Effect of Sodium Zirconium Cyclosilicate on Serum Potassium and Bicarbonate in Patients with Hyperkalemia and Metabolic Acidosis Associated with Chronic Kidney Disease: Rationale and Design of the NEUTRALIZE Study

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Abstract

Introduction: Sodium zirconium cyclosilicate (SZC) is a selective potassium (K\textsuperscript{+}) binder for hyperkalemia management that provides rapid and sustained correction of hyperkalemia. The NEUTRALIZE study is investigating whether SZC, in addition to correcting hyperkalemia and maintaining normal serum K\textsuperscript{+}, can provide sustained increases in serum bicarbonate (HCO\textsubscript{3}\textsuperscript{−}) in patients with hyperkalemia and metabolic acidosis associated with chronic kidney disease (CKD).

Methods: This is a prospective, randomized, double-blind, placebo-controlled phase 3b study of US adults with stage 3–5 CKD not on dialysis with hyperkalemia (K\textsuperscript{+} >5.0–≤5.9 mmol/L) and low-serum HCO\textsubscript{3}\textsuperscript{−} (16–20 mmol/L). In the open-label correction phase, all eligible patients receive SZC 10 g three times daily for up to 48 h. Patients who achieve normokalemia (K\textsuperscript{+} ≥3.5–≤5.0 mmol/L) are then randomized 1:1 to once-daily SZC 10 g or placebo for a 4-week, double-blind, placebo-controlled maintenance phase. The primary endpoint is the proportion of patients with normokalemia at the end of treatment (EOT) without rescue therapy for hyperkalemia. Key secondary endpoints include mean change in serum HCO\textsubscript{3}\textsuperscript{−}, the proportion of patients with an increase in serum HCO\textsubscript{3}\textsuperscript{−} of ≥2 or ≥3 mmol/L without rescue therapy for metabolic acidosis, and the proportion of patients with serum HCO\textsubscript{3}\textsuperscript{−} ≥22 mmol/L at EOT.

Conclusions: NEUTRALIZE will establish whether SZC can provide sustained increases in serum HCO\textsubscript{3}\textsuperscript{−} while lowering serum K\textsuperscript{+} in patients with hyperkalemia and CKD-associated metabolic acidosis and may provide insights on the mechanism(s) underlying the increased serum HCO\textsubscript{3}\textsuperscript{−} with SZC treatment.

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Introduction

Patients with chronic kidney disease (CKD) often develop metabolic acidosis, largely because of the kidney’s diminished capacity to excrete acid in the form of ammonium (NH4+) [1]. In the Chronic Renal Insufficiency Cohort study conducted in the USA, the estimated prevalence of metabolic acidosis (i.e., serum bicarbonate [HCO3−] <22 mmol/L) was 13% in patients with stage 3 CKD, 37% in stage 4 CKD, and 80% in stage 5 CKD [2]. Metabolic acidosis associated with CKD is an independent risk factor for CKD progression [3]. In a French observational study of patients with stage 1–4 CKD, those in the lowest tertile of venous total carbon dioxide (CO2) were significantly more likely to have a fast decline in measured glomerular filtration rate (GFR) [4]. Metabolic acidosis can also be associated with an increased risk of metabolic bone disease, cardiovascular events, and mortality [1].

In addition to metabolic acidosis, patients with CKD commonly develop hyperkalemia, primarily as a result of a reduction in potassium (K+) excretion as GFR declines [5, 6]. According to a US retrospective study, the estimated annual prevalence of metabolic acidosis in patients with CKD and hyperkalemia (K+ >5.0 mmol/L) ranged between 25% and 29% from 2014 to 2017 [7]. Hyperkalemia is also associated with an increased risk of all-cause mortality, particularly in patients with CKD, heart failure, or diabetes [8]. More recently, hyperkalemia was shown to be independently associated with an increased risk of all-cause mortality, cardiovascular events, hospitalizations, and intensive care unit admissions in a Canadian retrospective study [9].

