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Original Article

ORIGINAL ARTICLE

Rationale and design of CONTINUITY: a Phase 4 randomized controlled trial of continued post-discharge sodium zirconium cyclosilicate treatment versus standard of care for hyperkalemia in chronic kidney disease

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ABSTRACT

Background. Individuals with chronic kidney disease (CKD) hospitalized with hyperkalemia are at risk of hyperkalemia recurrence and re-hospitalization. We present the rationale and design of CONTINUITY, a study to examine the efficacy of continuing sodium zirconium cyclosilicate (SZC)—an oral, highly selective potassium (K^+) binder—compared with standard of care (SoC) on maintaining normokalemia and reducing re-hospitalization and resource utilization among participants with CKD hospitalized with hyperkalemia.

Methods. This Phase 4, randomized, open-label, multicenter study will enroll adults with Stage 3b–5 CKD and/or estimated glomerular filtration rate <45 mL/min/1.73 m^2, within 3 months of eligibility screening, hospitalized with a serum potassium (sK^+) level of >5.0–≤6.5 mmol/L, without ongoing K^+ binder treatment. The study will include an in-hospital phase, where participants receive SZC for 2–21 days, and an outpatient (post-discharge) phase. At discharge, participants with sK^+ 3.5–5.0 mmol/L will be randomized (1:1) to SZC or SoC and monitored for 180 days. The primary endpoint is the occurrence of normokalemia at 180 days. Secondary outcomes include incidence and number of hospital admissions or emergency department visits both with hyperkalemia as a contributing factor, and renin–angiotensin–aldosterone system inhibitor down-titration. The safety and tolerability of SZC will be evaluated. Ethics approval has been received from all relevant ethics committees. Enrollment started March 2022 and the estimated study end date is December 2023.

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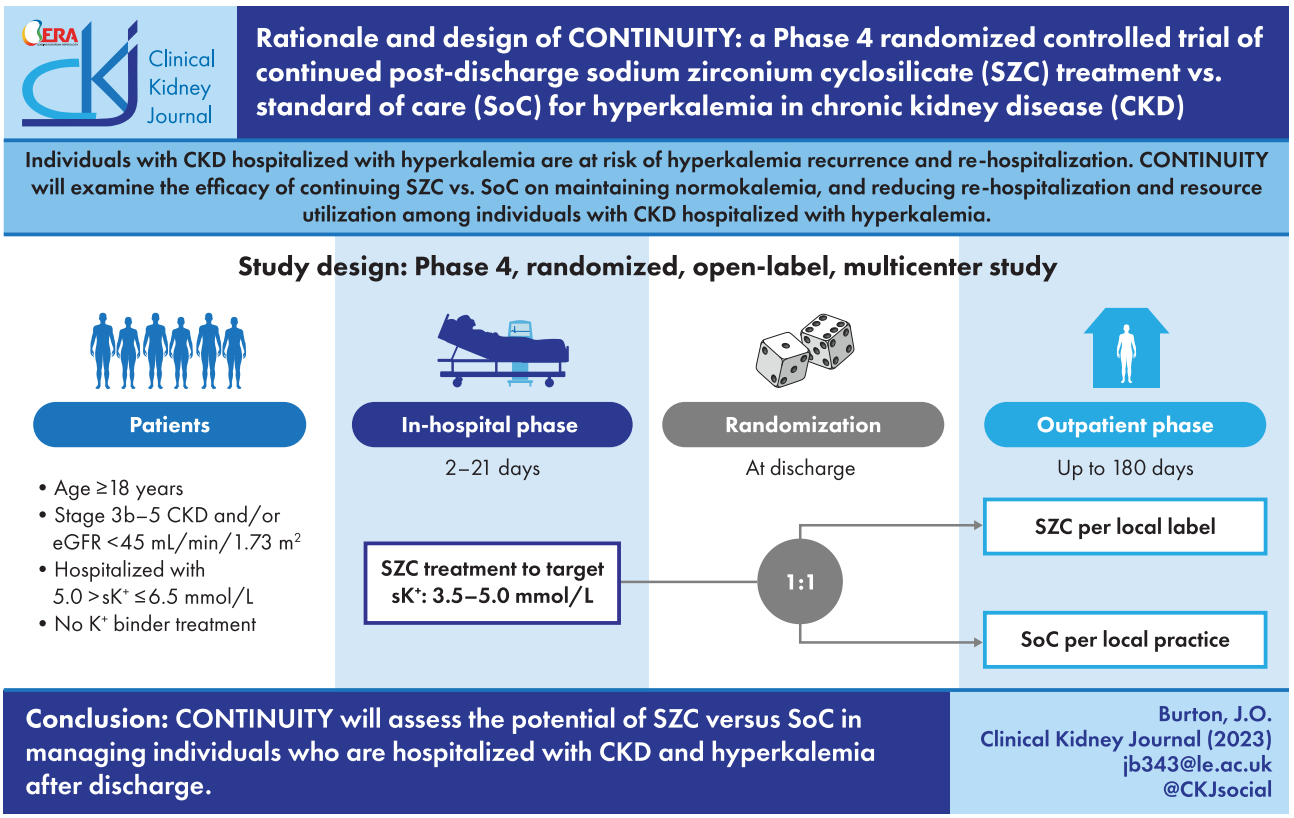
Conclusions. This study will assess the potential of SZC versus SoC in managing people with CKD and hyperkalemia post-discharge.
Trial registration. ClinicalTrials.gov identifier: NCT05347693; EudraCT: 2021-003527-14, registered on 19 October 2021.

