements for Serious Breaches".	Update required to comply with regulatory requirement (e.g. EU CTR) and global company requirement.
Appendix A6	Updated information about timelines for submission of trial results summaries to EU CTIS.	Update required to comply with EU CTR.

Section # and Name	Description of Change	Brief Rationale
Appendix A7	Updated information about retention timelines of records and documents to 25 years after study archiving or as required by local regulations.	Update required to comply with EU CTR and global company requirement.
Throughout	Hospital admission has been replaced by hospitalisation preceding enrolment. Minor editorial and document formatting revisions.	Clarification edit. Minor, therefore have not been summarised.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: An Open-Label, Randomised, Phase 4 Study of Continuing Sodium Zirconium Cyclosilicate (SZC) after Discharge in Participants with Chronic Kidney Disease treated for Hyperkalaemia

Short Title: Continuing sodium zirconium cyclosilicate (SZC) after discharge study (CONTINUITY)

Rationale: This is an open-label, randomised study in participants with chronic kidney disease (CKD) treated for hyperkalaemia (HK) whilst in hospital. The study will compare SZC to standard of care (SoC) with the goal of determining:

1. If continued use of SZC maintains normokalaemia (NK) better than SoC after participant discharge from the hospital.
2. If continued use of SZC after discharge will reduce HK related healthcare resource utilisation compared to SoC.

Objectives and Endpoints:

Primary objective(s)	**Outcome measure**	**Hypothesis tested (if relevant)**
To evaluate the efficacy of continuing SZC as part of the discharge medications, compared to SoC, in maintaining NK.	Occurrence (yes/no) of NK (potassium [K^+] between 3.5 and 5.0 mmol/L, inclusive) at 180 days post-discharge.	Null: No difference in the occurrence (yes/no) of a participant being NK at 180 days post-discharge between the SZC and SoC arms.
Secondary objective(s)	**Outcome measure**	**Hypothesis tested (if relevant)**
To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of the composite outcome of all-cause hospital admissions, or emergency department (ED) visits with HK as a contributing factor, or all-cause death, or use of rescue therapy for HK.	Time to first occurrence of all-cause hospital admissions, or ED visits with HK as a contributing factor, or all-cause death, or use of rescue therapy for HK at any time post-discharge up to 180 days.	Null: No difference in event rates corresponding to time to first occurrence of any component of the composite outcome between the SZC and SoC arms.

To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of all-cause hospital admissions or ED visits with HK as a contributing factor.	Time to first occurrence of all-cause hospital admission, or ED visit with HK as a contributing factor at any time post-discharge up to 180 days.	Null: No difference in event rates corresponding to time to first occurrence of all-cause hospital admission, or ED visit with HK as a contributing factor between the SZC and SoC arms.
To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the number of all-cause hospital admissions or ED visits with HK as a contributing factor.	Number of all-cause hospital admission, or ED visits with HK as a contributing factor at any time post-discharge up to 180 days.	Null: No difference in the incidence rate of all-cause hospital admission, or ED visit with HK as a contributing factor between the SZC and SoC arms.
To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of hospital admissions or ED visits with HK as a contributing factor.	Time to first occurrence of hospital admission or ED visit, both with HK as a contributing factor at any time post-discharge up to 180 days.	Null: No difference in event rates corresponding to time to first occurrence of hospital admission or ED visit with HK as a contributing factor between the SZC and SoC arms.
To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the number of hospital admissions or ED visits with HK as a contributing factor.	Number of hospital admission or ED visits, both with HK as a contributing factor at any time post-discharge up to 180 days.	Null: No difference in the incidence rate of hospital admission or ED visit with HK as a contributing factor between the SZC and SoC arms.
To evaluate the effect of continuing SZC as part of the discharge medications compared to SoC on reducing the risk of renin-angiotensin-aldosterone system inhibitors (RAASi) down-titration (including discontinuation).	Time to first occurrence of RAASi down-titration (or discontinuation) at any time post-discharge up to 180 days.	Null: No difference in event rates corresponding to time to first occurrence of RAASi down-titration (including discontinuation) between the SZC and SoC arms.
Safety objective(s)	**Outcome measure**	**Hypothesis tested (if relevant)**
To assess the safety and tolerability of SZC compared to SoC.	Safety and tolerability will be evaluated in terms of adverse events (AEs), vital signs, clinical laboratory, and electrocardiogram (ECG). Assessments related to AEs cover:	Not applicable.

	• Occurrence/frequency • Relationship to SZC as assessed by investigator. • Intensity • Seriousness • Death • AEs leading to discontinuation of SZC.	

For exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design:

This is a Phase 4, randomised, controlled, open-label, parallel group, multicentre study in participants with CKD treated for HK, whilst admitted to the hospital. There will be 3 phases:

- The in-hospital phase:

  Screening visit: Will occur while the participants are in an inpatient unit, in order to check eligibility criteria. Participants will be eligible if: they have a diagnosis of CKD (any stage) or estimated glomerular filtration rate (eGFR) < 90 ml/min/1.73 m^2; and they are HK (as defined by site's local practice and $K^+ \leq 6.5$ mmol/L) or they were HK and are now NK while receiving treatment for HK. The study plans to enrol approximately equal numbers of participants with mild HK (K^+ between > 5.0 and ≤ 5.5 mmol/L) and with moderate/severe HK (K^+ between > 5.5 and ≤ 6.5 mmol/L), with a minimum of 30% of the enrolled participants in either group. Participants will be eligible if they are not on SZC or patiromer **before** this current ED visit/hospital admission and fulfill all inclusion/exclusion criteria. Participants in whom SZC or patiromer has been initiated **during** this current ED visit/hospitalisation preceding enrolment can be enrolled in the study.

  The inpatient phase:

  Baseline visit: Can occur the same day as the screening visit if all inclusion/exclusion criteria are fulfilled. Treatment with SZC will be initiated as per local label at baseline visit and will be based on K^+ measurement performed within the previous 24 hours:

  - Participants with HK (K+ between > 5.0 and ≤ 6.5 mmol/L): 1) stop current K-binder if any, 2) start SZC correction dose (note: participants currently on SZC should continue SZC correction dose, up to 72 hours).
  - Participants currently receiving any treatment for the current episode of HK and are already NK at baseline (K+ ≤ 5.0 mmol/L): 1) stop any

current K-binder, 2) start SZC maintenance dose (note: participants currently on SZC maintenance dose should continue SZC maintenance dose).

- All treatment decisions, including modification to the ongoing therapy for HK, must be based on the investigator's medical judgement of the participant's best interest.

Typically, NK is achieved within 24 to 48 hours. If participants are still hyperkalaemic after 48 hours of treatment, the same regimen can be continued for an additional 24 hours. If NK is not achieved after 72 hours of treatment, other treatment approaches should be considered, and the participant discontinued from the study.

Participants reaching NK (K^+ between 3.5 and 5.0 mmol/L, inclusive) within 72 hours will be started on maintenance dose of SZC until discharge.

Discharge visit: The day they get discharged from the hospital, participants will be randomised to one of the 2 parallel arms at this visit and enter the outpatient phase. To be randomised, participants have to be NK (K^+ between 3.5 and 5.0 mmol/L, inclusive) and should be started on a maintenance dose for SZC. The discharge visit will take place 1 to 21 days after the baseline visit. Medical monitor's approval may be sought for allowing longer duration hospital stays for specific participants.

- The outpatient phase:

  Participants will be treated with either SZC, as per local label, or SoC, as per local practice for 180 days.

  Visits will occur 7, 30, 60, 90, 120, 150, 180 (end of treatment [EOT]) days after discharge visit (randomisation). Only visits at 7, 90, and 180 days will be on-site visits: the remaining being telephone visits.

- The follow-up phase:

  A follow-up site visit (end of study visit) will occur approximately 7 days after EOT.

Data will be collected at on-site visits, via telephone visits and medical chart reviews.

The study will be conducted in approximately 30 to 50 sites in 4 to 7 countries in Europe.

Disclosure Statement: This is a parallel-group treatment study with 2 treatment arms that are open label.

Masking: No masking

Number of Participants:

Assuming a 20% drop-out rate from enrolment to randomisation and a 20% drop out post-discharge (post-randomisation), approximately 163 participants will be enrolled, resulting in approximately 130 participants discharged and randomised, to achieve 104 evaluable participants (52 per arm).

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not assigned treatment in the study, are considered "screen failures", unless otherwise specified by the protocol.

Intervention Groups and Duration:

All participants will be treated with SZC as per local label (correction and/or maintenance treatment) during the in-hospital phase. The duration of in-hospital phase will be 1 to 21 days post-enrolment; medical monitor's approval may be sought for allowing longer duration hospital stays for specific participants.

At discharge, participants who are NK (K^+ between 3.5 and 5.0 mmol/L, inclusive) and have been started on a maintenance dose for SZC will be randomised in a 1:1 ratio to one of the following arms and subsequently enter the outpatient phase:

- Arm A: Participants discharged with SZC, as per local label, to manage HK until end of outpatient phase
- Arm B: Participants discharged with SoC, as per local practice, to manage HK until end of the study.

Note: Participants intended to receive a K-binder at discharge (as per the site routine medical practice) will not be randomised and will be discontinued from the study. Still, it is allowed that participants randomised into Arm B have any K-binder prescribed at Day 7 post-discharge (or after Day 7 post-discharge), to treat confirmed HK or in case there is an increase in K^+ level since discharge that, in the investigator's opinion, requires therapy.

The duration of outpatient phase will be approximately 180 days.

After the outpatient phase, participants will enter into the follow-up phase which will last 7 days. Study drug will be discontinued for participants in Arm A. These participants will be treated as per local practice (SoC). Participants in Arm B will continue SoC treatment.

The total study duration for each participant will then be approximately 6 months.

Adjudication Committee: Yes

Statistical Methods:

Analyses will be further detailed in the statistical analysis plan which will be finalised within 90 days of first participant enrolled. It should be noted that death without prior hospitalisation or ED visits is seen as negligible. As such, the way death is treated (as outcome or censoring) will not dramatically affect the outcomes.

Primary Endpoint

Occurrence (yes/no) of NK (K^+ between 3.5 and 5.0 mmol/L, inclusive) at 180 days post-discharge will be analysed using a logistic regression model with response as the dependent variable and randomised treatment group as the independent variable. Participants who discontinue treatment with a K^+ measurement at 180 days post-discharge will have this value used irrespective of treatment discontinuation. Use of rescue therapy for HK will be considered to be non-response. Down-titration (including discontinuation) of RAASi (ie, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists) will be considered to be non-response. Participants who die of any cause prior to 180 days post-discharge or who are lost to follow-up for any reason will be considered to be non-response. Sensitivity analyses will evaluate the impact of considering this as non-response versus only evaluating completers will be assessed.

Secondary Efficacy Endpoints

1. *Time to first occurrence of any component of all-cause hospital admission, or ED visit with HK as a contributing factor, or all-cause death, or use of rescue therapy for HK at any time post-discharge up to 180 days* will be analysed using a log-rank test. In addition, a Cox proportional hazards model will be used for estimation with randomised treatment group as the independent variable. Participants who discontinue treatment will continue to be followed up to the first component of the composite endpoint. Rescue therapy for HK will be considered an event. Participants who require hospital admission or ED visits without HK as a contributing factor will continue to be followed up to the first component of the composite endpoint. Participants who die of any cause will be considered an event. Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint.

2. *Time to first occurrence of any component of all-cause hospitalisation admission or ED visit with HK as a contributing factor, at any time post-discharge up to 180 days* will be analysed using a log-rank test. In addition, a Cox proportional hazards model will be used for estimation with randomised treatment group as the independent variable. Participants who discontinue treatment or who have ED visit without HK as a contributing factor will continue

to be followed up to the first component of the composite endpoint. Participants who die of any cause, use rescue therapy for HK or are lost to follow-up will be censored at the date of death, use of rescue therapy, or loss to follow-up, respectively. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint.

3. *Number of all-cause hospital admission, or ED visit with HK as a contributing factor, at any time post-discharge up to 180 days* will be analysed using a negative binomial regression model. Participants who discontinue treatment, use rescue therapy for HK or who have an ED visit without HK as a contributing factor, will continue to be followed up for the first component of the composite endpoint. Participants who die of any cause or are lost to follow-up will be censored at the date of death or loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint.

4. *Time to first occurrence of any component of hospital admission or ED visit, both with HK as a contributing factor, at any time post-discharge up to 180 days* will be analysed using a log-rank test. In addition, a Cox proportional hazards model will be used for estimation with randomised treatment group as the independent variable. Participants who discontinue treatment or who have hospital admission or ED visit without HK as a contributing factor will continue to be followed up to the first component of the composite endpoint. Participants who die of any cause, use rescue therapy for HK or are lost to follow-up will be censored at the date of death, use of rescue therapy, or loss to follow-up, respectively. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint.

5. *Number of hospital admission or ED visit both with HK as a contributing factor, at any time post-discharge up to 180 days* will be analysed using a negative binomial regression model. Participants who discontinue treatment, use rescue therapy for HK or who have a hospital admission, or an ED visit without HK as a contributing factor, will continue to be followed up for the first component of the composite endpoint. Participants who die of any cause or are lost to follow-up will be censored at the date of death or loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint.

6. *Time to first occurrence of RAASi down-titration (including discontinuation) at any time post-discharge up to 180 days* will be analysed using a log-rank test. In addition, a Cox proportional hazards model will be used for estimation with randomised treatment group as the independent variable. Participants who discontinue treatment will continue to be followed up to the first component of the composite endpoint. Participants who die of any cause or are lost to follow-up will be censored at their date of death or loss to follow-up, respectively.

Safety Endpoints

Safety will be assessed in terms of AEs, serious adverse events (SAEs), AEs leading to treatment discontinuation, clinical laboratory data, vital signs, and ECG. Appropriate summaries of these data will be presented by treatment group.

Adverse events will be presented for each treatment group by system organ class, and preferred term covering number and percentage of participants reporting at least 1 event and number of events where appropriate. An overview of AEs will present for each treatment group the number and percentage of participants with any AE, AEs with outcome of death, SAEs, and AEs leading to discontinuation of investigational medicinal product (IMP). Separate AE tables will be provided taken into consideration relationship as assessed by the investigator, maximum intensity, seriousness, death and events leading to discontinuation of IMP.

Sample Size:

Sample size determination is based on the main secondary efficacy endpoint (Time to first occurrence of any component of all-cause hospital admission, or ED visit with HK as a contributing factor, or all-cause death or use of rescue therapy for HK at any time post-discharge up to 180 days). Using a log-rank test for equality of survival curves, a significance level of 5%, a power of 80% and a hazard ratio of 0.329 with survival proportions of 83% for SZC and 56.8% for SoC, a sample size of 52 evaluable participants per arm (N = 104 total) would be required. Assuming a 20% drop-out rate from enrolment to randomisation, and a 20% drop out post-discharge (post-randomisation), a total of approximately 163 participants will be enrolled.

Analysis Populations:

Safety Set Open: All participants who received at least one dose of SZC during the study up until discharge/randomisation.