Sodium zirconium cyclosilicate (SZC) is a novel selective K+ binder that is currently approved for the treatment of hyperkalemia [10]. SZC is a nonabsorbed, nonpolymeric, crystalline agent that preferentially entraps K+ in exchange for hydrogen (H+) [10] and sodium (Na+) throughout the gastrointestinal tract [11]. In phase 3 clinical studies, SZC effectively lowered serum K+ (median time to K+ decline 2.2 h) and provided sustained normokalemia (K+ 3.5–5.0 mmol/L) during 12 months of follow-up [12–16].

In addition to its effects on serum K+, in post hoc analyses, SZC had acute effects on serum HCO3− during correction of hyperkalemia, with rapid dose-dependent placebo-adjusted increases in serum HCO3− of 1.02 mmol/L with SZC 5 g three times daily (TID) to 1.78 mmol/L with SZC 10 g TID within 48 h [17]. The rise in serum HCO3− during the 48-h correction phase was independent of CKD stage [17] and was sustained during the 29-day maintenance phase with SZC 10–15 g once daily (QD) [17] and for 11 months of continued open-label treatment [15]. Furthermore, SZC was associated with dose-dependent decreases in blood urea nitrogen (BUN) during correction (first 48 h) and maintenance (21 days) treatment compared with placebo in patients with CKD [13, 18, 19]. The mechanism(s) underlying the increase in serum HCO3− with SZC are not fully understood but may be due to direct binding and removal of NH4+ by SZC in the gastrointestinal tract and/or an increase in renal ammonia (NH3) production with correction of hyperkalemia, which would allow for increased renal acid excretion [17].

The post hoc analyses of previous clinical studies showing dose-dependent increases in serum HCO3− with SZC did not systematically examine patients with CKD with a combination of hyperkalemia and low serum HCO3− [17, 19]. In addition, the effect of SZC on serum HCO3− may have been confounded by patients receiving sodium bicarbonate therapy, although it should be noted that increases in serum HCO3− were also seen in patients not receiving sodium bicarbonate. Moreover, the impact of SZC on urine NH4+ excretion was not evaluated [17, 19]. Thus, further study is needed to elucidate if SZC causes clinically meaningful increases in serum HCO3− in patients with CKD-associated hyperkalemia and metabolic acidosis. Here, we describe the rationale and design of the NEUTRALIZE study (NCT04727528), which aims to investigate whether SZC can: (1) correct hyperkalemia and maintain normal serum K+ levels and (2) provide sustained increases in serum HCO3− in patients with CKD-associated hyperkalemia and metabolic acidosis.

Materials and Methods

Study Design

NEUTRALIZE is an ongoing prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter phase 3b study that is being conducted in US adults with hyperkalemia and metabolic acidosis associated with CKD. The study includes a screening visit, a 4-week treatment period, and an off-treatment follow-up visit 1 week after the end of treatment (EOT). The treatment period consists of an open-label correction phase of up to 48 h for all eligible participants, followed by a randomized, placebo-controlled maintenance phase from study days 3–29 (Fig. 1).

Study Oversight and Eligibility

The study is being conducted in accordance with the approved protocol and with international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Science International Ethical Guidelines, applicable Inter-
Table 1. Summary of the inclusion and exclusion criteria for the NEUTRALIZE study