LAY SUMMARY

High levels of potassium in the blood are potentially life-threatening and are more common in people who have chronic kidney disease. When people with chronic kidney disease are hospitalized because blood potassium levels are elevated, the likelihood of this problem recurring is high, potentially resulting in more hospital admissions. The CONTINUITY study is designed to investigate whether a new potassium-lowering therapy—sodium zirconium cyclosilicate—could prevent a recurrence of high blood potassium levels after discharge from hospital. People with advanced kidney disease in hospital with high blood potassium levels will be randomly allocated to one of two groups: those taking sodium zirconium cyclosilicate and those receiving standard treatment. CONTINUITY is the first study of this design to investigate the effectiveness and safety of a new potassium-lowering treatment for people with chronic kidney disease admitted to hospital with high potassium levels. The study is estimated to complete in December 2023.

GRAPHICAL ABSTRACT



Keywords: chronic kidney disease, chronic renal insufficiency, clinical trial, heart failure, hyperkalemia

INTRODUCTION

Hyperkalemia is defined as elevated serum potassium (sK^+) above the normal range and is a potentially life-threatening electrolyte imbalance disorder. Individuals with impaired renal function, including those with chronic kidney disease (CKD) and/or on renin–angiotensin–aldosterone system inhibitors (RAASis) are at risk of developing hyperkalemia [1, 2].

Hyperkalemia affects approximately 10% of all hospitalized patients [3, 4]. It may induce or worsen cardiac arrhythmias and is associated with adverse clinical events and increased mortality [1, 5–7]; it is therefore often treated as a medical emergency requiring urgent treatment. Individuals hospitalized with hyperkalemia are at increased risk of subsequent recurrence and re-hospitalization, which impact healthcare resource utilization (HCRU) and costs [8–11]. Furthermore, persisting high K^+ levels post-discharge, following an acute severe hyperkalemia episode, have been associated with a greater risk of mortality [12]. Therefore, steps to minimize hyperkalemia