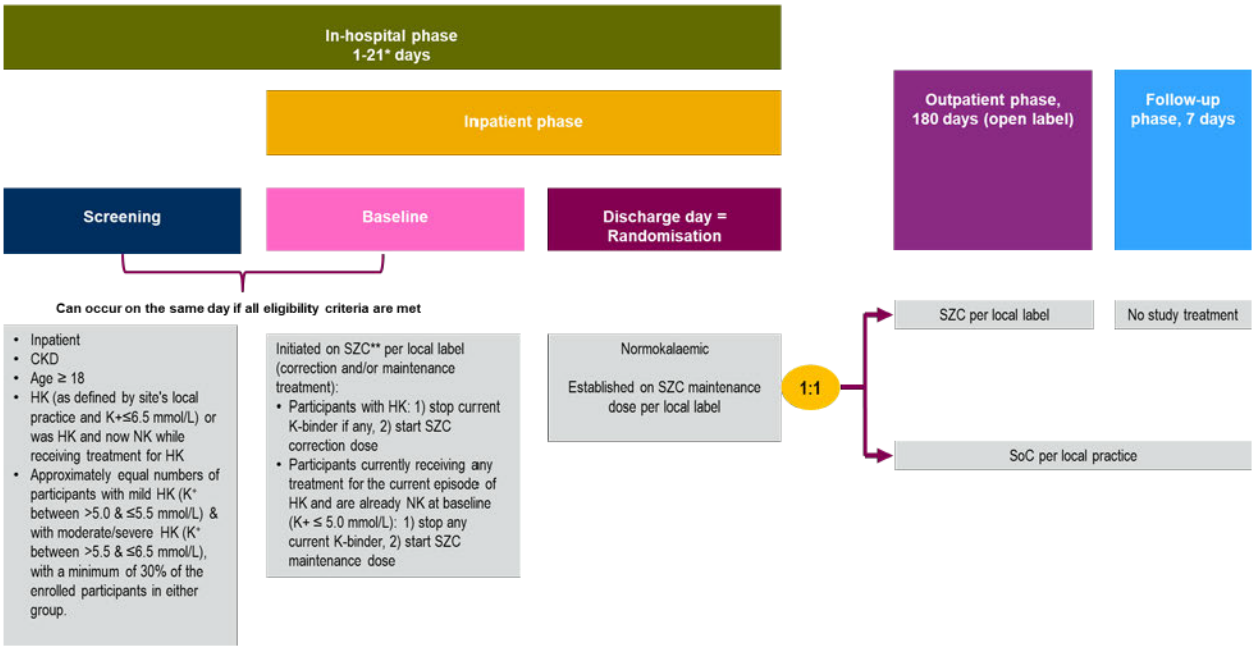
Safety Set Randomised: All randomised participants who received at least 1 dose of SZC post-discharge in Arm A and all randomised participants in Arm B.

Full Analysis Set (FAS): All randomised participants. The FAS will be used as the primary population for the primary, secondary, and exploratory efficacy endpoints.

Per Protocol Set (PPS): The FAS participants without any important protocol deviations leading to exclusion from the PPS.

1.2 Schema

Figure 1 Study Design



Abbreviations: CKD = chronic kidney disease; ED = emergency department; HK = hyperkalaemia; K/K^+ = potassium; NK = normokalaemia; SoC = standard of care; SZC = sodium zirconium cyclosilicate.
* Study medical monitor's approval may be sought for allowing longer duration hospital stays for specific participants.
** K^+ measurement within 24 hours of treatment initiation should be obtained before starting treatment.

1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedure	In-hospital phase (1 to 21 days)[a]			Outpatient phase (Visits 4 to 10)							E/D[h]	Follow-up phase	Details in CSP Section or Appendix
	Screening	Baseline[a]	Day of discharge from the hospital[b]	+7 days[n]	+30 days[c,h,n]	+60 days[c,h,n]	+90 days[c,h,n]	+120 days[c,h,n]	+150 days[c,h,n]	+180 days[c,h,n] (EOT)		+7 days after EOT[h,o]	
Visit	1	2	3	4	5 (phone)	6 (phone)	7	8 (phone)	9 (phone)	10		11	
Visit Window (+/-)				1	6	6	6	6	6	6		3	
Informed consent	X												
Inclusion and exclusion criteria	X												Sections 5.1 and 5.2
Randomisation			X										Section 6.2
Routine Clinical Procedures													
Demography	X												
Complete physical examination[d]	X												Section 8.2.1
Targeted physical examination[e]			X	X			X			X	X	X	Section 8.2.1
Medical history	X												
Concomitant medication	At every visit and may be conducted by phone if not tied to a visit												Section 6.7
Vital signs[f]	X	X	X	X			X			X	X	X	Section 8.2.2

Procedure	In-hospital phase (1 to 21 days)[a]			Outpatient phase (Visits 4 to 10)							E/D[h]	Follow-up phase	Details in CSP Section or Appendix
	Screening	Baseline[a]	Day of discharge from the hospital[b]	+7 days[n]	+30 days[c,h,n]	+60 days[c,h,n]	+90 days[c,h,n]	+120 days[c,h,n]	+150 days[c,h,n]	+180 days[c,h,n] (EOT)		+7 days after EOT[h,o]	
Visit	1	2	3	4	5 (phone)	6 (phone)	7	8 (phone)	9 (phone)	10		11	
Visit Window (+/-)				1	6	6	6	6	6	6		3	
Routine Safety Measurements													
Adverse events	At every visit and may be conducted by phone if not tied to a visit												Section 8.3
Urine pregnancy test (women of child-bearing potential only)	X												
Clinical safety laboratory assessments (including urine dipstick)[g]		X	X				X			X	X		Section 8.2.4
Electrocardiogram	X		X	X			X			X	X	X	Section 8.2.3
Study Assessments													
Local laboratory K^+ [i]	X		X	X			X			X	X	X	Section 8.1.1
Central laboratory K^+ [j]		X	X				X			X	X		Section 8.1.1
Data collection on hospital admissions and ED visits (with HK and all-cause), ICU visits, outpatient visits, use of rescue therapy, RAASi dose changes/discontinuations, dialysis initiation, and eGFR (site visits)				X	X	X	X	X	X	X	X	X	Section 8.8

Procedure	In-hospital phase (1 to 21 days)[a]			Outpatient phase (Visits 4 to 10)							E/D[h]	Follow-up phase	Details in CSP Section or Appendix
	Screening	Baseline[a]	Day of discharge from the hospital[b]	+7 days[n]	+30 days[c,h,n]	+60 days[c,h,n]	+90 days[c,h,n]	+120 days[c,h,n]	+150 days[c,h,n]	+180 days[c,h,n] (EOT)		+7 days after EOT[h,o]	
Visit	1	2	3	4	5 (phone)	6 (phone)	7	8 (phone)	9 (phone)	10		11	
Visit Window (+/-)				1	6	6	6	6	6	6		3	
Study Treatment Administration[j]													
Study intervention dispensation in-hospital phase[k]		X[l]											Section 6.4
Study intervention dispensation outpatient phase[m]			X	X			X						Section 6.4

Abbreviations: CSP = clinical study protocol; E/D = early study intervention discontinuation; ED = emergency department; eGFR = estimated glomerular filtration rate; EOT = end of treatment; HK = hyperkalaemia; ICU = intensive care unit; K^+ = potassium; RAASi = renin-angiotensin-aldosterone system inhibitors.

[a] Baseline and screening can occur the same day.

[b] Will be minimum 24 hours after treatment initiation (for participants who achieve normokalaemia [K^+ between 3.5 and 5.0 mmol/L, inclusive]). Participants with $K^+ > 5.0$ mmol/L or $K^+ < 3.5$ mmol/L at discharge will be discontinued from study treatment and will be followed per protocol.

[c] After date of discharge.

[d] A complete physical examination will be performed at screening (Visit 1) and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.

[e] The targeted physical examination includes the following: skin, extremities, cardiovascular including assessment of signs of heart failure, lungs, and abdomen.

[f] The vital signs include systolic and diastolic blood pressure, and pulse rate. Body weight and height will be measured at the screening visit. Weight (weighed on the same scale in the same state of dress) collected at each site visit.

[g] Clinical safety laboratory assessments via central laboratory: B-Haemoglobin (Hb), B-Leukocyte count, B-Leukocyte differential count (absolute count), B-Platelet count, B-Hematocrit (Hct), S-Sodium (Na^+), S-Potassium (K^+), S-Bicarbonate (Total CO_2), S-Chloride (Cl^-), S-Glucose, S-Creatinine, S-Blood Urea Nitrogen (BUN), Urea (BUN)/Creatinine Ratio, eGFR using the CKD-EPI formula, S-Anion gap , S-Albumin, S-Total Protein, S-Calcium (Ca^{++}), S-Magnesium (Mg^{++}), S-Phosphate (PO_4), S-Bilirubin, total, S-Alkaline phosphatase (ALP), S-Alanine amino transferase (ALT), S-Aspartate amino transferase (AST). Clinical safety laboratory assessments via local laboratory: urinalysis (dipstick), ie, U-Hb/Erythrocytes/Blood, U-Protein/Albumin, and U-Glucose.

[h] Data collected during on-site and telephone visits will be combined with data collected from participant medical chart review, if deemed necessary.

[i] For screening, K^+ results obtained during routine medical care may be used (HK as defined by site's local practice and K^+ must between > 5.0 and ≤ 6.5 mmol/L). Still a local K^+ measurement should be obtained within 24 hours of study treatment initiation. During the correction treatment phase K^+ level is assessed at least once a day, by local laboratory or any other validated method. Local laboratory (or any other validated method) only may be used at all other visits, including any unscheduled visit. Potassium may be checked more often than indicated here, if medically appropriate.

[j] Baseline samples for K^+ are analysed at the central laboratory and the results are not needed to assess eligibility. Samples will be analysed by central and local laboratories at day of discharge, + 90, + 180 days, and E/D visits while central laboratory only will be used at baseline.

[k] Treatment with sodium zirconium cyclosilicate (SZC) will be established while the participant is in the hospital. Only participants randomised to SZC will be dispensed study intervention during the outpatient phase. Any time study drug dose is adjusted, or if in either treatment arm a concomitant medication which may affect K^+ levels is changed (eg, use of renin angiotensin-aldosterone system inhibitors [angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, mineralocorticoid receptor antagonists] or diuretics), the participant needs to return to the site 7 (± 2) days later for a K^+ measurement and recording of adverse events and concomitant medications. During the inpatient phase, drug dispensation will occur every day.

[l] Central laboratory K^+ results at baseline are not necessary to initiate the study intervention as long as all eligibility criteria are met (only local assessment of K^+ within 24 hours of treatment initiation is required).

[m] If dose titration occurs at any time during the outpatient phase, unscheduled dispensation visits will be performed.

[n] Relative to the date of randomisation (Visit 3)

[o] Relative to the date of Visit 10/EOT.

2 INTRODUCTION

Sodium zirconium cyclosilicate (SZC) is as an orally-administered, non-polymer non-absorbable, inorganic, crystalline cation-exchanger that represents a novel therapy for hyperkalaemia (HK). It selectively binds potassium (K^+) ions in exchange for hydrogen and sodium ions throughout the gastrointestinal tract, thereby reducing serum K^+ concentration (Spinowitz et al, 2019). The K^+ is removed from the body through fecal excretion. So far, SZC (registered under the trade name of Lokelma®) has been registered in several countries worldwide, including United Kingdom, Germany, France, Italy, Netherlands, Belgium, and Spain.

2.1 Study Rationale

Hyperkalaemia is a common problem seen in hospital patients. Currently, few patients treated for HK in hospital are discharged with treatment to maintain normokalaemia (NK). Following discharge, these patients are at risk for hospital admission and emergency department (ED) visits for recurrent HK. A recent observational study in Japan demonstrated that patients with HK were more often readmitted to hospital, stayed longer, and had more ED/outpatient visits than patients with NK (Kanda et al, 2020). In patients suffering from chronic kidney disease (CKD), this translated into healthcare costs which were nearly 3 times higher for patients with HK compared to patients having NK. Similar findings have also been reported from the United States (Betts et al, 2020). In addition, it was shown that increased HK severity was associated with an increasing occurrence of hospital admissions (Davis et al, 2019).

Sodium zirconium cyclosilicate is a novel K^+ binder therapy to correct HK and maintain NK. Efficacy and safety of SZC has been established through a robust clinical development program. However, there is currently no outcome study that has investigated whether continued use of SZC reduces health care resource utilisation versus standard of care (SoC). The current study will examine the continued use of SZC in a CKD population with HK. The primary objective of the study is to evaluate the efficacy of continuing SZC, as per local label, as part of the discharge medications compared to SoC, as per local practice, in maintaining NK in participants with CKD treated for HK. The study will also assess whether continued use of SZC at discharge will reduce the incidence of all-cause hospital admissions and ED visits with HK as a contributing factor, or all-cause death, or use of rescue therapy for HK, or renin-angiotensin-aldosterone system inhibitors (RAASi) down-titration (including discontinuation) compared to SoC as per local practice, which may support health technology assessment.

2.2 Background

Hyperkalaemia is a potentially life-threatening electrolyte disorder and is primarily caused by renal dysfunction leading to reduced excretion of K^+. The incidence of HK in CKD patients has been reported to range between 7.7% and 73% (Kovesdy, 2017).

In a study of approximately 36,000 patients with an estimated glomerular filtration rate (eGFR) < 60 ml/min per 1.73 m^2, HK was associated with increased all-cause mortality (Nakhoul et al, 2015).

Because HK can induce or worsen cardiac arrhythmias, it is associated with significantly increased mortality (Kovesdy, 2017).

Treatment of severe HK is then a medical emergency but it should be followed by continuous long-term treatment to prevent recurrence. So far, the common practice for managing chronic HK is focused on eliminating HK predisposing factors. Patients are then advised to reduce high K^+ intake in diets but also to withdraw or reduce medications known to raise K^+ levels. Among these medications, RAASi, for example, are commonly prescribed in patients with CKD, and are often discontinued to manage HK, in spite of their recognised cardiovascular and renal benefits in this population (Kovesdy, 2017). Furthermore, withholding RAASi may lead to incremental healthcare costs associated with poor outcomes, such as end-stage renal disease, hospitalisations due to cardiovascular causes, and cardiovascular mortality (Dunn et al, 2015).

Maintaining the use of these beneficial medications while implementing various strategies to control K^+ balance is desirable and could be obtained by long-term use of K^+ binders (Kovesdy, 2017). A treatment of up to 12 months with SZC utilising a dose titration scheme with the starting dose of 5 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 in a long-term study (Spinowitz et al, 2019). However, in the US, only 0.1% of patients with a HK-related inpatient stay received a binder at discharge (Davis et al, 2019).