| Inclusion criteria | Exclusion criteria |
|--------------------|-------------------|
| Age ≥ 18 years     | Pseudohyperkalemia |
| Stage 3–5 CKD (eGFR ≤ 59 mL/min/1.73 m²) and not on dialysis | Dialysis requirement within 3 months |
| Two consecutive serum K⁺ levels (taken 1 h apart) > 5.0–≤ 5.9 mmol/L | History of kidney transplantation or acute/chronic worsening of kidney function (i.e., ≥ 30% decline in eGFR within 3 months) |
| Two serum HCO₃⁻ levels (taken 1 h apart) between 16 and 20 mmol/L, inclusive | Cardiac arrhythmias requiring immediate treatment; current acute decompensated HF or hospitalization for HF within 4 weeks; MI, UA, stroke, or TIA within 12 weeks; coronary revascularization within 12 weeks; or symptomatic hypotension, symptomatic or uncontrolled AF, asymptomatic VT, or QT prolongation |
| Able to undergo repeated blood draws or effective venous catheterization | Low HCO₃⁻ requiring emergency intervention or treatment |
| Informed consent   | Active or suspected diabetic ketoacidosis; history of diabetic gastroparesis; bariatric surgery; bowel obstruction; or swallowing disorders |
|                    | Current exacerbation of COPD/asthma or hospitalization for COPD/asthma within 4 weeks |
|                    | Active malignancy requiring treatment |
|                    | Life expectancy of < 3 months |
|                    | Active treatment (within 7 days prior to screening) with a K⁺ binder (i.e., SZC, SPS, or patiromer), sodium bicarbonate, or lactulose |
|                    | Prior or concurrent participation in another clinical study with the administration of study drug within 1 month |
|                    | Known hypersensitivity to SZC |
|                    | Current pregnancy |
|                    | Evidence of COVID-19 within 2 weeks prior to screening |

AF, atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; HCO₃⁻, bicarbonate; HF, heart failure; K⁺, potassium; MI, myocardial infarction; SPS, sodium polystyrene sulfonate; SZC, sodium zirconium cyclosilicate; TIA, transient ischemic attack; UA, unstable angina; VT, ventricular tachycardia. *Eligible participants must meet all of the inclusion criteria. †Participants are excluded if any of the exclusion criteria are met.
national Council for Harmonisation Good Clinical Practice guidelines, and all applicable local and national regulations. Study sites must comply with the approved protocol and the requirements of the Institutional Review Board/Independent Ethics Committee. The study is ongoing at approximately 35 sites across the USA. The inclusion and exclusion criteria for the study are summarized in Table 1. Patients aged ≥18 years with stage 3–5 CKD (estimated GFR ≤59 mL/min/1.73 m²) not on dialysis are eligible to participate in the study if they have two consecutive serum K⁺ levels >5.0–≤5.9 mmol/L and two serum HCO₃⁻ levels 16–20 mmol/L (taken approximately 1 h apart). Patients requiring dialysis are excluded from the study.

**Study Treatment**

Following a short screening period (Study Day 1), all eligible patients will enter the open-label correction phase in which they receive SZC 10 g TID for up to 48 h (Fig. 1). Patients who achieve normokalemia (serum K⁺ ≥3.5–≤5.0 mmol/L) after 24 h (Day 2) will enter the randomized, placebo-controlled maintenance phase, whereas patients with serum K⁺ ≥5.1 mmol/L will continue SZC TID for another 24 h. Participants who do not achieve normokalemia will be discontinued from the study.

Patients who achieve normokalemia during the open-label correction phase will be randomized 1:1 to receive SZC 10 g QD or placebo QD during the 4-week, double-blind, placebo-controlled maintenance phase. Patients with serum K⁺ <3.5 mmol/L at any time during the open-label correction phase or serum K⁺ ≥5.1 mmol/L at the end of the open-label correction phase will be discontinued from the study drug. During the first 2 weeks of the maintenance phase, the SZC/placebo dose will be titrated as needed to maintain serum K⁺ levels by increasing or decreasing the dose by 5-g increments at 1-week intervals to between 5 g every other