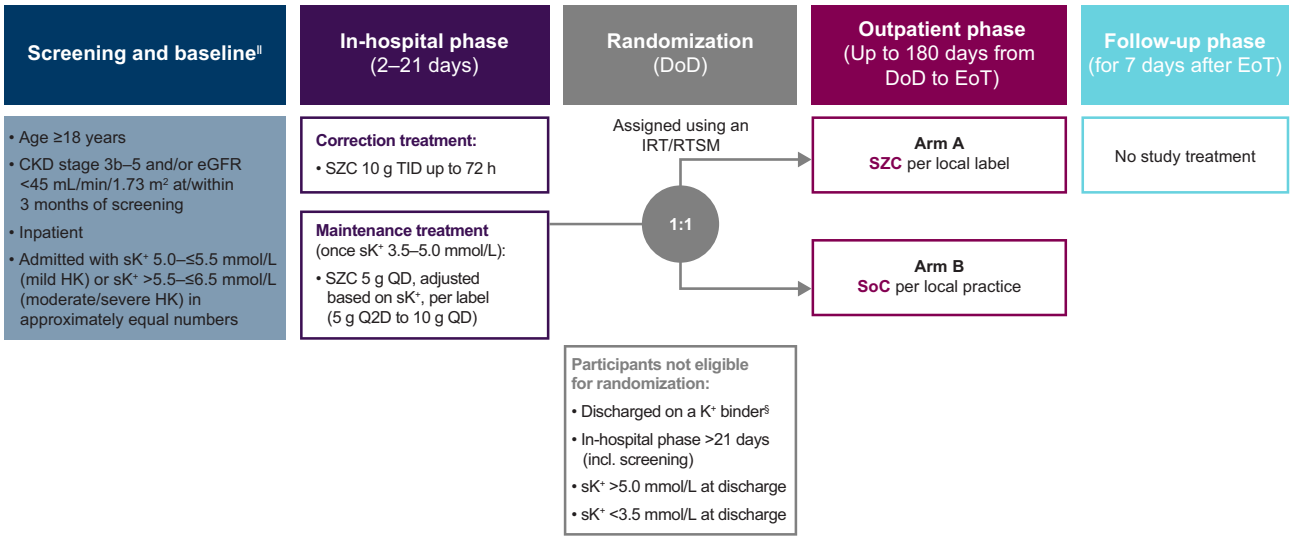


Figure 1: Study design. ‖Baseline and screening can occur on the same study day. §Participants randomized to Arm B can be prescribed a K^+ binder at, or after Day 7 post-discharge to treat HK. DoD, day of discharge; EoT, end of treatment; HK, hyperkalemia; IRT, interactive response technology; QD, once daily; Q2D, every other day; RTSM, randomization and trial supply management; TID, three times daily.

recurrence may reduce readmission rates and healthcare costs and improve patient outcomes.

Current standard of care (SoC) approaches to manage hyperkalemia in the outpatient setting commonly include discontinuing or reducing the dose of RAASi therapy, reducing dietary K^+ intake and adding diuretics, or taking oral K^+ binders [13]. However, alterations to RAASi therapy are associated with higher cardiovascular or renal adverse events in the long term [13]. Other approaches of hyperkalemia management are suboptimal; sodium polystyrene sulfonate has not been tested in the long term, and low K^+ diets are difficult to adhere to [13].

Sodium zirconium cyclosilicate (SZC) is an anti-hyperkalemia therapy (oral K^+ binder) indicated for use in adults [14–16]. In Phase 3 trials, after achieving normokalemia, individualized once-daily SZC therapy maintained a normal range of sK^+ levels for up to 1 year in adult outpatients [17–20]. However, these studies were either single-arm or open-label extensions among any individuals with hyperkalemia. Data on the efficacy of long-term K^+ binders in reducing re-hospitalization of patients with CKD and hyperkalemia are scarce, and it is currently unclear whether SZC prevents hyperkalemia recurrence and HCRU compared with SoC post hospital discharge. Therefore, the ongoing Phase 4 CONTINUITY study (ClinicalTrials.gov Identifier: NCT05347693; EudraCT: 2021-003527-14) was designed to compare the efficacy of continued post-discharge treatment with SZC versus SoC in maintaining normokalemia and reducing hyperkalemia-related hospital admissions and emergency department (ED) visits in people with CKD. Here, we describe the rationale and design of the CONTINUITY study.

MATERIALS AND METHODS

Study design

This is a Phase 4, randomized, controlled, open-label, parallel-group, multicenter study in participants with CKD who were hospitalized with hyperkalemia. The study will be conducted in 30–50 study sites across 4–7 European countries (Belgium, France, Germany, Italy, Netherlands, Spain and the UK). This study is currently recruiting people with CKD; the first person was enrolled on 24 March 2022, and the estimated date of the last person, last visit, is December 2023.

The study will include both an in-hospital and an outpatient (post-discharge) phase (Fig. 1). All participants will be treated with SZC in the in-hospital phase to correct hyperkalemia and to maintain normokalemia (sK^+ level of 3.5–5.0 mmol/L) as per local label. At discharge, participants with an sK^+ level of 3.5–5.0 mmol/L and established on a maintenance dose of SZC will be randomized (1:1) to either SZC per local label (Arm A) or SoC as per local practice (Arm B) and will enter the outpatient phase. Definition of SoC is at the discretion of the treating physician; however, those participants for whom there is a clinical indication to be discharged with any K^+ binder (i.e., clinical equipoise does not exist) are not eligible for randomization and will be discontinued from the study. SZC dose titrations will be allowed based on sK^+ levels as per local label. During the outpatient phase, participants will be monitored for 180 days via seven planned follow-up on-site visits or phone calls, followed by an on-site visit at 7 days after end of treatment. Participants who have an in-hospital phase exceeding 21 days or who have not achieved normokalemia will not be eligible for randomization.