Hyperkalaemia is reported in less than 5% of the population, worldwide (Lederer and al, 2020) but may affect up to 10% of hospitalised patients (Rossignol et al, 2016). In addition to clinical consequences, HK is associated with increased health care costs and healthcare resource utilisation (HRU):

- Betts et al. found that patients with HK incurred $15,983 higher total healthcare costs and $9,293 higher inpatient costs (58% of the total cost difference) than patients without HK within 1 year. When hospitalised, patients with HK were 40% more likely to be re-admitted within 1 year compared with matched patients without HK. Similar to the findings from another work (Fitch et al, 2017), the study also showed that the difference in HRU and healthcare costs between patients with and without HK increased with CKD severity (Betts et al, 2018).
- There is limited evidence regarding outcomes following discharge from a HK-related hospitalisation. Post-discharge hospital admission rates are important hospital quality metrics to measure the effectiveness of hospital care with societal economic implications.

In another study, Betts assessed the post-discharge economic and hospital admission burdens associated with HK-related hospitalisations in the real world (Betts et al, 2020). Compared to patients hospitalised for reasons unrelated to HK, patients with HK-related hospitalisations had 56% to 58% higher rates of hospital admission within 30, 60, and 90 days after discharge. In this study, the total inpatient days within 1 year was nearly twice higher for hospitalisations related to HK as compared to hospitalisations not related to HK.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

This study will recruit participants who have mild-to-moderate HK. There is a risk of HK in those participants who are randomised to SoC and a risk of hypokalaemia in participants randomised to SZC. Hence, HK and hypokalaemia are the major medical risks for participants in this study. The following study design features were included to minimise the risk to participants:

- All participants will receive active treatment with SZC during the inpatient phase and only participants that have normalised K^+ will be randomised into the study, minimising the risk of HK in the randomised treatment phase.
- Visit 7 days post-discharge ensures that the participant's K^+ level is stable post-discharge, and medications can be changed as needed. Such adjustment may involve initiation of any K-binder in the SoC arm (Note: In the SZC arm, concomitant use of other K-binders is prohibited although rescue therapy with K-binder is allowed, see Section 6.7.1).
- The K^+ measurements at on-site study visits will provide investigators with up-to-date K^+ values, thereby allowing dose adjustments/discontinuation to occur as appropriate during the study visit.
- Any time study drug dose is adjusted, or in either treatment arm, if a concomitant medication which may affect K^+ levels is changed (eg, use of RAASi or diuretics), the participant needs to return to the site 7 (± 2) days later for a K^+ measurement and recording of adverse events (AEs) and concomitant medications.
- Hypokalaemia has been reported with SZC. The SZC dose titration and stopping rules, and rescue therapy rules based on K^+ monitoring, are included in this protocol to minimise the risk of HK and hypokalaemia.
- The risk of severe HK upon randomisation to SoC will be mitigated with monitoring of K^+ from the beginning of the randomised treatment through the end of treatment (EOT) visit.
- The risk of HK after the EOT visit will be mitigated by monitoring K^+, 1 week after the EOT.

- Oedema-related events (grouped terms include preferred terms (PTs) of oedema, oedema peripheral, generalized oedema, fluid retention, hypervolemia, localized oedema, and peripheral swelling) have been reported by patients treated with SZC, in particular at higher doses. Physical examinations to assess oedema will be performed and the participant will be weighed at pre-specified visits to ensure development of oedema will be detected early and appropriately managed.

More detailed information about the known and expected benefits and potential risks of SZC may be found in the Investigator's Brochure (IB).

Table 2 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
SZC		
Hypokalaemia	Common (≥ 1/100 to < 1/10). In clinical trials, 4.1% of SZC patients developed hypokalaemia with a K^+ value less than 3.5 mmol/L.	Monitoring K^+ and dose adjustments.
Oedema related events (includes fluid retention, generalised oedema, hypervolaemia, localised oedema, oedema, oedema peripheral, peripheral swelling)	Common (≥ 1/100 to < 1/10). In clinical trials with SZC, the most commonly reported adverse reaction was oedema related events which were reported by 5.7% SZC patients; 1.7%, 2.7%, 5.2%, and 14.3% of patients randomised to placebo, or SZC 5, 10, or 15 g once daily up to one month, respectively.	Physical examinations to assess oedema will be performed and the participant will be weighed at pre-specified visits to ensure development of oedema will be detected early. Oedema management as per investigators medical judgement.
Constipation	Common (≥1/100 to <1/10) In clinical studies conducted in countries with a predominantly Asian population, constipation with an estimated frequency of 8.9% occurred in patients receiving SZC; and was resolved with dose adjustment or treatment discontinuation.	Dose adjustment or discontinuation as per investigators medical judgement.

Abbreviations: K^+ = potassium; SZC = sodium zirconium cyclosilicate.

2.3.2 Benefit Assessment

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

The primary benefit for participants randomised to SZC treatment is expected to be the maintenance of NK after discharge from the hospital. Further, should the study hypothesis prove true, participants taking SZC will benefit from less frequent hospitalisations.

The approved dose adjustment algorithm will be used as per local label whenever a K^+ measurement is available, enabling participants to achieve and maintain NK. In accordance with the algorithm, the dose may be increased, reduced, or kept unchanged, depending on the current K^+ levels, adapting the dosing regimen to each participant and preventing unnecessarily high exposure to the product.

Participants treated with SoC may not obtain the same benefit in terms of HK management but may benefit from a closer follow-up. Participants will receive rescue medicine whenever clinically indicated.

Participants, irrespective of their treatment allocation, may benefit from more intense monitoring and attention to their underlying condition.

In the larger perspective, the main potential benefit of conducting this study lies in the possibility to generate scientific evidence for improved management of patients with CKD treated for HK, and potentially reduce the time spent at the hospital.

2.3.3 Overall Benefit: Risk Conclusion

Based on the known potential risks to study participants, the experience of SZC over the 4 years post-approval, the risk mitigations included in this protocol, and the long-term potential benefits of simplifying management of participants with HK associated with CKD, it is concluded that the study as proposed exposes recruited participants to an acceptable risk.

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

3 OBJECTIVES AND ENDPOINTS

The protocol objectives and endpoints are provided in Table 3.

Table 3 Objectives and Endpoints

Objectives	Estimand description/Endpoints
Primary	
• To evaluate the efficacy of continuing SZC as part of the discharge medications, compared to SoC, in maintaining NK	• Population: Full analysis set • Endpoint: Occurrence (yes/no) of NK (K^+ between 3.5 and 5.0 mmol/L, inclusive) at 180 days post-discharge. • Intercurrent event strategy: Participants who discontinue treatment with a K^+ measurement at 180 days post-discharge will have this value used irrespective of treatment discontinuation (treatment policy strategy). Use of rescue therapy for HK will be considered to be non-response (composite variable strategy). The RAASi down-titration (including discontinuation) will be considered to be non-response (composite variable strategy). Participants who die of any cause prior to 180 days post-discharge or who are lost to follow-up for any reason will be considered to be non-response (composite variable strategy). • Population level summary (analysis): Logistic regression analysis with response (occurrence) as the dependent variable and randomised treatment group as the independent variable. The odds ratio along with the two-sided 95% confidence intervals and two-sided p-value (significance declared <0.05) will be displayed.

Secondary	
• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of the composite outcome of all-cause hospital admissions, or ED visits with HK as a contributing factor, or all-cause death, or use of rescue-therapy for HK	• Population: Full analysis set • Endpoint: Time to first occurrence of all-cause hospital admissions, or ED visits with HK as a contributing factor, or all-cause death, or use of rescue therapy for HK at any time post-discharge up to 180 days. • Intercurrent event strategy: Participants who discontinue treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Rescue therapy for HK will be considered an event (composite variable strategy). Participants who require ED visits without HK as a contributing factor will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause will be considered an event (composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). • Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.

• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of all-cause hospital admissions or ED visits with HK as a contributing factor	• Population: Full analysis set • Endpoint: Time to first occurrence of all-cause hospital admission, or ED visit with HK as a contributing factor at any time post-discharge up to 180 days. • Intercurrent event strategy: Participants who discontinue treatment or who have ED visit without HK as a contributing factor will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause, use rescue therapy for HK or are lost to follow-up will be censored at the date of death, use of rescue therapy or loss to follow-up, respectively. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). • Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.

• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the number of all-cause hospital admissions or ED visits with HK as a contributing factor	• Population: Full analysis set • Endpoint: Number of all-cause hospital admission, or ED visits with HK as a contributing factor at any time post-discharge up to 180 days. • Intercurrent event strategy: Participants who discontinue treatment, use rescue therapy for HK or who have an ED visit without HK as a contributing factor, will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause or are lost to follow-up will be censored at the date of death or loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). • Population level summary (analysis): Mean number of all-cause hospital admissions or ED visits, with HK as a contributing factor by randomised treatment group. Negative binomial regression model with randomised treatment group as the independent variable and including duration of time in study as an offset. The incidence rate (SZC/SoC), along with 95% confidence intervals and two-sided p-values will be displayed.

• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of hospital admissions or ED visits with HK as a contributing factor	• Population: Full analysis set • Endpoint: Time to first occurrence of hospital admission or ED visit, both with HK as a contributing factor at any time post-discharge up to 180 days. • Intercurrent event strategy: Participants who discontinue treatment or who have hospital admission or ED visit without HK as a contributing factor will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause, use rescue therapy for HK or are lost to follow-up will be censored at the date of death, use of rescue therapy or loss to follow-up, respectively. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). • Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.

• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the number of hospital admissions or ED visits with HK as a contributing factor	• Population: Full analysis set • Endpoint: Number of hospital admission or ED visits with HK as a contributing factor, at any time post-discharge up to 180 days. • Intercurrent event strategy: Participants who discontinue treatment, use rescue therapy for HK or who have a hospital admission, or an ED visit without HK as a contributing factor, will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause or are lost to follow-up will be censored at the date of death or loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). • Population level summary (analysis): Mean number of hospital admissions or ED visits, with HK as a contributing factor by randomised treatment group. Negative binomial regression model with randomised treatment group as the independent variable and including duration of time in study as an offset. The incidence rate (SZC/SoC), along with 95% confidence intervals and two-sided p-values will be displayed.
• To evaluate the effect of continuing SZC as part of the discharge medications compared to SoC on reducing the risk of RAASi down-titration (or discontinuation)	• Population: Full analysis set • Endpoint: Time to first occurrence of RAASi down-titration (or discontinuation) at any time post-discharge up to 180 days. • Intercurrent event strategy: Participants who discontinue treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause or are lost to follow-up will be censored at their date of death or loss to follow-up, respectively. • Population level summary (analysis): Log-rank test for testing, Cox proportional hazards ratio for estimation with randomised treatment group as the independent variable.

Safety	
• To assess the safety and tolerability of SZC compared to SoC	Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical safety laboratory, and ECG. • Population: Safety set open and safety set randomised • Endpoint: Assessments related to AEs cover: - Occurrence/frequency - Relationship to SZC as assessed by investigator - Intensity - Seriousness - Death - AEs leading to discontinuation of SZC. • Intercurrent event strategy: Discontinuation of treatment and use of rescue therapy for HK will follow the treatment policy strategy (ie, regardless of the intercurrent event). • Population level summary (analysis): Categorical summary by treatment group as received.

Exploratory	
• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of the composite outcome of hospital admissions or ED visits with HK as a contributing factor or all-cause death	• Population: Full analysis set • Endpoint: Time to first occurrence of any component of hospital admission or ED visit, both with HK as a contributing factor, or all-cause death at any time post-discharge up to 180 days. • Intercurrent event strategy: Participants who discontinue treatment, use rescue therapy for HK, or require hospital admissions or ED visits without HK as a contributing factor will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who are lost to follow-up will be censored at their date of loss to follow-up. Participants who die of any cause will be considered an event (composite variable strategy). Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). • Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.

• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of hospital admissions with HK as a contributing factor or all-cause death	• Population: Full analysis set • Endpoint: Time to first occurrence of either hospital admission with HK as a contributing factor or all-cause death at any time post-discharge up to 180 days. • Intercurrent event strategy: Participants who discontinue treatment, have an ED visit without hospital admission with HK as a contributing factor, hospital admission or ED visits without HK as a contributing factor or use rescue therapy for HK will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who die of any cause will be considered an event (composite variable strategy). Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). • Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.

• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of ED visits with HK as a contributing factor or all-cause death	• Population: Full analysis set • Endpoint: Time to first occurrence of either ED visit with HK as a contributing factor or all-cause death at any time post-discharge up to 180 days. • Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who require any hospital admission or ED visits without HK as a contributing factor or who use rescue therapy will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause will be considered an event (composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). • Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.

• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of the composite outcome of all-cause hospitalisations, ED visits, all-cause death, or use of rescue therapy for HK	• Population: Full analysis set • Endpoint: Time to first occurrence of any component of all-cause hospitalisations, ED visits, use of rescue therapy for HK or all-cause death in each arm at any time post-discharge up to 180 days. • Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Rescue therapy for HK will be considered an event (composite variable strategy). Participants who require any hospital admission or ED visit will be considered an event (composite variable strategy). Participants who die of any cause will be considered an event (composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). • Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.

• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, on mean K^+ levels	• Population: Full analysis set • Endpoint: K^+ level up to 180 days post-discharge. • Intercurrent event strategy: K^+ levels from participants after discontinuation of treatment, hospital admissions or ED visits for any reason will be included in the analysis (treatment policy strategy). Participants who use rescue therapy for HK will have K^+ levels prior to rescue therapy for HK used in the analysis (while on treatment strategy). Participants who have RAASi down-titration (including discontinuation) will have K^+ levels prior to the RAASi down-titration used in the analysis (while on treatment strategy). Participants who die of any cause or who are lost to follow-up prior to 180 days post-discharge will have all available K^+ included in the analysis (treatment policy strategy). • Population level summary (analysis): Mixed model repeated measures analysis with randomised treatment group as an independent variable. The coefficient estimates, standard error, 95% confidence intervals for coefficient estimate, and p-values will be reported.
• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the number of hospital admissions with HK as a contributing factor	• Population: Full analysis set • Endpoint: Number of hospital admissions with HK as a contributing factor, at any time post-discharge up to 180 days. • Intercurrent event strategy: Participants who discontinue treatment, use rescue therapy for HK, have RAASi down-titration (including discontinuation), experience all-cause death or loss to follow-up prior to 180 days post-discharge will have all available hospital admission data used irrespective of the intercurrent event (treatment policy strategy). • Population level summary: Mean number of hospital admissions with HK as a contributing factor, by randomised treatment group. Negative binomial regression model with randomised treatment group as a main effect and including duration of time in study as an offset. The incidence rate ratio (SZC/SoC), along with 95% confidence intervals and two-sided p-values will be displayed.

• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the total LOS in hospitalisations with HK as a contributing factor	• Continuous variable summary statistics (median and mean) of total LOS with HK as a contributing factor by randomised treatment group. Wilcoxon rank-sum test by randomised treatment group.
• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the total LOS in all-cause hospitalisations	• Continuous variable summary statistics (median and mean) of total LOS in all-cause hospitalisations by randomised treatment group. Wilcoxon rank-sum test by randomised treatment group.
• To evaluate the effect of continuing SZC as part of discharge medications, compared to SoC in reducing the incidence of K-binder use	• Time to first occurrence of K-binder use in each arm at any time post-discharge up to 180 days.
• To evaluate the effect of continuing SZC as part of discharge medications, compared to SoC in reducing the frequency and duration of K-binder use	• Time to discontinuation of K-binder from initiation in each arm in the first instance of K-binder use post-discharge up to 180 days. • Frequency of the use of K-binder to treat HK at any time post-discharge up to 180 days in each arm.
• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of rescue therapy for HK use	• Time to first occurrence of rescue therapy use in each arm at any time post-discharge up to 180 days.
• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of the composite outcome of all-cause hospitalisations, ED visits, or outpatient visits	• Time to first occurrence of all-cause hospitalisations, ED visits, or outpatient visits in each arm at any time post-discharge up to 180 days.
• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in the change in eGFR	• Rate of change in (slope) eGFR from inpatient phase to 90 and 180 days post-discharge respectively, in each arm.
• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in the incidence of dialysis initiation	• Time to first occurrence of dialysis initiation in each arm at any time post-discharge up to 180 days.
• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of ICU admissions	• Time to first occurrence of ICU admissions in each arm at any time post-discharge up to 180 days.

• To evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, on the ability to continue RAASi	• Descriptive summary of use of, and changes in use of, RAASi, at up to 90 and 180 days post-discharge, respectively, in each arm.

Abbreviations: AE = adverse event; ECG = electrocardiogram; ED = emergency department; eGFR = estimated glomerular filtration rate; HK = hyperkalaemia; HR = hazard ratio; ICU = intensive care unit; K^+ = potassium; LOS = length of stay; NK = normokalaemia or normokalaemic; RAASi = renin-angiotensin-aldosterone system inhibitor; SoC = standard of care; SZC = sodium zirconium cyclosilicate.

4 STUDY DESIGN

4.1 Overall Design

- This is a Phase 4, randomised, controlled, open-label, parallel-group, multicentre study in participants with CKD treated for HK whilst in hospital.
- Participants from 30 to 50 sites in 4 to 7 countries will be screened for enrolment. Assuming a 20% drop out rate from enrolment to randomisation and a 20% drop out post-discharge (post-randomisation), approximately 163 participants will have to be enrolled to achieve 104 evaluable participants (52 per arm). In total, up to a maximum of 163 participants will be enrolled, resulting in approximately 130 participants discharged and randomised and 104 evaluable participants (52 per arm).
- The study plans to enrol approximately equal numbers of participants with mild HK (K^+ between > 5.0 and ≤ 5.5 mmol/L) and with moderate/severe HK (K^+ between > 5.5 and ≤ 6.5 mmol/L), with a minimum of 30% of the enrolled participants in either group.
- During the in-hospital phase, participants will be treated with SZC as per local label (correction and/or maintenance treatment, see Section 6.1), starting at baseline and based on local K^+ measurement obtained within 24 hours of treatment initiation:
  - Participants with HK (K+ between > 5.0 and ≤ 6.5 mmol/L): 1) stop current K-binder if any, 2) start SZC correction dose (note: participants currently on SZC should continue SZC correction dose, up to 72 hours).
  - Participants currently receiving any treatment for the current episode of HK and are already NK at baseline (K+ ≤ 5.0 mmol/L): 1) stop any current K-binder, 2) start SZC maintenance dose (note: participants currently on SZC maintenance dose should continue SZC maintenance dose).
  - All treatment decisions, including modification of the ongoing therapy for HK, must be based on the investigator's medical judgement of the participant's best interest.
- At discharge, NK participants who have been treated with SZC for between 1 and 21 days whilst in hospital and are started on SZC maintenance dose will be randomised in a 1:1 ratio to one of the following arms:
  - Arm A: Participants discharged with SZC, as per local label, to manage HK until the end of the outpatient phase
  - Arm B: Participants discharged with SoC, as per local practice, to manage HK until the end of study.
  - Note: Participants intended to be discharged with a K-binder (as per the site routine medical practice) will not be randomised and will be discontinued from the study. Still, participants randomised into Arm B may have a K-binder prescribed at Day 7 post-discharge (or after Day 7 post-discharge), to treat confirmed HK or in case there

is an increase in K^+ level since discharge that, in the investigator's opinion, requires therapy.

- The total duration of the study for each participant will be up to approximately 6 months.
- Study visit schedule is as follows:
  - In-hospital phase:
    - The screening visit will occur while the participant is at the hospital (up to 21 days before discharge; medical monitor's approval may be sought for allowing longer duration hospital stays for specific participants) in order to check eligibility criteria
    - Inpatient phase:
      - The baseline visit (can occur the same day as the screening visit) where treatment with SZC will be initiated
      - The discharge visit, 1 to 20 days after baseline; medical monitor's approval may be sought for allowing longer duration hospital stays for specific participants). Randomisation will occur at day of discharge.
  - Outpatient phase:
    - Visits will occur at 7, 30, 60, 90, 120, 150, and 180 (EOT) days after randomisation. Only visits at 7, 90 and 180 days after randomisation will be on-site visits, the remaining being telephone visits. If dose titration occurs at any time during the outpatient phase, unscheduled dispensation visits will be performed.
  - Follow-up phase:
    - A follow-up on-site visit (end of study visit) will occur approximately 7 days after EOT.
- Data will be collected at on-site visits, via telephone visits and medical chart reviews.
- An adjudication committee will be involved in the study (see Appendix A 5).

4.2 Scientific Rationale for Study Design

Hospitalised CKD patients with HK are at higher risk of recurrent HK and of readmission than hospitalised CKD patients without HK.

CONTINUITY will recruit hospitalised participants with CKD (see inclusion criterion #3 for details) and HK (see inclusion criterion #4 for details). After treatment with SZC, the participants reaching NK will be randomised to either SZC or SoC treatment at discharge. The study aims to show that prescribing SZC as a part of the discharge medications in this population will result in an increased likelihood of maintained NK and a reduced incidence of all-cause hospital admissions or ED visits with HK as a contributing factor, compared with participants discharged with SoC.

The study interventions are SZC (as per local label) and SoC (as per local practice) groups. Participants in both groups will have K^+ normalised at the beginning of the outpatient phase and monitoring of K^+ will occur during study. Titration of SZC will be based on K^+ values, according to Section 6.2 to ensure participants receive SZC at an individually optimised dose. Clear guidance is in place for rescue therapy for HK (see Section 6.7.1) as well as for study discontinuation (see Section 7).

The SoC as per local practice is used as comparator as there is currently no standardised therapy to treat patients with CKD and HK after discharge from the hospital.

The study is designed to align as much as possible with real-world clinical practice, with low number of mandated on-site follow-up visits (at Days 7, 90, and 180 post-discharge) and by using medical chart reviews and telephone contacts in between for complementary data collection.

CONTINUITY is a Phase 4 study, and as such it is designed to provide necessary and sufficient data to determine if there is an additional benefit of prescribing SZC at discharge in the selected population. The primary objective is to evaluate the efficacy of continuing SZC as part of the discharge medications, compared to SoC, in maintaining NK. The main secondary objective is to evaluate the effect of continuing SZC as part of the discharge medications, compared to SoC, in reducing the incidence of the composite outcome of all-cause hospital admissions or ED visits with HK as a contributing factor. Other secondary objectives include the outcome of hospital admissions with HK as a contributing factor. The definition of hospital admissions and ED visits *with HK as a contributing factor*, rather than *due to* HK, is based on the fact that HK is rarely determined as the primary cause of these health care encounters. An adjudication committee will be formed to determine whether HK was a contributing cause of the encounter. Note: This adjudication committee will also review the reported concomitant medications to determine RAASi down-titration/discontinuation events and use of rescue therapy for HK.

4.2.1 Participant Input into Design

Not applicable.

4.3 Justification for Dose

During both in-hospital and outpatient phases, SZC will be dosed according to its local label; see Sections 6.1 and 6.2.

Clinical studies in participants with HK consistently demonstrated that initial treatment with SZC 10 g three times daily (TID) for 24 hours up to 72 hours resulted in clinically meaningful K^+ reduction with a majority of participants achieving NK within 24 to 48 hours. Moreover, participants with higher baseline K^+ levels had greater reductions in K^+ levels (Hoy, 2018).

Onset of efficacy was rapid with K^+ reduction observed as early as 1 hour after dose intake (Hoy, 2018).

After correction of HK, continued maintenance treatment for 28 days with SZC 5, 10, or 15 g daily resulted in continued effective control of K^+ within the NK range. The proportion of participants who remained NK at the EOT with SZC 5, 10, and 15 g daily increased dose-dependently (range: 71% to 85%) and was superior to placebo.

Long-term maintenance treatment with SZC for up to 12 months has also been studied. Once daily (QD) dosing with SZC, starting from 5 g QD and subsequently individualized, provided maintenance of NK for up to 12 months, with 87% of participants achieving $K^+ \leq 5.1$ mmol/L at Day 365 (Spinowitz et al, 2019).

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 scheduled procedure at visit 11, as shown in the Schedule of Activities (SoA; Table 1).

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for 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.Rescreening of participants is allowed as detailed in Section 5.4.

The distribution of participants across the range of K^+ levels will be operationally controlled by ensuring that the following ratios are met:

- Approximately 50% enrolled participants with mild HK (K^+ between > 5.0 and $\leq$ 5.5 mmol/L) and approximately 50% with moderate/severe HK (K^+ between > 5.5 and $\leq$ 6.5 mmol/L)
- A minimum of 30% of enrolled participants in each group.

5.1 Inclusion Criteria

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

Age

1 Must be 18 years of age or older, at the time of signing the informed consent

Type of Participant and Disease Characteristics

2 Admitted to hospital (inpatient care; directly or from ED)

3 With:

- Diagnosed CKD (any stage)

or

- eGFR < 90 mL/min/1.73 m^2 at, or within 3 months of, study screening, based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al, 2009). Note: Race/ethnicity should not be included in CKD-EPI equation calculation.

4 Local laboratory K^+ measurement within 24 hours of baseline visit (visit 2), where result is either:

- Hyperkalaemic as defined by site's local practice and $K^+ \leq 6.5$ mmol/L
- Or, normokalaemic: K^+ between ≥ 3.5 and ≤ 5.0 mmol/L, where patient started and is receiving treatment for this episode of HK.

Sex

5 Male or female

Informed Consent

6 Capable and willing 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 protocol.

5.2 Exclusion Criteria

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

Medical Conditions

1 Hospitalisation for an acute cardiovascular event within 12 weeks prior to screening

2 Unable to take oral SZC drug mix

3 -

4 With a life expectancy of less than 6 months

5 Any medical condition that, in the opinion of the investigator makes the participant not suitable for inclusion

6 -

7 QT interval corrected by the Fridericia method (QTcF) > 550 msec

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

9 Congenital long QT syndrome

10 Clinically significant arrythmias as judged by the investigator

11 -

12 -

Prior/Concomitant Therapy

13 Ongoing treatment with SZC or patiromer before current ED visit/hospital admission (ongoing treatment with other K-binders before current ED visit/hospital admission is allowed). Note: Initiation of SZC or patiromer during the current ED visit/hospitalisation preceding enrolment is allowed.

14 Chronic haemodialysis or peritoneal dialysis or the recipient of or scheduled date for a kidney transplant. Note: Emergency/unscheduled haemodialysis to treat HK during the current ED visit/hospitalisation preceding enrolment is allowed.

Prior/Concurrent Clinical Study Experience

15 Participation in another clinical study with an investigational medicinal product (IMP) administered during the month before screening.

16 Known hypersensitivity to SZC or any of the excipients of the product

Other Exclusions

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

18 Judgment 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

19 Previous randomisation in the present study

20 For women only: Women of child-bearing potential (WOCBP; ie, those who are not chemically or surgically sterilised or who are not post-menopausal) who are not willing to use one of the methods of contraception described hereafter, or who are not stable on the contraception method for the last one month, from the time of signing the informed consent throughout the study and 7 days after the last dose:

a) Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal

b) Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable

c) Intrauterine device

d) Intrauterine hormone-releasing system

e) Bilateral tubal occlusion

f) Vasectomised partner (vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP participant and that the vasectomised partner has received medical assessment of the surgical success

g) Sexual abstinence: it is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

21 For WOCBP only: Women who have a positive pregnancy test at screening OR women who are breastfeeding.

5.3 Lifestyle Considerations

No lifestyle restrictions are required in the study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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 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) and should be recorded in the electronic Case Report Form (eCRF).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened (maximum twice) if:

- screen failure is due to not meeting K^+ or eGFR inclusion criteria
- exclusion criteria are no longer applicable
- technical issues are encountered at enrolment site visit.

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

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 study protocol.

6.1 Screening and Inpatient Phase

Participants with HK (see inclusion criterion #4) and not on SZC or patiromer before this current ED visit/hospital admission (initiation of SZC or patiromer during ED visit/hospitalisation preceding enrolment is allowed), will start SZC, as per local label, during the inpatient phase. Initiation of SZC treatment will be based on local measurement of K^+, obtained within 24 hours prior to first dose of on-study SZC:

- Correction treatment: 10 g, TID for up to 72 hours. Typically, NK is achieved within 24 to 48 hours. If participants are still hyperkalaemic after 48 hours of treatment, the same regimen can be continued for an additional 24 hours. If NK is not achieved after 72 hours of treatment, other treatment approaches should be considered, and the participant discontinued from the study due to lack of SZC effect. Participants who received any HK treatment during current ED visit/hospitalisation preceding enrolment and are NK at baseline can directly start the maintenance dose of SZC (see hereafter).
- Maintenance treatment (once NK [K^+ between 3.5 and 5.0 mmol/L, inclusive] is reached): 5 g, QD. Dose will be adjusted based on K^+ (see Table 4). The recommended maintenance dose range is from 5 g every other day to 10 g daily.

Participants with NK and who have been started on a maintenance dose for SZC (per local label) at the time of discharge will be randomised at discharge to either Arm A (SZC per local label) or Arm B (SoC, as per local practice) and enter the outpatient phase.

The following participants will not be eligible for randomisation:

- Participant intended to be discharged on a K-binder as per the site routine medical practice (discontinued from the study)
- Participant with an in-hospital phase exceeding 21 days (including screening), except when study medical monitor's approval was sought for longer duration of hospital stays for specific participants
- Participants with $K^+ > 5.0$ mmol/L at discharge; these participants will be discontinued from the study treatment and followed up as per protocol
- Participants with $K^+ < 3.5$ mmol/L at discharge; these participants will be discontinued from study treatment and will be followed per protocol.

6.2 Outpatient Phase

Participants randomised to Arm A will be discharged with SZC dosed per local label (from 5 g every other day to 10 g daily) to manage K^+ until the EOT (180 days post-discharge).

As per label, SZC dose titration will be allowed based on K^+ levels as detailed in Table 4.

Table 4 Dose Titration and Discontinuation Criteria During the Outpatient Phase

K^+ (mmol/L)	Dose Titration and Discontinuation Criteria for Abnormal K^+
< 3.0	• Treatment permanently discontinued (see Section 7.1.1). Check ECG and treat according to medical judgment.
3.0 - 3.4	• Check ECG, permanently discontinue treatment if serious arrhythmia found and treat according to medical judgment.