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**Table 2. Schedule of key study assessments in the NEUTRALIZE study**

| Procedure | Screening | Open-label phase | Randomized phase (visit 2 or 3–7) | Follow-up |
|-----------|-----------|-----------------|----------------------------------|-----------|
| Visit     | 1         | 1               | 2                                | 3         |
| Study day | 1         | 1               | 2                                | 2 or 3    |
| Routine clinical procedures | | | | |
| Demographics | X | X               | X                                | X         |
| Physical exam | X | X               | X                                | X         |
| Medical history | X | X               | X                                | X         |
| Concomitant medications | | | | |
| At every visit and may be conducted by phone (if not part of a visit) | | | | |
| Vital signs | X | X               | X                                | X         |
| Weight | X | X               | X                                | X         |
| Routine safety measurements | | | | |
| AEs | At every visit and may be conducted by phone (if not part of a visit) | | | |
| Clinical safety laboratory tests | X | X | X | X |
| ECG | X | | | X |
| Efficacy laboratory measurements | | | | |
| Central laboratory K⁺, HCO₃⁻, Cl⁻ | (X) | (X) | X | X | X | X |
| i-STAT tests | X, X | X | X | X | X | X |
| Spot urine tests | X | X | X | X | X | X |
| Serum aldosterone | X | X | | |
| Optional genomics blood sample | X | | | |
| Study drug administration | | | | |
| Drug dispensation (open-label phase) | X | X | | |
| Drug dispensation (randomized phase) | X | X | X | X |
| Randomization | X | X | X | X |
| Dose titration (if needed) | X | X | X | X |

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Ca²⁺, calcium; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; Cl⁻, chloride; CO₂, carbon dioxide; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; HCO₃⁻, bicarbonate; K⁺, potassium; Mg²⁺, magnesium; Na⁺, sodium; NH₄⁺, ammonium; PO₄, phosphate; UACR, urinary albumin-to-creatinine ratio. a Includes hematology (hemoglobin, hematocrit, leukocyte count, and platelet count), urinalysis by dipstick (urinary hemoglobin/erythrocytes/blood, protein/albumin, and glucose), and serum chemistry (serum Na⁺, K⁺, HCO₃⁻ [total CO₂], Cl⁻, glucose, creatinine, BUN, BUN-to-creatinine ratio, eGFR [using CKD-EPI formula], anion gap [blood from i-STAT], albumin, total protein, Ca²⁺, Mg²⁺, PO₄, total bilirubin, ALP, ALT, and AST). b Measurements are taken after the patient has fasted for 4 h (meals can transiently change acid-base status). c When measured on Visits 1, 3, 7, and 8, these results were also included as part of the clinical safety assessment. d Includes HCO₃⁻ as total CO₂, K⁺, creatinine, and anion gap; at screening, 2 measurements will be taken 1 h (±15 min) apart. e Central laboratory measurement of urinary albumin, NH₄⁺, citrate, pH, and creatinine, and calculated anion gap (based on urinary Na⁺, K⁺, and Cl⁻). UACR, and NH₄⁺-to-creatinine ratio.
day to 15 g QD. A stable SZC/placebo dose is recommended during the last 2 weeks of the maintenance phase.

**Study Assessments**

Patient demographics (e.g., age, sex, race, and ethnicity), comprehensive medical and surgical history, and baseline laboratory results, including hematology and clinical chemistry, will be collected at screening and at specified study visits (Table 2). In order to exclude pseudohyperkalemia, the study requires two consecutive K⁺ levels from two blood samples, taken approximately 1 h apart, to fall within the inclusion criteria. All study staff will be trained on proper blood sample collection. Patients will be instructed to relax the muscles of their forearm throughout the blood drawing procedure to minimize hemolysis. Standard laboratory procedures will be used to determine whether blood samples contain clots or show signs of hemolysis in the plasma. Point-of-care K⁺ and HCO₃⁻ will be used to screen patients for study inclusion, determine eligibility for the randomized, placebo-controlled phase and to titrate the SZC/placebo dose. Central laboratory serum K⁺ and point-of-care HCO₃⁻ levels will be used for study endpoint assessments. Spot urine tests will be conducted during the randomized phase and include central laboratory measurement of urinary albumin, NH₄⁺, citrate, pH, creatinine, Na⁺, chloride, and K⁺ (to enable calculation of the urine anion gap) and calculated urinary albumin-to-creatinine, citrate-to-creatinine, and NH₄⁺-to-creatinine ratios. We consider direct measurement of urinary NH₄⁺ to be a more accurate measurement of urinary acid excretion than other surrogate measurements, such as the urinary anion gap or osmolality gap. All samples will be stored consistent with standard operating procedures to preserve sample integrity for analysis.