Rescue medication is allowed at the discretion of the treating physician to reduce sK^+ levels in the case of severe hyperkalemia (as defined by the treating physician and site). Any therapeutic intervention initiated to manage high K^+ levels will be considered rescue therapy. This may include K^+ binders other than SZC in Arm A and K^+ binders including SZC in Arm B. As per local practices, SZC should be withdrawn if another K^+ binder is initiated (in Arm A).

Inclusion and exclusion criteria

The full inclusion and exclusion criteria are shown in Table 1. The study will enroll adults aged ≥18 years, diagnosed with Stage 3b–5 CKD and/or estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2, at or within 3 months prior to study screening, who are admitted to hospital with

Table 1: Inclusion and exclusion criteria.

Inclusion criteria
Male or female ≥18 years old
Admitted to hospital (inpatient care; directly or from ED)
Diagnosed with Stage 3b–5 CKD and/or eGFR <45 mL/min/1.73 m^2, at or within 3 months of study screening, based on the Chronic Kidney Disease Epidemiology Collaboration equation[a]
Hyperkalemia at current hospital admission or ED visit as defined by site local practice and sK^+ between >5.0 and ≤6.5 mmol/L
Capable and willing of giving signed informed consent
Exclusion criteria
Myocardial infarction, stroke, seizure or a thrombotic/thromboembolic event[b] within 12 weeks prior to screening
Unable to take oral SZC drug mix
Life expectancy of <6 months
Any medical condition that, in the opinion of the investigator or sponsor, may pose a safety risk to the participant, confound safety or efficacy assessments, and jeopardize the quality of data, or interfere with study participation
Presence of cardiac arrhythmias or conduction defects that require immediate treatment
QT interval corrected by the Fridericia method >550 ms
History of QT prolongation associated with other medications that required discontinuation of that medication
Congenital long QT syndrome
Symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia; atrial fibrillation controlled by medication is permitted
Alcohol or drug abuse within 2 years prior to screening
Ongoing treatment with any K^+ binder at index hospital admission[c]
Chronic hemodialysis or peritoneal dialysis or the recipient of or scheduled date for a kidney transplant
Participation in another clinical study with an investigational product administered during the month before screening
Known hypersensitivity to SZC or any of the excipients of the product
Involvement in the planning and/or conduct of the study (AstraZeneca staff and/or study site staff)
Judgment by the investigator that the participant is unlikely to comply with study procedures, restrictions and requirements
Previous randomization in the present study
Women of child-bearing potential who are not willing to use defined methods of contraception
Women who have a positive pregnancy test at screening or women who are breastfeeding

[a]Race/ethnicity will not be included in the equation calculation.
[b]E.g., deep vein thrombosis or pulmonary embolism, but excluding vascular access thrombosis.
[c]Initiation of SZC during the index hospital admission is allowed.

hyperkalemia defined by the study site local practice and with an sK^+ level between >5.0 and ≤6.5 mmol/L. Hyperkalemia was not required to be the primary reason for hospitalization. Participants prescribed ongoing treatment with a K^+ binder at hospital admission, requiring renal replacement therapy (including chronic hemodialysis, peritoneal dialysis or a kidney transplant) or who are unable to take oral SZC will be excluded.

Objectives

The study objectives and endpoints are shown in Table 2. The primary study objective is to evaluate the efficacy of continued SZC treatment versus SoC post-discharge in maintaining normokalemia (sK^+ level of 3.5–5.0 mmol/L). The main secondary objective is to evaluate the effect of continuing SZC treatment versus SoC post-discharge on reducing the incidence of the composite outcome of hyperkalemia-related admissions or ED visits, all-cause death or use of rescue therapy for hyperkalemia. Other secondary objectives are to evaluate the efficacy of continued SZC treatment versus SoC post-discharge on reducing the number of hyperkalemia-related hospital admissions or ED visits, and on reducing the incidence of hyperkalemia-related hospital admissions or ED visits. Whether hyperkalemia was a contributing cause of hospitalization or ED visits will be based on clinical judgement and confirmed by an adjudication committee comprising independent nephrologists blinded to study treatments. A further secondary objective is to evaluate the effect of continuing SZC versus SoC on reducing the risk of RAASi down-titration or discontinuation. Exploratory objectives will include an evaluation of the effect of continuing SZC versus SoC in reducing the incidence of K^+ binder use, on mean sK^+ levels and on the ability to continue RAASi treatment. The safety and tolerability of SZC compared with SoC will be evaluated in terms of adverse events, vital signs, clinical safety laboratory assessments and electrocardiogram measures.