K^+ (mmol/L)	Dose Titration and Discontinuation Criteria for Abnormal K^+
	• If no serious arrhythmia found, investigator to consider to down-titrate[a] or pause SZC and treat according to medical judgment. Participants with heart failure should pause study drug. • Increase monitoring until $K^+ \geq 3.5$ mmol/L.[a] • Evaluate for underlying risk for hypokalaemia. If hypokalaemia resolves and participant deemed appropriate to restart treatment (for participants who have paused SZC), then the investigator should consider to restart SZC at a lower dose.[a]
3.5 - 5.0	• No change in SZC dose is recommended.
5.1 – 5.5	• Increase SZC dose by 5 g QD increments up to a maximum of 10 g QD.[a] • Increase monitoring until K^+ in normal range.
5.6 – 6.0	• Check ECG, discontinue treatment if serious arrhythmia found and treat according to medical judgment. • If no serious arrhythmia, increase SZC dose by 5 g QD increments up to a maximum of 10 g QD.[a] • Further K^+ monitoring and treatment per investigator medical judgment based on participant risk and benefit. • Increase monitoring frequency until K^+ in normal range.
> 6.0	• Treatment permanently discontinued (see Section 7.1.1); initiate rescue therapy (see Section 6.7.1 for rescue therapy). • Check ECG and treat according to medical judgment.

Abbreviations: ECG = electrocardiogram; K^+ = potassium; QD = once daily; RAASi = renin angiotensin-aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate.

[a] Any time study drug dose is adjusted, or if in either treatment arm, a concomitant medication which may affect K^+ levels is changed (eg, use of RAASi or diuretics), the participant needs to return to the site 7 (± 2) days later for a K^+ measurement and recording of adverse events and concomitant medications.

Participants randomised to Arm B will be discharged without SZC and will receive SoC per local practice for managing their K^+ until the EOT (180 days post-discharge). The SoC will be at the discretion of the treating physician; however, participants intended to be discharged with a K-binder will not be randomised. However, participants in Arm B may have a K-binder prescribed at Day 7 post-discharge (or after Day 7 post-discharge) to treat confirmed HK or in case there is an increase in K^+ level since discharge that, in the investigator's opinion, requires therapy.

The K^+ levels will be measured at on-site visits at Days 7 (local laboratory), 90 (local and central laboratories), and 180 (local and central laboratories) (see Sections 8.1.1 and 8.2.4). Overall monitoring frequency will depend upon a variety of factors including other medications, progression of CKD, and dietary K^+ intake. It is the responsibility of the treating physicians to check the participant K^+ as medically appropriate/in accordance with the label (for both SZC and SoC arms). In addition to the scheduled on-site visits, participants should return to the site for a local K^+ measurement 7 (± 2) days after any dose adjustment to SZC.

Additionally, participants in either treatment arm should have their K^+ measured locally 7 (± 2) days after changes are made to medications that affect K^+ levels (eg, use of RAASi or diuretics).

Such additional K^+ checks and site visits will take place as clinically indicated and the resulting data, including AEs and concomitant medication information, relating to these visits will also be collected during the study.

6.3 Study Interventions Administered

6.3.1 Investigational Products

Table 5 provides information on the IMP.

Table 5 Investigational Products

Intervention Name	Sodium zirconium cyclosilicate (SZC)
Dose Formulation/Unit Dose Strength	White to grey crystalline powder for oral suspension in 5 g sachets
Route of Administration	Oral
Use	Investigational product
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Study treatment will be provided in sachets. Each sachet will be labeled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement. Label text will be translated into local language.

During the inpatient phase, SZC will be dispensed daily to all participants.

During the outpatient phase, SZC will be supplied, at the site, to the participants randomised to Arm A at the timepoints indicated in the SoA (Table 1), in the amount expected to account for its usage as per the investigator's prescription, including possible dose modifications that might occur before the next scheduled dispensation visit. Sodium zirconium cyclosilicate may also be dispensed at unscheduled visits. Home delivery may be considered as alternative mode of supplying drug where local regulations allow.

For each participant, the investigator will select the SoC treatment (based on the most appropriate option for the participant) that the participant would receive if randomised to the SoC arm prior to randomisation of the participant. This must be completed for all participants.

The information will be recorded in the Interactive Response Technology/Randomisation and Trial Supply Management (IRT/RTSM) system.

6.4 Preparation/Handling/Storage/Accountability

The oral suspension to be administered to participants during the inpatient phase of the study should be prepared in the following way: the entire contents of the sachet should be emptied in a drinking glass containing approximately 45 ml of water and stirred well. The tasteless liquid should be drunk while still cloudy. The powder will not dissolve. If the powder settles, the liquid should be stirred again and taken. If needed, rinse the glass with more water to ensure that all of the content is taken. If 2 sachets (total dose of 10 g) are needed, the same volume of water (45 ml) should be used (ie, no increase in volume of water).

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

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.

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).

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

6.5 Measures to Minimise Bias: Randomisation and Blinding

This is an open-label study; however, the specific intervention to be taken by a participant will be randomly assigned using an IRT/RTSM. Before the study is initiated, call-in directions for the IRT and/or the log-in information and directions for the RTSM will be provided to each site. The site will contact the IRT/RTSM prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable eCRF, if required. Once a randomisation number has been assigned it must not be re-assigned. Potential bias will be reduced by central randomisation.

Study intervention will be dispensed at the study visits summarised in the SoA (Table 1) and may also be dispensed at unscheduled visits.

Dispensed but not used study intervention in unopened sachets may be re-dispensed to the

same or other study participants in the inpatient phase.

Returned study intervention in unopened packets or sachets may be re-dispensed to the same study participant during the outpatient phase.

6.6 Study Intervention Compliance

When participants are dosed at the site, which will occur during the inpatient phase, they will receive SZC directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the hospital will be recorded in the source documents and recorded in the eCRF. The dose of SZC 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 interventions at home (SZC or SoC), compliance with study interventions will be assessed at each visit (both on-site and telephone visits). Compliance will be assessed by counting returned sachets and direct questioning during the visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF and in the source documentation.

A record of the number of SZC sachets for SZC 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 or increases will also be recorded in the eCRF.

There will not be accountability for participants allocated to SoC.

6.7 Concomitant Therapy

Sodium zirconium cyclosilicate 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 gastric pH-dependent bioavailability.

Examples of drugs that should be taken 2 hours before or after SZC to avoid possible raised gastric pH drug interaction are listed below:

Class of Drug	Drugs
Azole antifungals	Ketoconazole, itraconazole, posaconazole
Anti-human immunodeficiency drugs	Atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir, rilpivirine
Tyrosine kinase inhibitors	Erlotinib, dasatinib, nilotinib

Note, this list is not exhaustive. Please refer to the SmPC of concomitant medications the participant gets administered for pH dependent bioavailability.

Sodium zirconium cyclosilicate can be co-administered with oral medications that do not exhibit pH-dependent bioavailability without spacing of dosing times.

In a drug-drug interaction study in healthy volunteers, co-administration of SZC 15 g with tacrolimus 5 mg resulted in a decreased tacrolimus area under concentration curve and maximum observed plasma concentration by 37% and 29%, respectively. Therefore, tacrolimus should be taken at least 2 hours before or after SZC. In the same study, co-administration of SZC and cyclosporin did not show a clinically meaningful interaction.

Potassium binders will not be authorized in Arm A, unless they are prescribed as rescue therapy (see Section 6.7.1).

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.

If the participant received one (or more) Coronavirus disease 2019 (COVID-19) vaccination(s) prior to enrolment, then this needs to be recorded in the eCRF.

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

6.7.1 Rescue Medicine

Rescue therapy is allowed and is at the discretion of the treating physician (see Table 4 for guidance for participants receiving SZC). For both arms, rescue therapy is defined as any therapeutic intervention considered necessary in accordance to local practice patterns to manage high K^+ in the setting of severe HK as defined by the treating physician and site. This may include, but not limited to:

1) beta-adrenergic agonists
2) calcium gluconate
3) sodium bicarbonate
4) intravenous insulin/glucose
5) K-binders[1]
6) any emergency dialysis or other forms of renal replacement treatments given with the goal of controlling the HK.

Rescue therapy should be followed by the appropriate SZC dose adjustment and proper documentation of the event.

The sponsor will not supply rescue therapy that will be obtained locally.

The date and time of rescue therapy administration, as well as the name and dosage regimen of the rescue therapy, must be recorded in the eCRF. Additionally, the adjudication committee will review reported concomitant medications to determine if any should be included as rescue therapy for HK.

Use of rescue therapy will be treated statistically as described in the statistical analysis plan (SAP). See Statistical Considerations, Section 9, for implications of the use of rescue therapy and/or other K-binders to the analysis of endpoints.

6.8 Dose Modification

For Arm A, see Table 4 for SZC dose titration.

For Arm B, SoC will be adjusted at the discretion of the treating physician or the investigator.

[1] While participants intended to be discharged on a binder will not be eligible for randomisation, a binder may be needed as rescue therapy. Rescue therapy with binder is defined as the addition of any binder, excluding SZC, to Arm A or the addition of any binder, including SZC, to Arm B. The study is open label, ie, the investigator shall be aware of whether participants are treated with SZC. As per local practice, SZC should be withdrawn if and when another binder is initiated.

6.9 Intervention After the End of the Study

No intervention will follow the end of the study. Decision to continue on SZC treatment or SoC will be at investigator's discretion.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

7.1.1 Permanent 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 be followed up according to the SoA (Table 1). See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

To minimize risk for events related to severe hypokalaemia, the following discontinuation criterion will be followed:

- Confirmed $K^+ < 3.0$ mmol/L by taking a second measurement after a ≥ 10-minute interval, at any time during the study, the participant should immediately receive appropriate medical intervention and study intervention should be permanently discontinued.

To minimize risk for events related to severe HK, the following discontinuation criterion will be followed:

- Confirmed $K^+ > 6.0$ mmol/L by taking a second measurement after a ≥ 10-minute interval, at any time during the study, the participant should immediately receive appropriate medical intervention and study intervention should be permanently discontinued.

To minimize risk for events related to prolongation of QT interval corrected (QTc), the following discontinuation criteria will be followed:

- If an absolute QTc > 550 ms, or an increase in QTc interval > 60 ms from baseline to more than 500 ms is reached, the participant should immediately receive appropriate medical intervention and be permanently discontinued from the study intervention. The QTcF algorithm is recommended. All participants meeting the QTc > 500 ms criterion should immediately have K^+ assessed, if not already done within 1 hour of performing the electrocardiogram (ECG).

For serious arrhythmia (eg, associated with $K^+ < 3.5$ or > 5.6 mmol/L), study drug should be permanently discontinued.

Other reasons for discontinuation of study intervention may include:

- Participant decision; the participant is at any time free to discontinue treatment, without prejudice to further treatment.
- Incorrectly randomised participant, in whom the inclusion/exclusion criteria violation would put the participant at undue risk. This will require a discussion with the medical team, who will provide a final outcome / action.
- Adverse event for which the investigator judges continued treatment may put the participant at undue risk.
- Severe noncompliance with the clinical study protocol (CSP)
- Pregnancy (see Section 8.3.8).

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

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

7.1.2 Temporary Discontinuation

If K^+ ranges from 3.0 to 3.4 mmol/L, the investigator will consider SZC administration to be either down-titrated or paused and hypokalaemia should be managed as per standard practice. Participants with heart failure should pause study drug. The participant should be evaluated for any risk factors for hypokalaemia, including any intercurrent illness or comorbidity. Sodium zirconium cyclosilicate administration can be resumed (if paused), if indicated, but only after the intercurrent medical condition that precipitated the hypokalaemia has improved and K^+ has returned to the target range of normal levels (3.5 to 5.0 mmol/L, inclusive). The investigator will consider re-starting SZC with a lower dose.

If participant temporarily ($\leq$ 14 days) discontinues study intervention for reasons other than hypokalaemia, SZC administration can be resumed once participant condition is stabilised according to investigator judgement, and if the participant is willing to take treatment.

Any time study drug dose is adjusted, or if a concomitant medication which may affect K^+ levels is changed (eg, use of RAASi or diuretics), the participant needs to return to the site 7 ($\pm$ 2) days later for a K^+ measurement and recording of AEs and concomitant medications.

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 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 no contact has been established by the time the study is completed (see Section 4.4), such that there is insufficient information to determine the participant's status at that time.

Participants who decline to continue participation in the study, including telephone contact, should be documented as 'withdrawal of consent" rather than "lost to follow-up'. Investigators should document attempts to re-establish contact with missing participants throughout the study period. If contact with a missing participant is re-established, the participant should not be considered lost to follow-up and evaluations should resume according to the protocol.

The following actions must be taken if a participant fails to return to the clinic or to answer a phone call 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.

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

8 STUDY ASSESSMENTS AND 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 (Table 1), 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 or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).

8.1 Efficacy Assessments

8.1.1 Primary Endpoint

Potassium will be measured after vital signs, ECG (when applicable), and physical examination (when applicable), at timepoints indicated in the SoA (see Table 1). Samples will be analysed by central and local laboratories at day of discharge, + 90 days, + 180 days, and early discontinuation (E/D) visits. Central laboratory will only be used at baseline. Local laboratory only may be used at all other visits, including + 7 days and any unscheduled visit, for treatment decision.

Central laboratory K^+ values will be used for study endpoint assessments while local laboratory assessments may be used for inclusion/exclusion criteria, titration decisions, and clinical decisions.

All K^+ samples should be examined and any overtly haemolysed samples must be redrawn.

Potassium will be measured to assess NK (3.5 to 5.0 mmol/L inclusive) occurrence at 180 days post-discharge.

Note: K^+ results will also be used for study intervention titration. Any time study drug dose is adjusted, a local K^+ measurement will need to be performed 7 (± 2) days later. Additionally, participants in either treatment arm should have their K^+ measured locally 1 week after changes are made to medications that affect K^+ levels (eg, use of RAASi or diuretics). These K^+ checks will be performed in addition to the scheduled study assessments, and the resulting data will also be collected in the study.

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

8.1.2 Main Secondary Endpoints

- **Hospital admissions** with HK as a contributing factor (based on clinical judgement and confirmed by adjudication committee, see Appendix A 5), and all-cause, respectively, including time of event and number of events, as well as length of stay (LOS) (as an exploratory endpoint).
- **ED visits** with HK as a contributing factor (based on clinical judgement and confirmed by adjudication committee, see Appendix A 5), including time of event.
- All-cause deaths, including time of event.
- Use of rescue therapy for HK (based on clinical judgement and confirmed by adjudication committee, see Appendix A 5), including time of event.

8.1.3 Additional Efficacy Assessments

The additional efficacy assessments for the remaining secondary and all exploratory objectives are outlined in Section 8.8.2.

8.2 Safety Assessments

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

8.2.1 Physical Examinations

- A complete physical examination will include assessments of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and neurological systems.
- A targeted physical examination will include assessments of the following: skin, extremities, cardiovascular including assessment of signs of heart failure, lungs, and abdomen.

Physical examination will be performed at timepoints as specified in the SoA (Table 1).

8.2.2 Vital Signs

The vital signs include weight, height, systolic and diastolic blood pressure (BP), and pulse

rate and will be assessed as outlined in the SoA (Table 1).

Blood pressure and pulse rate should be measured with a completely automated device in triplicate with at least 1-minute intervals between measurements after being comfortably at rest in a seated position with the back and feet supported (ie, by chair back and floor or platform, respectively) quietly for at least 5 minutes. Manual techniques will be used only if an automated device is not available.

The position of the participant should be comfortable with the arm where the BP is recorded to be within the level of heart (the middle of the cuff on the upper arm is at the level of the right atrium [the midpoint of the sternum]). The participant will be instructed to relax as much as possible and to not talk during the measurement procedure. The same device should preferably be used for the participant during the course of the study and in the same arm.

The first reading of the BP and pulse rate should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the eCRF.

Height and weight measured at screening visit. For subsequent visits collection of weight only, using the same scale and in the same state of dress.

8.2.3 Electrocardiograms

An ECG will be performed at timepoints as specified in the SoA (Table 1) and according to clinical judgment in connection with severe hypokalaemia ($K^+ < 3.0$ mmol/L), severe HK ($K^+ > 6.0$ mmol/L), or any symptoms or clinical events suggesting cardiac arrhythmia.

The QTcF should be recorded at each ECG measurement.

The ECG data should be recorded in the eCRF, including QTcF, in connection with reporting AEs that concern arrhythmia.

For study participants with pacemakers:

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

8.2.4 Clinical Safety Laboratory Assessments

Urinalysis and blood for the determination of clinical chemistry and hematology, as well as urine pregnancy test, will be taken at the visits indicated in the SoA (Table 1). Note: In case of

false positive, false negative or indeterminate results of the urine pregnancy test, investigators should confirm results with whatever suitable method investigator feels is appropriate.

Assessments of hematology and clinical chemistry will be performed by a central laboratory while urinalysis, and urine pregnancy tests will be analysed locally. Potassium will be analysed centrally at baseline and both centrally and locally at day of discharge, + 90 days, + 180 days, and E/D visits. At + 7 days, K^+ will be measured locally, only.

Potassium measured locally (by a validated method, eg, biochemistry measurement or blood gas analyser) will be used for participant 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 K^+ results as rapidly as possible. At + 7 and + 90 days, if the site can obtain the results in a reasonable time (as determined by the investigator and the participant), the samples for the local laboratory can be drawn at the beginning of each visit, and then the participant medications titrated and/or IMP dispensed before the participant 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 participants leaving the visit, the investigator may call the participants or bring them back the following day for instructions regarding concomitant medication titration and IMP dosing. Alternatively, if more feasible for the participant 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 participant's clinic visit.

The results of K^+ 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.

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.

A listing of laboratory safety variables is provided in Table 6.

Table 6 Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	Clinical Chemistry (serum)
B-Hemoglobin (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-Hematocrit (Hct)	S-Glucose
	S-Creatinine
	S-Blood Urea Nitrogen (BUN)
	Urea (BUN)/Creatinine Ratio
	Estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula
Urinalysis (dipstick)	S-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)

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be retained as source data. For information on how AEs based on laboratory tests should be recorded and reported (see Section 8.3.5).

8.2.5 Other Safety Assessments

The eGFR will be calculated using the CKD-EPI formula as previously published (Levey et al, 2009).

8.3 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.

Adverse events 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.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from time of signature of the ICF, throughout the treatment period and including the follow-up period.

Serious AEs will be recorded from the time of signing of the ICF.

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

8.3.2 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 IMPs (yes or no)
- Action taken with regard to IMPs
- Outcome.

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- Reason why AE is classed as serious
- 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.

8.3.3 Causality Collection

The investigator should assess causal relationship between study treatment 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 study treatment?'.

For SAEs, causal relationship should also be assessed for other medication and study procedures. 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.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant, reported in response to the open question from the study site staff, 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.

8.3.5 Adverse Events Based on Examinations and Tests

If a participant's K^+ value is confirmed at < 3.5 mmol/L, the event should be reported as an AE.

The results from the CSP-mandated laboratory tests, vital signs, and ECG will be summarised in the clinical study report.

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

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).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

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

8.3.6 Reporting of Serious Adverse Events

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

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative. If the EDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the investigator/study site staff how to proceed. Investigators or other site personnel will send relevant eCRF modules by fax to the designated AstraZeneca representative.

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

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

8.3.7 Reporting of AEs/SAEs in Relation to COVID-19

All AEs/SAEs should be reported in line with instructions for safety reporting documented in the CSP. For participants experiencing signs and symptoms indicating an infection, an attempt will be made to determine whether the COVID-19 virus is the infectious organism and the AE will be recorded accordingly. If a participant presents with clinical signs and symptoms suggestive of COVID-19, a test will be requested where possible:

- If the test is positive, record "COVID-19 positive" in the Adverse Event Field.
- If the test is negative, record "COVID-19 negative" in the Adverse Event Field, along with the AE/SAE signs and symptoms and/or other diagnosis.

If a test has not been performed or result is not available and signs and symptoms, as judged by the Investigator, are suggestive of COVID-19 infection, record "COVID-19 suspected" in the AE field. If the investigator has other concurrent diagnoses for the participant's signs and symptoms (eg, pneumonia), these will be recorded as separate AEs.

8.3.8 Pregnancy

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

- Pregnancy discovered before the study participant has received any study intervention
- Pregnancy in the partner of male participants.

8.3.8.1 Maternal Exposure

Women of childbearing potential who are planning on becoming pregnant are not allowed to be included in this study. Should a pregnancy still occur, the IMP under study 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 IMP may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/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 8.3.6) and within 30 days for all other pregnancies.

The same timelines apply when the 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.

8.3.8.2 Paternal Exposure

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

8.3.9 Medication Error, Drug Abuse, and Drug Misuse

8.3.9.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (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 event of medication error, drug abuse, or misuse (see Section 8.3.6) and **within 30 days** for all other events.

8.3.9.2 Medication Error

For the purposes of this clinical study, a medication error is an **unintended** failure or mistake in the treatment process as per protocol in administering any study drug that either causes harm to the participant or has the potential to cause harm to the participant.

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

8.3.9.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of study drug as per protocol for a perceived reward or desired non-therapeutic effect.

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

8.3.9.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of the study drug for medicinal purposes outside of the authorised product information 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.

8.4 Overdose

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

During the maintenance period, a dose higher than 10 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 will 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) and within 30 days for all other events.

8.5 Human Biological Samples

8.5.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5.2 Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.5.3 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

Samples for biomarkers are not evaluated in this study.

8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

8.8 Medical Resource Utilisation and Health Economics

8.8.1 Data Source

This study intends to collect primary and secondary data on health care resource utilisation

associated with medical encounters. The data will be collected at on-site visits (primary data) or via telephone visits (primary data) or medical chart reviews (secondary data) as described in the SoA (Table 1). Data collection will be carried out by means of a web-based data capture system (eCRF) which will adhere to all applicable data protection regulations and requirements with regard to electronic records and database validation.

Generally, at each visit, the participant will be asked about any health care encounters since the last visit. The participant will be asked to provide details, and permission to contact the treating physician for access to medical records. The investigator may need to request transfer of records from outpatient visits or admission to hospitals not having joint electronic medical records.

8.8.2 Outcome variables

Protocol-mandated procedures, tests, and encounters are excluded.

The outcome assessments for the primary endpoint and the main secondary endpoint are described in Sections 8.1.1 and 8.1.2, respectively. The outcome assessments for the remaining secondary endpoints and all exploratory endpoints are listed below.

Secondary outcome variables

- Hospital admissions with HK as a contributing factor (based on clinical judgement and confirmed by adjudication committee, see Appendix A 5) and all-cause, respectively, including time of event, number of events, and LOS.

  Hospital admissions where HK was not a contributing factor will also be collected.
- Emergency department visits with HK as a contributing factor (based on clinical judgement and confirmed by adjudication committee, see Appendix A 5) and all-cause, respectively, including time of event and number of events.

  Emergency department visits where HK was not a contributing factor will also be collected.
- Outpatient visits (all-cause)
- Mean K^+ levels
- Use of rescue therapy (see Section 6.7.1)
- All-cause death.

Exploratory outcomes variables

- Intensive care unit (ICU) visits
- eGFR
- Use of K-binders to treat HK post-discharge
- Dialysis initiation

- Use of RAASi.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The statistical hypothesis for the primary endpoint is:

Null: No difference in the occurrence (yes/no) of a participant being NK at 180 days post-discharge between the SZC and SoC arms.

Alternate: Difference in the occurrence (yes/no) of a participant being NK at 180 days post-discharge between the SZC and SoC arms.

The statistical hypotheses for the time to event secondary endpoints (#1, #2, #4, and #6) are:

Null: No difference in event rates corresponding to time to first occurrence of any component of the composite outcome between the SZC and SoC arms.

Alternate: Difference in event rates corresponding to time to first occurrence of any component of the composite outcome between the SZC and SoC arms.

The statistical hypothesis for secondary endpoint #3 is:

- Null: No difference in the incidence rates of hospital admission or ED visit with HK as a contributing factor between the SZC and SoC arms.

Alternate: A difference in the incidence rate of hospital admission or ED visit with HK as a contributing factor between the SZC and SoC arms.

9.2 Sample Size Determination

The sample size calculation for this study is based on the main secondary endpoint (Time to first occurrence of any component of all-cause hospital admission, or ED visit with HK as a contributing factor, or all-cause death or use of rescue therapy for HK at any time post-discharge up to 180 days); the sample size would be smaller if based on the primary endpoint of maintained NK.

9.2.1 Primary Endpoint

For the primary endpoint a sample size estimate would calculate;

- Two group χ^2 test
- Significance level: 5% (two-sided)
- Power: 80%

- Proportions with NK (K^+ between 3.5 and 5.0 mmol/L, inclusive) at 180 days post-discharge), (Davis et al, 2019; Spinowitz et al, 2019):
  - Arm A (SZC): 0.88
  - Arm B (SoC): 0.59

The above test specifics and assumptions yield a sample size of 36 participants per arm (total N = 72). Assuming a 20% drop out rate from enrolment to randomisation and a 20% drop out post-discharge (post-randomisation), a total of approximately 113 participants will be enrolled. This is exceeded by the number of participants required for the secondary endpoint sample size calculation (Section 9.2.2)

The above effect-size assumptions do not contemplate the potential impact of RAASi down-titration on response. Since this is expected to diminish the response rate in the SoC arm relative to the treatment arm, these conservative assumptions should provide a slight underestimate of power.

9.2.2 Main Secondary Endpoint

Prior data: Based on assumptions over a 6-month period of 16.2% all-cause hospitalisation for SZC arm (Pollack et al, 2023) and 40% for SoC arm (Thomsen et al; 2017, Kanda et al; 2020, Horne et al; 2019), 0.8% ED visits with HK as a contributing factor in the SZC arm (Pollack et al; 2023) and 3.2% for SoC (Tafesse et al; 2020, Kashihara et al; 2019, Kanda et al; 2020), it is assumed that 17% and 43.2% of patients in the SZC and SoC arm will experience an event respectively.

Sample size estimate:

- Log-Rank Test for Equality of Survival Curves
- Significance level: 5%
- Power: 80%
- Hazard ratio (HR; SZC/SoC): 0.329
- Proportions without the main secondary composite outcome (event-free) at 180 days post-discharge:
  - Arm A (SZC): 83% (17% with the outcome/event of interest)
  - Arm B (SoC): 56.8% (43.2% with the outcome/event of interest).

The above test specifics and assumptions yield a sample size of 52 evaluable participants per arm (total N = 104). Assuming a 20% drop-out rate from enrolment to randomisation, and a 20% drop out post-randomisation, a total of approximately 163 participants will be enrolled.

9.3 Populations for Analyses

The following populations are defined:

Table 7 Populations for Analysis

Analysis Set	Description	Treatment Assignment
Full Analysis Set (FAS)	The FAS, the primary, secondary, and exploratory efficacy analysis set, will include all randomised participants	Participants will be analysed according to their randomised treatment.
Per Protocol Set (PPS)	The FAS participants without any important protocol deviations leading to exclusion from the PPS.	Participants will be analysed according to their randomised treatment.
Safety Set Open (SSO)	The SSO will include all participants who receive at least one dose of sodium zirconium cyclosilicate (SZC) during the study up until discharge/randomisation.	Participants will be analysed as a single group.
Safety Set Randomised (SSR)	The SSR will include all randomised participants receiving at least 1 dose of SZC post-discharge in Arm A, and all randomised participants in Arm B.	Participants will be analysed according to treatment actually received.

The number of participants 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 8 Analysis Periods

Period	Description
Inpatient period	The inpatient period refers to the period from the date of first study intervention dispensation of sodium zirconium cyclosilicate until the date of randomisation at discharge (exclusive).
Outpatient period	The outpatient period refers to the period from the date of randomisation until the earliest date of last assessment during the follow-up period, withdrawal of consent, last contact with the participant, or death (inclusive).

9.4 Statistical Analyses

The SAP will be drafted and approved within 90 days of the date of the first participant enrolled, and any further changes during the course of the study will be finalised prior to Database Lock. The SAP 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

The full analysis set (FAS) will be the primary analysis set for the efficacy analyses, while the safety set randomised (SSR) will be used for the safety analyses. Safety analyses will also be performed for the safety set open (SSO). Data from all screened participants will be used to

describe the flowchart of participants from screening to fulfilment of eligibility criteria and randomisation.

All baseline characteristics, efficacy, and safety variables will be summarised using descriptive statistics as appropriate. Continuous variables will be summarised by descriptive statistics (including number of participants [n], mean, standard deviation, minimum, median, and maximum). Categorical variables will be summarised with frequencies and percentages. The extent of missing data will be reported.

To control for type I error, a hierarchical testing procedure will be followed when formally testing the primary and secondary efficacy analysis endpoints. The hierarchical testing procedure will follow a stepwise algorithm where each endpoint is only formally tested if the preceding null hypothesis is rejected (two-sided p-value < 0.05). If the preceding null hypothesis is not rejected, then the evaluation of the endpoint will be reduced to that of an exploratory endpoint. A draft order for hierarchical testing is outlined in the current order described for the primary and secondary objectives (see Section 3), and the final order will be detailed in the SAP.

The endpoint and statistical analysis sections follow the ICH E9 (R1) addendum on estimands and sensitivity analyses in clinical trials, including the language for strategies to address intercurrent events:

Treatment Policy Strategy

The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs. For example, when specifying how to address the use of additional medication as an intercurrent event, the values of the variable of interest are used regardless of whether or not the participant takes additional medication.

Hypothetical Strategies

A scenario is envisaged in which the intercurrent event would not occur, or that different intercurrent events would occur or that intercurrent events would occur with alternative frequency: the value of the variable to reflect the clinical question of interest is the value which the variable would have taken in the hypothetical scenario defined. A wide variety of hypothetical scenarios can be envisaged. For example, for a participant that will suffer an AE and discontinue treatment, it might be considered whether the same participant would not have the AE or could continue treatment in spite of the AE.