Study procedures

The schedule of assessments is outlined in Table 3. Corrective treatment with SZC will be initiated at baseline. During the outpatient phase (Visits 4–10), Visits 4, 7 and 10 (at 7, 90 and 180 days after randomization, respectively) will be on-site, with the remaining being telephone visits. An on-site end of study visit will be performed approximately 7 days after end of treatment.

If SZC dose titration occurs at any time during the outpatient phase, unscheduled additional drug dispensation visits will be performed. SZC will be permanently discontinued in the event of severe hypokalemia or hyperkalemia, defined by two confirmed K^+ measurements of <3.0 or >6.0 mmol/L, respectively, taken ≥10 min apart. Investigators will consider temporarily pausing or down-titrating SZC if K^+ measurements are between 3.0 and 3.4 mmol/L; patients will be managed as per standard practice and SZC treatment will be resumed upon hypokalemia resolution. If K^+ measurements are between 5.1 and 5.5 mmol/L,

Table 2: Study objectives and endpoints.

Objective	Endpoint
Primary	Efficacy: occurrence (yes/no) of normokalemia (sK^+ 3.5–5.0 mmol/L, inclusive) at 180 days post-discharge (use of rescue therapy, down-titration or discontinuation of RAASi, death, or lost to follow-up will all be considered a non-response)
Secondary	To evaluate the effect of continuing SZC versus SoC on time to first occurrence at any time post-discharge up to 180 days of:
	Hospital admission or ED visit with hyperkalemia as a contributing factor, all-cause death, or use of rescue therapy for hyperkalemia Hospital admission or ED visit, both with hyperkalemia as a contributing factor RAASi down-titration (or discontinuation)
	At any time up to 180 days post-discharge, to evaluate the effect of continued SZC versus SoC on: Number of hospital admissions or ED visits with hyperkalemia as a contributing factor
Exploratory	To evaluate the effect of continuing SZC versus SoC at any time post-discharge up to 180 days on:
	Time to first occurrence of any component of hospital admission or ED visit, both with hyperkalemia as a contributing factor, or all-cause death Time to first occurrence of either hospital admission with hyperkalemia as a contributing factor, or all-cause death Time to first occurrence of either ED visit with hyperkalemia as a contributing factor, or all-cause death Time to first occurrence of any component of all-cause hospitalizations, ED visits, use of rescue therapy for hyperkalemia or all-cause death in each arm Time to first occurrence of all-cause hospitalizations, ED visits or outpatient visits in each arm Time to first occurrence of ICU admission Number of hospital admissions with hyperkalemia as a contributing factor Total length of stay in hospitalizations with hyperkalemia as a contributing factor Total length of stay in all-cause hospitalizations by randomized treatment group
	To evaluate the effect of continuing SZC versus SoC on mean sK^+ level up to 180 days post-discharge: Mean sK^+ level
	To evaluate the effect of continuing SZC versus SoC in reducing the incidence of K^+ binder use at any time post-discharge up to 180 days on: Time to first occurrence of K^+ binder use in each arm
	To evaluate the effect of continuing SZC versus SoC in reducing the frequency and duration of K^+ binder use at any time post-discharge up to 180 days on: Time to discontinuation of K^+ binder from initiation in each arm in the first instance of K^+ binder use Frequency of the use of K^+ binder to treat hyperkalemia in each arm
	To evaluate the effect of continuing SZC versus SoC in reducing the incidence of rescue therapy for hyperkalemia at any time post-discharge up to 180 days: Time to first occurrence of rescue therapy use in each arm
	To evaluate the effect of continuing SZC versus SoC in the change in eGFR post-discharge to 90 and 180 days: Rate of change in (slope) eGFR from inpatient phase in each arm
	To evaluate the effect of continuing SZC versus SoC in the incidence of dialysis initiation at any time post-discharge up to 180 days:
	Time to first occurrence of dialysis initiation in each arm
	To evaluate the effect of continuing SZC versus SoC on the ability to continue RAASi post-discharge up to 90 and 180 days: Use of, and changes in use of, RAASi, in each arm
Safety	Safety and tolerability of SZC compared with SoC in terms of adverse events, vital signs, clinical safety laboratory assessments and ECG

ECG, electrocardiogram; ICU, intensive care unit.

or between 5.6 and 6.0 mmol/L with no serious arrhythmia or other risk to the individual, daily SZC dose will be increased by 5-g increments (to a maximum of 10 g) until K^+ returns to within the normal range.