Composite Variable Strategies

An intercurrent event is considered in itself to be informative about the participant's outcome and is therefore incorporated into the definition of the variable. For example, a participant who discontinues treatment because of toxicity may be considered not to have been

successfully treated. If the outcome variable was already success or failure, discontinuation of treatment for toxicity would simply be considered another mode of failure. Terminal events, such as death, are perhaps the most salient example of the need for the composite strategy.

While On Treatment Strategies

For this strategy, response to treatment prior to the occurrence of the intercurrent event is of interest. Terminology for this strategy will depend on the intercurrent event of interest (eg, "while alive", when considering death as an intercurrent event). If a variable is measured repeatedly, its values up to the time of the intercurrent event may be considered relevant for the clinical question, rather than the value at the same fixed timepoint for all participants. Like the composite strategy, the while on treatment strategy can be thought of as impacting the definition of the variable.

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 including approaches related to estimands, missing data, validity and modification of statistical analysis methods. Further details will be included within the SAP.

9.4.3 Efficacy

9.4.3.1 Primary Endpoints

Occurrence (yes/no) of NK (K^+ between 3.5 and 5.0 mmol/L, inclusive) at 180 days post-discharge

- Population: FAS
- Endpoint: Occurrence (yes/no) of NK (K^+ between 3.5 and 5.0 mmol/L, inclusive) at 180 days post-discharge
- Intercurrent event strategy: Participants who discontinue treatment with a K^+ measurement at 180 days post-discharge will have this value used irrespective of treatment discontinuation (treatment policy strategy). Use of rescue therapy for HK will be considered to be non-response (composite variable strategy). The RAASi down-titration (including discontinuation) will be considered to be non-response (composite variable strategy). Participants who die of any cause prior to 180 days post-discharge or who are lost to follow-up for any reason will be considered to be non-response (composite variable strategy).
- Population level summary (analysis): Logistic regression analysis with response (occurrence) as the dependent variable and randomised treatment group as the

independent variable. The odds ratio along with the two-sided 95% confidence intervals and two-sided p-value (significance declared < 0.05) will be displayed.

Sensitivity Analyses

The analyses of the primary endpoint will be repeated by varying the estimand:

- Population level summary (analysis): Providing there are sufficient participants within each covariate to support the analysis, the logistic regression model will include randomised treatment group and the following baseline variables: age (as a spline), sex, presence of heart failure, diabetes, RAASi use, CKD stage, and baseline K^+ (mild HK defined by K^+ between > 5.0 and ≤ 5.5 mmol/L and moderate/severe HK defined by K^+ between > 5.5 and ≤ 6.5 mmol/L) as independent variables.
- Intercurrent event strategy: As primary estimand, but participants needing rescue therapy for HK will follow the treatment policy strategy (ie, regardless of the intercurrent event).
- Intercurrent event strategy: As primary estimand, but participants with RAASi down-titration (including discontinuation) will follow the treatment policy strategy (ie, regardless of the intercurrent event).
- Intercurrent event strategy: As primary estimand but participants who die or are lost to follow-up prior to 180 days post-discharge will not be evaluated (completers analysis only).
- Hypothetical strategy: As primary estimand, but participants who are lost to follow-up after 90 days will have their K^+ status at 90 days, if available, carried forward to 180 days and included in the analysis.
- Alternative population: As primary estimand but the per protocol set (PPS) will be used as the population for analysis.

9.4.3.2 Secondary Endpoints

For each secondary endpoint, sensitivity analysis will be conducted including an analysis using the PPS population.

1. Time to first occurrence of any component of all-cause hospital admission, or ED visits with HK as a contributing factor, or all-cause death, or use of rescue therapy for HK at any time post-discharge up to 180 days.

- Population: FAS
- Endpoint: Time to first occurrence of either component of the composite outcome at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Rescue therapy for HK will be considered an event (composite variable strategy).

Participants who require ED visits without HK as a contributing factor will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause will be considered an event (composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).

- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.

Sensitivity Analysis

(i) Participants with all-cause hospital admissions will only be included where HK is a contributing factor.

(ii) Participants who down-titrate RAASi (or discontinue) will be censored at the date of down-titration.

(iii) Providing there are sufficient events within each covariate (> 5 events) to support the analysis, the analyses of time-to-event secondary endpoints will be repeated in the FAS using an alternative population level summary where the Cox proportional hazards model will include randomised treatment group and the following baseline variables: age (as a spline), sex, presence of heart failure, diabetes, RAASi use, CKD stage and baseline K^+ (mild HK defined by K^+ between > 5.0 and ≤ 5.5 mmol/L and moderate/severe HK defined by K^+ between > 5.5 and ≤ 6.5 mmol/L) as independent variables.

(iv) Additionally, the analysis will be repeated with the PPS analysis population. An additional sensitivity analysis will be conducted where participants who are lost to follow-up will be accounted for using an inverse probability weighting approach where similar participants who were not lost to follow-up will be re-weighted (hypothetical strategy). Full details regarding sensitivity analyses will be described in the SAP.

Subgroup analyses will be performed of the primary endpoint and of the main secondary endpoint, eg, by age, sex, presence of heart failure, diabetes, RAASi use, CKD stage, and baseline K^+ (mild HK defined by K^+ between > 5.0 and ≤ 5.5 mmol/L and moderate/severe HK defined by K^+ between > 5.5 and ≤ 6.5 mmol/L) at baseline, and by duration of hospitalisation. Additional participant subgroups may be considered, and further details on these analyses will be provided in the SAP.

2. Time to first occurrence of any component of all-cause hospital admission, or ED visit with HK as a contributing factor at any time post-discharge up to 180 days.

- Population: FAS
- Endpoint: Time to first occurrence of either component of the composite outcome at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue treatment or who have ED visit without HK as a contributing factor will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause, use rescue therapy for HK or are lost to follow-up will be censored at the date of death, use of rescue therapy or loss to follow-up, respectively. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).
- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.
- Sensitivity analyses will be conducted as per secondary endpoint #1 excluding the sensitivity analysis for RAASi down-titration.

3. Number of all-cause hospital admission, or ED visits with HK as a contributing factor, at any time post-discharge up to 180 days.

- Population: FAS
- Endpoint: Number of all-cause hospital admissions or ED visits with HK as a contributing factor at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue treatment, use rescue therapy for HK or who have an ED visit without HK as a contributing factor, will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause or are lost to follow-up will be censored at the date of death or loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).
- Population level summary (analysis): Mean number of all-cause hospital admissions or ED visits with HK as a contributing factor by randomised treatment group. Negative binomial regression model with randomised treatment group as the independent variable

and including duration of time in study as an offset. The incidence rate (SZC/SoC), along with 95% confidence intervals and two-sided p-values will be displayed.

- Sensitivity analyses will be conducted using the PPS analysis population and a multivariable negative binomial regression model including age (as a spline), sex, presence of heart failure, diabetes, RAASi use, CKD stage and baseline K^+ (mild HK defined by K^+ between > 5.0 and ≤ 5.5 mmol/L and moderate/severe HK defined by K^+ between > 5.5 and ≤ 6.5 mmol/L) as independent variables.

4. Time to first occurrence of any component of hospital admission or ED visit, both with HK as a contributing factor at any time post-discharge up to 180 days.

- Population: FAS
- Endpoint: Time to first occurrence of either component of the composite outcome at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue treatment or who have hospital admission or ED visit without HK as a contributing factor will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause, use rescue therapy for HK or are lost to follow-up will be censored at the date of death, use of rescue therapy or loss to follow-up, respectively. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).
- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.
- Sensitivity analyses will be conducted as per secondary endpoint #1 excluding the sensitivity analysis for RAASi down-titration.

5. Number of hospital admissions or ED visits with HK as a contributing factor, at any time post-discharge up to 180 days.

- Population: FAS
- Endpoint: Number of hospital admissions or ED visits with HK as a contributing factor at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue treatment, use rescue therapy for HK or who have a hospital admission, or an ED visit without HK as a contributing factor, will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause or are lost to follow-up will

be censored at the date of death or loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).

- Population level summary (analysis): Mean number of hospital admissions or ED visits, with HK as a contributing factor by randomised treatment group. Negative binomial regression model with randomised treatment group as the independent variable and including duration of time in study as an offset. The incidence rate (SZC/SoC), along with 95% confidence intervals and two-sided p-values will be displayed.
- Sensitivity analyses will be conducted using the PPS analysis population and a multivariable negative binomial regression model including age (as a spline), sex, presence of heart failure, diabetes, RAASi use, CKD stage and baseline K^+ (mild HK defined by K^+ between > 5.0 and ≤ 5.5 mmol/L and moderate/severe HK defined by K^+ between > 5.5 and ≤ 6.5 mmol/L) as independent variables.

6. Time to first occurrence of RAASi down-titration (*or* discontinuation) *at any time post-discharge up to 180 days.*

- Population: FAS
- Endpoint: Time to first occurrence of RAASi down-titration (or discontinuation) at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause or are lost to follow-up will be censored at their date of death or loss to follow-up, respectively.
- Population level summary (analysis): Log-rank test for testing, Cox proportional hazards ratio for estimation with randomised treatment group as the independent variable.
- Sensitivity analyses will be conducted as per secondary endpoint #1, excluding the sensitivity analysis for RAASi down-titration.

9.4.3.3 Exploratory Endpoints

Full analysis details for the exploratory endpoints will be described in the SAP.

1. Time to first occurrence of any component of hospital admission or ED visit, both with HK as a contributing factor, or all-cause death at any time post-discharge up to 180 days.

- Population: FAS
- Endpoint: Time to first occurrence of any component of the composite outcome at any

time post-discharge up to 180 days.

- Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who require hospital admission or ED visits without HK as a contributing factor or use rescue therapy will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause will be considered an event (composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).

- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.

- Sensitivity analyses will be conducted as per secondary endpoint #1.

2. Time to first occurrence of either hospital admission with HK as a contributing factor or all-cause death at any time post-discharge up to 180 days.

- Population: FAS

- Endpoint: Time to first occurrence of either component of the composite outcome at any time post-discharge up to 180 days.

- Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who require hospital admission without HK as a contributing factor or any ED visits or who use rescue therapy will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause will be considered an event (composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).

- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with

randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.

- Sensitivity analyses will be conducted as per secondary endpoint #1.

3. Time to first occurrence of either ED visit with HK as a contributing factor or all-cause death at any time post-discharge up to 180 days.

- Population: FAS
- Endpoint: Time to first occurrence of either component of the composite outcome at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who require any hospital admission or ED visits without HK as a contributing factor or who use rescue therapy will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Participants who die of any cause will be considered an event (composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).
- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.
- Sensitivity analyses will be conducted as per secondary endpoint #1.

4. Time to first occurrence of any component of all-cause hospitalisations, ED visits, use of rescue therapy for HK, or all-cause death in each arm at any time post-discharge up to 180 days.

- Population: FAS
- Endpoint: Time to first occurrence of any component of all-cause hospitalisations, ED visits, use of rescue therapy for HK or all-cause death in each arm at any time post-discharge up to 180 days.

- Intercurrent event strategy: Participants who discontinue of treatment will continue to be followed up to the first component of the composite endpoint (treatment policy strategy). Rescue therapy for HK will be considered an event (composite variable strategy). Participants who require any hospital admission or ED visit will be considered an event (composite variable strategy). Participants who die of any cause will be considered an event (composite variable strategy). Participants who are lost to follow-up will be censored at the date of loss to follow-up. Participants who have RAASi down-titration (including discontinuation) will continue to be followed up to the first component of the composite endpoint (treatment policy strategy).

- Population level summary (analysis): Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. Log-rank test for testing will be used to calculate a two-sided p-value, Cox proportional hazards ratio for estimation, with randomised treatment group as the independent variable. The HR and the two-sided 95% confidence interval will be presented. The risk difference and two-sided 95% confidence interval will be presented.

- Sensitivity analyses will be conducted as per secondary endpoint #1.

5. Potassium level up to 180 days post-discharge.

- Population: FAS

- Endpoint: K^+ levels up to 180 days post-discharge.

- Intercurrent event strategy: K^+ levels from participants after discontinuation of treatment, hospital admissions, or ED visits for any reason will be included in the analysis (treatment policy strategy). Participants who use rescue therapy for HK will have K^+ levels prior to rescue therapy for HK used in the analysis (while on treatment strategy). Participants who have RAASi down-titration (including discontinuation) will have K^+ levels prior to the RAASi down-titration used in the analysis (while on treatment strategy). Participants who die of any cause or who are lost to follow-up prior to 180 days post-discharge will have all available K^+ included in the analysis (treatment policy strategy).

- Population level summary (analysis): Mixed model repeated measures (MMRM) analysis with randomised treatment group as an independent variable. The coefficient estimates, standard error, 95% confidence interval for coefficient estimate, and p-values will be reported.

Sensitivity Analysis

- Providing there are sufficient participants within each covariate to support the analysis an

alternative population level summary using the FAS population where the MMRM analysis will include randomised treatment group and the following baseline variables: age (as a spline), sex, presence of heart failure, diabetes, RAASi use, CKD stage and baseline K^+ (mild HK defined by K^+ between > 5.0 and ≤ 5.5 mmol/L and moderate/severe HK defined by K^+ between > 5.5 and ≤ 6.5 mmol/L) as independent variables.

6. Number of hospital admissions with HK as a contributing factor at any time post-discharge up to 180 days.

- Population: FAS
- Endpoint: Number of hospital admissions with HK as a contributing factor, at any time post-discharge up to 180 days.
- Intercurrent event strategy: Participants who discontinue treatment, use rescue therapy for HK, have RAASI down-titration (including discontinuation), experience all-cause death or loss to follow-up prior to 180 days post-discharge will have all available hospital admission and ED visit data used irrespective of the intercurrent event (treatment policy strategy).
- Population level summary: Mean number of hospital admissions with HK as a contributing factor, by randomised treatment group. Negative binomial regression model with randomised treatment group as a main effect and including duration of time in study as an offset. The incidence rate ratio (SZC/SoC), along with 95% confidence intervals and two-sided p-values will be displayed.

Sensitivity Analysis

- Providing there are sufficient, an alternative population level summary using the FAS population where the negative binomial regression model will include randomised treatment group and the following baseline variables: age (as a spline), sex, presence of heart failure, diabetes, RAASi use, CKD stage, and baseline K^+ (mild HK defined by K^+ between > 5.0 and ≤ 5.5 mmol/L and moderate/severe HK defined by K^+ between > 5.5 and ≤ 6.5 mmol/L) as independent variables.
- The proportion of participants per arm who are lost to follow-up will be summarised. If a greater than 10% difference by treatment arm in the proportion who are lost to follow-up is observed, then a sensitivity analysis will be conducted utilising the mean cumulative count method (Dong et al, 2015) which reflects a summarisation of all events that occur in a population by a given time (eg, by 90 days).

7. Total LOS for hospitalisations (including multiple hospitalisations) with HK as a contributing factor in each arm at any time post-discharge up to 180 days.

The Wilcoxon rank-sum test by randomised treatment group will be used to calculate a two-sided p-value. Continuous variable summary statistics (median and mean) of total LOS with HK as a contributing factor by randomised treatment group will be presented.

8. Total LOS for all-cause hospitalisations (including multiple hospitalisations) in each arm at any time post-discharge up to 180 days.

Analysed as per exploratory endpoint #7 but duration of hospitalisation where HK is not a contributing factor will be part of the endpoint, and not treated as an intercurrent event

9. Frequency of the use of K-binders to treat HK at any time post-discharge up to 180 days in each arm.

A negative binomial regression model with randomised treatment group as a main effect and duration of time in study as an offset will be used to analyse the number of uses of K-binders to treat HK.

10. Time to first occurrence of K-binder use to treat HK post-discharge at any time post-discharge up to 180 days in each arm.

Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. A log-rank test will be used to calculate a two-sided p-value. A Cox proportional hazards ratio will be used for analysis with randomised treatment group, and other covariates described in the SAP. The HR and the two-sided 95% confidence interval will be presented.

11. Duration of time on K-binders from initiation in the first instance of K-binder use post-discharge up to 180 days in each arm.

Kaplan-Meier plots of the survival function for the SZC and SoC treatment groups will be presented. A log-rank test will be used to calculate a two-sided p-value. This exploratory endpoint will be analysed using a Cox proportional hazards ratio with randomised treatment group, and other covariates described in the SAP. The HR and the two-sided 95% confidence interval will be presented.

12. Time to first occurrence of rescue therapy use to treat HK at any time post-discharge up to 180 days in each arm.

This exploratory endpoint will be analysed per exploratory endpoint #10.

13. Time to first occurrence of all-cause hospitalisations, ED visits or outpatient visits at any

time post-discharge up to 180 days in each arm.

This exploratory endpoint will be analysed per exploratory endpoint #10.

14. Rate of change in (slope) eGFR between treatment arms.

An MMRM analysis with randomised treatment group as a main effect, days post-discharge, an interaction effect between randomised treatment group and days post-discharge, as well as other covariates described in the SAP will be used to estimate the slope of eGFR by randomised treatment group.

15. Time to first occurrence of dialysis initiation at any time post-discharge up to 180 days in each arm.

This exploratory endpoint will be analysed per exploratory endpoint #10.

16. Time to first occurrence of ICU admissions at any time post-discharge up to 180 days in each arm.

This exploratory endpoint will be analysed per exploratory endpoint #10.

17. Use of RAASi at 90 and 180 days post-discharge by treatment arm.

This exploratory endpoint will descriptively summarise the use of RAASi in each treatment arm. This will include, but need not be limited to: frequency (%) of participants on RAASi at discharge who remained on RAASi at 90 and 180 days post-discharge, respectively; frequency (%) of participants on RAASi at discharge who have increased RAASi dose by 90 and 180 days post-discharge, respectively; frequency (%) of participants on RAASi at discharge who have decreased RAASi dose by 90 and 180 days post-discharge, respectively; frequency (%) of participants who initiated RAASi by 90 and 180 days post-discharge, respectively.

9.4.4 Safety

Safety will be assessed in terms of AEs, SAEs, AEs leading to treatment discontinuation, clinical laboratory data, vital signs, and ECG. Appropriate summaries of these data will be presented by treatment group.

Adverse events will be classified using the Medical Dictionary for Regulatory Activities system organ class (SOC) and PT. A treatment-emergent AE (TEAE) is defined as an AE with the start date on or after the first dose date and up to (and including) 7 days after the last dose date. Only TEAEs will be included in table summaries.

Adverse events will be presented for each treatment group by SOC, and PT covering number and percentage of participants reporting at least 1 event and number of events where appropriate.

An overview of AEs will present for each treatment group the number and percentage of participants with any AE, AEs with outcome of death, SAEs, and AEs leading to discontinuation of IMP.

Separate AE tables will be provided taken into consideration relationship as assessed by the investigator, maximum intensity, seriousness, death, and events leading to discontinuation of IMP.

Key participant information will be presented for participants with AEs with outcome of death, SAEs, and AEs leading to discontinuation of IMP.

An AE listing for the safety analysis set will cover details for each individual AE; an AE listing for participants who were not exposed to IMP is presented separately.

Full details of AE analyses will be provided in the SAP.

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

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

Clinical safety laboratory assessments will be summarised and listed. Shift tables will be provided for select tests, where shift from screening baseline 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 SSO and SSR. In general, safety assessments will be reported descriptively by treatment group. 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 Adjudication Committee

For details on the Adjudication Committee, refer to Appendix A 5.

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 Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure (IB), and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (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 organization, 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 Code of Federal Regulations (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 Serious Adverse Events

- Prompt notification by the investigator to the sponsor of an 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 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 European Union (EU) Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency 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 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.

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

An adjudication committee will be formed. This committee will be composed of independent nephrologists, blinded to study treatment assignment. The objective of this committee is to evaluate whether the hospital admissions or ED visits meet the pre-specified Charter definition of HK as contributing factor for these encounters. The committee will also review the reported concomitant medications to determine RAASi down-titration/discontinuation events and use of rescue therapy for HK.

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://www.astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the 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 (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.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations [CROs]).
- Study monitors will perform ongoing source data verification 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 a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal 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.
  - 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.
- 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 8 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 first act of recruitment is the first site activated will be the study start date.

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:

1) 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
2) Inadequate recruitment of participants by the investigator
3) Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(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 9 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 AE is the development of any untoward medical occurrence in a participant 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 (for example 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 even if no study intervention has been administered.

B 2 Definitions of Serious Adverse Event

A serious adverse event (SAE) 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.

Adverse Events for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. However, in certain situations, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

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 an SAE, 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 intravenous 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. However, 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 judgment. 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

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 Interactive Response Technology/Randomisation and Trial Supply Management [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

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 IMP or AstraZeneca non-investigational medicinal product (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 Management of Study Procedures During the COVID-19 Pandemic

C 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.

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the sponsor.

C 2 Risk Assessment for COVID-19 Pandemic

Sodium zirconium cyclosilicate is a K-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).

C 3 Measures to Mitigate the Risks Associated with COVID-19

- This study will start or resume enrolment only when the sponsor and investigator deem it 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 to ask for signs and symptoms related to COVID-19.

C 4 Suspected COVID-19 After Screening

Participant is Severely Ill or Hospitalised

If the participant becomes symptomatic after screening 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 may temporarily (≤ 14 days), or permanently discontinue study

intervention at the discretion of the site investigator.

Participant is NOT Severely Ill or Hospitalised

If the participant becomes symptomatic after screening 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 study intervention is in the best interest of the participant.

Regardless if study intervention is continued or not, the participant is encouraged to attend the study visits according to the schedule.

C 5 COVID-19 During the Study

Re-consent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete on-site study visits and assessments and alternative means for carrying out the visits and assessments may be necessary (eg, remote visits). Re-consent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in the SoA (Section 1.3). Local and regional regulations and/or guidelines regarding re-consent of study participants should be checked and followed.

Visiting the study sites for the sole purpose of obtaining re-consent should be avoided.

Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix, the term telemedicine visit refers to remote contact with the study participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, visits that are scheduled to be on site may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs and concomitant medications to be reported and documented.

Data Capture During Telemedicine Visits

Data collected during telemedicine visits will be captured by the qualified health care professional from the study site.

Appendix D Protocol Amendment History

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

Amendment 1.0: 02 August 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:

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Study intervention dispensation has been added at visit 4 (7 days after discharge).	To allow for study intervention dispensation if dose needs to be adjusted

Amendment 2.0: 07 July 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.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Objectives and Endpoints 4.2 Scientific Rationale for Study Design 9.1 Statistical Hypothesis 9.2.1 Primary Endpoint 9.4.3.1 Primary Endpoints 9.4.3.2 Secondary Endpoints 9.4.3.3 Exploratory Endpoints Appendix A Regulatory, Ethical, and Study Oversight Considerations	Down-titration (including discontinuation) of renin-angiotensin-aldosterone system inhibitors (RAASi; ie, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists) is now defined as a non-response. Changes in RAASi doses during the study will be reviewed and assessed by the Adjudication Committee.	Due to the known potential of RAASi down-titration to achieve normokalaemia, it is needed to include this in the primary composite as treatment failure
1.1 Synopsis 3 Objectives and Endpoints 9.1 Statistical Hypothesis 9.4.3.2 Secondary Endpoints	Secondary objective #2 is edited and is now focusing on incidence of hospitalisation preceding enrolments or emergency department (ED) visits, both with hyperkalaemia (HK) as a contributing factor.	To be more relevant to clinical decision making
1.1 Synopsis 3 Objectives and Endpoints 9.1 Statistical Hypothesis 9.4.3.2 Secondary Endpoints	Secondary objective #3 is edited and is now focusing on number of hospitalisation preceding enrolments or ED visits, both with HK as a contributing factor.	To be more relevant to clinical decision making
1.1 Synopsis 3 Objectives and Endpoints 9.1 Statistical Hypothesis 9.4.3.2 Secondary Endpoints	A new secondary objective is added to evaluate effect of sodium zirconium cyclosilicate (SZC) on reducing the risk of RAASi down-titration.	Though undesirable, RAASi down-titration is a treatment option for managing HK: recent guidelines describe reducing RAASi as a last resort
1.1 Synopsis 3 Objectives and Endpoints 9.1 Statistical Hypothesis 9.4.3.2 Secondary Endpoints 9.4.3.3 Exploratory Endpoints	Secondary objectives #4 to #10 are moved to exploratory objectives.	To simplify the secondary endpoints

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities 4.2 Scientific Rationale for Study Design 5.1 Inclusion Criteria 6.1 Screening and Inpatient Phase	Inclusion criterion #4: Definition of HK for eligibility is modified. Clarifications are also provided for sources of these potassium (K^+) values.	To better describe the appropriate and addressable population
1.1 Synopsis 1.2 Schema 4.1 Overall Design 5 Study Population 9.4.3.1 Primary Endpoints 9.4.3.2 Secondary Endpoints 9.4.3.3 Exploratory Endpoints	The study now plans to enrol approximately equal numbers of participants with mild HK (K^+ between > 5.0 and ≤ 5.5 mmol/L) and with moderate/severe HK (K^+ between > 5.5 and ≤ 6.5 mmol/L), with a minimum of 30% of the enrolled participants in either group. As a consequence, K^+ levels were adjusted in sensitivity analyses sections for primary, secondary, and exploratory endpoints.	To describe the benefit seen for mild HK versus moderate/severe HK with SZC post-discharge
1.1 Synopsis 4.1 Overall Design 4.2 Scientific Rationale for Study Design 5.2 Exclusion Criteria 6.1 Screening and Inpatient Phases	It is clarified that participants treated by a K-binder at the current ED visit/hospital admission can be enrolled in the study under certain conditions.	Clarification edit
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities 4.1 Overall Design 6.1 Screening and Inpatient Phases	Discharge can now occur up to 21 days after baseline (instead of 14, previously).	Based on feedback from investigative sites, participants staying for more than 14 days in hospital may still be good candidates for this study
1.1 Synopsis 2.3.1 Risk Assessment 4.1 Overall Design 6.2 Outpatient Phase	It is clarified that participants randomised to Arm B can be prescribed a K-binder at, or after Day 7 post-discharge to treat HK.	Clarification edit
1.1 Synopsis 9.4.4 Safety	Clarifications on adverse event analyses.	Clarification edit

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 6.2 Outpatient Phase 8.1.1 Primary Endpoints 8.2.4 Clinical Safety Laboratory Assessments	Clarifications are added about which laboratory (local or central laboratory) will analyse the samples.	Clarification edit
1.3 Schedule of Activities 6.3.1 Investigational Products 6.5 Measures to Minimise Bias: Randomisation and Blinding	It is clarified that during inpatient phase, SZC will be dispensed daily.	Clarification edit
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities 4.1 Overall Design 6.1 Screening and Inpatient Phase	It is clarified that central laboratory results for K^+ are not mandatory to start SZC treatment at the baseline visit as long as all eligibility criteria are met (only a K^+ measurement not older than 24 hours is necessary).	Clarification edit
2.3.1 Risk Assessment	Fluid overload is deleted from the preferred terms included in oedema-related events.	To be aligned with the latest Investigator's Brochure
5.2 Exclusion Criteria	Exclusion criteria #3 and #14 are combined into one exclusion criterion.	Clarification edit
5.2 Exclusion Criteria	The new exclusion criteria (#3 and #14 combined) are edited to exclude all kidney transplant recipients.	To correct a mistake in the previous version of the protocol where only living donor kidney transplant recipients were excluded
5.2 Exclusion Criteria Appendix C 4 COVID-19 prior to Screening	Exclusion criterion #11 (exclusion of participants with evidence of Coronavirus disease 2019 within 2 weeks prior to screening) is deleted.	A new risk assessment was performed and led to the conclusion that this exclusion criterion was not needed anymore
5 Study Population 5.4 Screen Failures Appendix A 3 Informed Consent	To allow for re-screening (up to 2).	To facilitate recruitment

Section # and Name	Description of Change	Brief Rationale
6.4 Preparation/Handling/Storage/ Accountability	Additional information for the final disposition of unused study interventions is provided.	Clarification edit
6.7 Concomitant Therapy	Tacrolimus is added in the list of drugs that should be taken 2 hours before or after SZC to avoid possible drug interaction.	To match updated European SmPC of Lokelma
1.3 Schedule of Activities 8.2.4 Clinical Safety Laboratory Assessments	It is clarified that in case of false positive, false negative or indeterminate result for urine pregnancy test, a second assessment will be performed. It is also clarified that K^+ assessed locally should be measured with a validated method, eg, biochemistry measurement or blood gas analyser.	Clarification edit
8.4 Overdose	Definition of overdose during SZC maintenance phase is modified from 15 to 10 g/day.	To be aligned with the maximum daily dose during the maintenance phase
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarised

Appendix E Abbreviations

Abbreviation or special term	Explanation
AE	adverse event
BP	blood pressure
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus disease 2019
CRO	contract research organization
CSP	clinical study protocol
CTIS	Clinical Trial Information System
DES	Data Entry Site
ECG	electrocardiogram
eCRF	electronic Case Report Form
ED	emergency department
E/D	early discontinuation
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	end of treatment
EU	European Union
FAS	full analysis set
GCP	Good Clinical Practice
HK	hyperkalaemia
HR	hazard ratio
HRU	healthcare resource utilisation
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB/IEC	Institutional Review Board
IRT/RTSM	Interactive Response Technology/Randomisation and Trial Supply Management
K^+ or K	potassium
LOS	length of stay

Abbreviation or special term	Explanation
MMRM	mixed model repeated measures
NIMP	non-investigational medicinal product
NK	normokalaemia or normokalaemic
PPS	per protocol set
PT	preferred term
QD	once daily
QTc	QT interval corrected
QTcF	QT interval corrected by the Fridericia method
RAASi	renin-angiotensin-aldosterone system inhibitor
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	Schedule of Activities
SoC	standard of care
SOC	system organ class
SSO	safety set open
SSR	safety set randomised
SZC	sodium zirconium cyclosilicate
TEAE	treatment-emergent adverse event
TID	three times daily
WOCBP	Woman of child bearing potential

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