sK^+ will be assessed centrally at all in-hospital visits (Visits 1–3) and at on-site outpatient visits (Visits 7 and 10); additional assessments may be made at the discretion of the investigator if clinically indicated. Portable devices (e.g., i-*STAT*) may be used to measure sK^+ at local investigators' discretion. Samples will be analyzed by both local and central laboratories at Visits 3, 7 and 10. Centrally analyzed sK^+ will be used for study endpoint assessment, while local sK^+ analyses may be used for inclusion/exclusion criteria, treatment initiation, titration decisions and clinical decisions. Any time that the SZC dose is adjusted or there is any change to medications that affect sK^+ levels, such as RAASi or diuretics, an sK^+ measurement will be performed 7 (±2) days later. Data on hospital admissions, ED/intensive care unit/outpatient visits, rescue therapy use, dialysis initiation and eGFR will be collected at all outpatient phase visits and follow-up visits (Visits 4–11) and entered into the electronic case report form. Adverse event data will be collected at every visit and may be conducted by phone if not

Table 3: Schedule of assessments.

Study procedure	Screening	Baseline[a]	In-hospital phase	Outpatient phase (up to 180 days from DoD)							Early DC	Follow-up phase (+7 days after EoT)
Study day	–1 to 1	1	2–21	9–21	32–44	62–74	92–104	122–134	152–164	182–194		189–208
Visit	1	2	3 (DoD)[b]	4	5 (phone)	6 (phone)	7	8 (phone)	9 (phone)	10		11
Informed consent	x											
Inclusion/exclusion criteria	x											
Randomization			x									
Vital signs[c]	x	x	x	x			x			x	x	x
Adverse events	At every visit and may be conducted by phone if not tied to a visit											
Clinical laboratory assessments[d]		x	x				x			x	x	
ECG	x		x	x			x			x	x	x
Laboratory K^+[e]	x	x	x	x			x			x	x	
Data on hospital admissions and ED visits (with hyperkalemia and all-cause), ICU visits, outpatient visits, use of rescue therapy, dialysis initiation and eGFR (site visits)				x	x	x	x	x	x	x	x	x

[a]Baseline and screening can occur on the same study day.
[b]Will be minimum of 24 h after treatment initiation [for participants who achieve normokalemia (K^+ level of 3.5–5.0 mmol/L inclusive)]. Participants with K^+ >5.0 or <3.5 mmol/L at discharge will be discontinued or withdrawn from the study, respectively, and followed up as per protocol.
[c]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.
[d]Clinical safety laboratory assessments via central laboratory. Blood: hemoglobin, leukocyte count, leukocyte differential count (absolute count), platelet count, hematocrit. Serum: sodium, potassium, bicarbonate (total CO_2), chloride, glucose, creatinine, BUN, urea (BUN)/creatinine ratio, eGFR using the CKD-EPI formula, anion gap, albumin, total protein, calcium, magnesium, phosphate, bilirubin (total), alkaline phosphatase, alanine amino transferase, aspartate amino transferase. Local assessments: urinalysis (dipstick): hemoglobin/erythrocytes/blood, protein/albumin, glucose, pregnancy tests. Potassium, also assessed locally will be measured by a validated method, e.g., biochemistry measurement or blood gas analyzer.
[e]Potassium may be checked more often than indicated, if medically appropriate.
BUN, blood urea nitrogen; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CO_2, carbon dioxide; DC, discontinuation; DoD, day of discharge; ECG, electrocardiogram; EoT, end of treatment; ICU, intensive care unit.

tied to a visit. Medical chart review data may be combined with those collected onsite/via telephone if necessary.

Statistical analysis

Sample size determination

The sample size calculation for this study is based on the main secondary study endpoint (time to first occurrence of the composite outcome of hyperkalemia-related admissions or ED visits, all-cause death, or use of rescue therapy for hyperkalemia) and was based on the log-rank test for equality of survival curves. Using prior data [21], it was assumed that 1% of participants in the SZC arm and 7% of participants in the SoC arm will experience an event from the composite outcome. Assuming a 20% initial screening failure rate to the in-hospital phase, a 15% screening failure rate from the in-hospital phase to the discharge visit, and a 20% drop-out post-randomization, a total of 632 participants will be screened and 430 participants will be randomized (215 per arm) to achieve 344 evaluable participants (172 per arm).

The calculation used the main secondary study endpoint rather than the primary study endpoint as the number of participants required for the primary endpoint is smaller. Assuming the proportions of participants with normokalemia at 180 days are 0.88 (SZC) and 0.59 (SoC) [17], and the screening failure rates are as outlined above, 132 participants would need to be screened.

Analysis methods

The full analysis set (all randomized participants) will be the primary analysis set for the primary, secondary and exploratory efficacy analyses, while the safety set (all randomized participants who received one or more dose of SZC treatment post-discharge in Arm A, and all randomized participants in Arm B) will be used for the safety analyses.

The statistical hypotheses for the primary and secondary endpoints are based on the null hypothesis, i.e., no difference in the outcomes measured between SZC and SoC. The primary endpoint will be analyzed using a logistic regression model, with response (occurrence) as the dependent variable and randomized treatment group as the independent variable. The odds ratio, along with the two-sided 95% confidence intervals (CIs) and two-sided *P*-value (significance declared $P < .05$), will be reported.

Time-to-event secondary endpoints will be analyzed using a log-rank test. Kaplan–Meier plots of the survival function for the SZC and SoC groups will be presented. A Cox proportional hazards model will be used for estimation, with the randomized treatment group as the independent variable. The hazard ratio and two-sided 95% CIs will be presented. sK^+ levels up to 180 days post-discharge will be analyzed using mixed model repeated measures, with the randomized treatment group as the independent variable. The coefficient estimates, standard error, 95% CI for coefficient estimate and *P*-values will be reported. The number of hyperkalemia-related hospital/ED admissions at any time post-discharge up to 180 days will be analyzed using a negative binomial regression model, with randomized treatment group as the main effect and including duration of time in study as an offset. The incidence rate ratio (SZC/SoC), 95% CIs and two-sided *P*-values 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, comprising a stepwise algorithm where each endpoint is only formally tested if the preceding null hypothesis is rejected (two-sided $P < .05$). If the preceding null hypothesis is not rejected, then the evaluation of the endpoint will be reduced to that of an exploratory endpoint.

Safety and tolerability will be evaluated in terms of adverse events, vital signs, clinical laboratory and electrocardiogram assessment. Adverse event assessments will include frequency of events, relationship to SZC (investigator determined), intensity, seriousness, death and events leading to discontinuation of SZC.

Baseline characteristics, efficacy and safety variables will be summarized using descriptive statistics. Continuous variables will be summarized by descriptive statistics (including number of participants, mean, standard deviation, minimum, median and maximum). Categorical variables will be summarized with frequencies and percentages. The extent of missing data will be reported. The number and percentage of adverse events will be reported by system organ class, preferred term and treatment group.

Ethics and dissemination

This study has received approval from all relevant ethics committees (first site, Provincial Drug Research Ethics Committee of Seville). It will adhere to consensus ethical principles derived from international guidelines, including the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation Good Clinical Practice Guidelines, and applicable laws and regulations. All participants will be required to sign an informed consent form.

DISCUSSION

Hyperkalemia occurs in up to 5% of the global population and in up to 10% of those hospitalized [3]. Individuals hospitalized with hyperkalemia often have comorbidities; for example, comorbid CKD has been reported in 30%–96% of people with hyperkalemia [8, 10, 11, 22–24]. CONTINUITY is the first randomized, prospective study to examine the efficacy of extended use of a novel K^+ binder post discharge compared with SoC on the maintenance of normokalemia and HCRU among people hospitalized with hyperkalemia and CKD. As there is currently no standardized therapy to treat people with CKD and hyperkalemia after discharge, the comparator in CONTINUITY is SoC as per local practice. This study focuses on people with Stage 3b–5 CKD and hyperkalemia due to the increased risk of morbidity and mortality in this population. People with comorbid heart failure are included in this study, as heart failure can contribute to hospitalization risk and HCRU post-discharge [8]. Additionally, this study will assess hyperkalemia over a period of 180 days. In people recently hospitalized with an acute episode of severe hyperkalemia (sK^+ >5.5 mEg/L), hyperkalemia recurrence was frequent within the first 6 months of discharge and the associated increased risk of death was significant [12]. Therefore, insight can be gained as to the effect of SZC in reducing mortality through maintenance of normokalemia. The cut-off for hyperkalemia at >5.0 mmol/L during screening is intended to minimize the inclusion of participants with coincident mild hyperkalemia, for example, due to dehydration in hospital.

The burden of hyperkalemia post-discharge is high. Observational studies have consistently reported higher rates of readmission and total healthcare costs in people with hyperkalemia-related versus -unrelated hospital admissions [8, 10]. Betts *et al*. found that when hospitalized, people with hyperkalemia were 56%–58% more likely to be readmitted

within 30–90 days compared with those matched without hyperkalemia; in addition, for people with CKD and/or heart failure, the duration of hospital stay per readmission was longer in those with hyperkalemia than in those without (8.4 versus 7.4 days, respectively) [8]. Furthermore, Davis *et al.* reported a higher recurrence of hyperkalemia within 30 days of discharge with increasing severity of hyperkalemia [10]. Analysis of data from 2010–14 in a US health record database showed that people with hyperkalemia incurred $30 379 higher total healthcare costs in the first year post-admission compared with matched normokalemia controls [8]. The clinical and economic impact of CKD and the associated cardiovascular complications represent a global burden [25, 26]. CONTINUITY will provide valuable information on the impact of SZC on HCRU following hospital discharge by measuring hospital readmissions.

Several strategies are used to treat hyperkalemia in the outpatient setting; however, these all have limitations. RAASi therapy may be reduced or discontinued to manage hyperkalemia [13], although RAASi therapies are renoprotective and reduce mortality in people with cardiorenal disorders [13, 27, 28], and discontinuation or suboptimal dosing is associated with adverse outcomes and increased risk of mortality [29, 30]. A low-K^+ diet can lower the risk of hyperkalemia but may be difficult to adhere to for those with additional dietary restrictions due to CKD, diabetes or heart failure [13]. The addition of diuretics is another treatment strategy for management of hyperkalemia, but diuretics are associated with side effects, including worsening kidney function [13], and may not be suitable for people with end-stage renal disease [31] or hypotension. Finally, the use of sodium bicarbonate is limited to patients with metabolic acidosis and adequate liver function, and has been associated with adverse effects including sodium loading, worsening hypertension, fluid retention and volume overload [13, 32].

The widely used K^+ binder sodium polystyrene sulphonate (SPS) has been associated with potentially severe gastrointestinal side effects [33, 34], and there are a lack of efficacy and safety data to support the long-term use of SPS in hyperkalemia [13]. Newer, more selective agents, such as patiromer and SZC, are effective at lowering sK^+ levels and are better tolerated [14, 35]. A recent analysis reported that <0.1% of individuals are discharged with SPS or patiromer to restore and maintain normokalemia following hospitalization [10]. Thus, improvements in the management of people hospitalized with hyperkalemia are needed to reduce the clinical burden post-discharge, and CONTINUITY will assess this using SZC.

The inclusion and exclusion criteria for CONTINUITY were selected to determine whether SZC is a beneficial addition to post-hospitalization medication packages, and, as such, the study excluded individuals who were already being prescribed K^+ binders. However, as these individuals are more likely to have advanced CKD and worse renal function, this exclusion criterion may have the unintended effect of limiting inclusion of those with advanced CKD.

While the body of literature on the cost and HCRU associated with hyperkalemia has grown in recent years, few studies have examined the impact of managing sK^+ long-term on mitigating healthcare costs and improving patient outcomes. Desai *et al.* examined the effect of patiromer exposure post-discharge on HCRU and expenditure, and reported a 65% lower odds of inpatient/ED visits and 34% lower relative total healthcare spending in individuals exposed to patiromer versus no exposure [22]. However, the study was not randomized and restricted to a single US healthcare database in a relatively small sample size (N = 1539 matched pairs). Another observational US study investigated the impact of long- versus short-term use of SZC on hospitalization with hyperkalemia during routine care and found that hospitalization rates during follow-up were lower with long-term SZC therapy compared with short-term SZC therapy [36]. The CONTINUITY study will add to this literature, using a more robust study design across several countries, with predefined and powered statistical analyses, randomization and a larger patient sample. The study is designed to align as much as possible with real-world clinical practice, with a low number of mandated on-site follow-up visits and by using medical chart reviews and telephone contacts in between on-site visits for complementary data collection.

In conclusion, CONTINUITY will examine the efficacy of SZC versus SoC in managing people with CKD and hyperkalemia post hospital discharge. This will help to evaluate the importance of maintaining normokalemia after discharge in routine clinical practice, and the clinical and HCRU impact of using SZC to improve the management of people with CKD and hyperkalemia.

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AUTHORS' CONTRIBUTIONS

All authors contributed to the study design and drafting of the article, and provided final approval of the version to be published.

DATA AVAILABILITY STATEMENT

On completion and publication of the results of the study, data may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

CONFLICT OF INTEREST STATEMENT

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