**Study Endpoints**

A summary of the primary, secondary, and exploratory endpoints is provided in Table 3. Consistent with the primary indication for SZC in the USA [10], the primary endpoint is the proportion of patients with normokalemia (central laboratory serum K⁺ ≥3.5–≤5.0 mmol/L) at the EOT (Day 29), without the need for rescue treatment for hyperkalemia (i.e., serum K⁺ >6.0 mmol/L) at any point during the maintenance phase. The safety assessments include the occurrence, frequency, and severity of adverse effects and their relationship to treatment, as assessed by the investigator, and monitoring of vital signs, clinical laboratory assessments (e.g., hematology, urinalysis by dipstick, and serum chemistry), and electrocardiography (Table 1).

**Statistical Considerations**

Approximately 400 patients will be screened and approximately 200 patients will be enrolled in the open-label correction phase in order to achieve 182 evaluable patients randomly assigned to the study intervention. A sample size of 91 patients each in the SZC and placebo arms will be needed to have >90% power to detect an absolute difference in HCO₃⁻ of 20% between baseline and EOT, using a 2-sided t test at a significance level of 5%. This calculation assumes an 8% drop-out rate between the open-label correction phase and the randomized maintenance phase and is based on the proportion of patients with serum HCO₃⁻ 16–20 mmol/L in previous studies who had a placebo-adjusted increase in serum HCO₃⁻ of ≥3 mmol/L with SZC [12, 15, 16].

Continuous variables will be summarized by study arm using the number of observations (n), mean, standard deviation, median, interquartile range, and minimum and maximum values. Categorical variables will be summarized by study arm using the number of patients and percentage. For all logistic regression analyses, odds
ratios, 95% confidence intervals, and 2-tailed t test p values (significance level <0.05) will be presented. All statistical analyses will be conducted using SAS® statistical software, version 9.3 (or later).

The primary, secondary, and exploratory endpoints will be analyzed in the full analysis set (defined as all patients who achieve normokalemia during the open-label correction phase and enter the randomized maintenance phase). Patients will be analyzed on an intent-to-treat basis. Safety endpoints will be analyzed in the open safety set (defined as all patients enrolled in the open-label correction phase who received ≥1 dose of the study drug and analyzed as a single group) and in the randomized safety set (defined as all patients who achieve normokalemia during the open-label correction phase and enter the randomized maintenance phase and analyzed according to randomized treatment). Sensitivity analyses will also be conducted in the per-protocol set (defined as all patients in the full analysis set without any important protocol deviations and analyzed according to randomized treatment).

In the primary endpoint analysis, the null hypothesis is that there is no difference between SZC and placebo in the proportion of patients with normokalemia at EOT without the need for rescue treatment for hyperkalemia at any time during the maintenance phase. The primary endpoint will be analyzed by logistic regression, with the proportion of patients with normokalemia as the dependent variable and the randomized study arm as the independent variable.

For each secondary endpoint, the null hypothesis is that there is no difference between SZC and placebo in the outcome measured. To control for type I error, a hierarchical testing procedure will be followed when formally testing secondary endpoints. Two-sided p values <0.05 will be considered statistically significant. Exploratory endpoints will be analyzed using analysis of covariance models with the randomized study arm as the main effect and the baseline variable as the covariate. The last observation carried forward approach will be used to manage missing data.

Discussion

NEUTRALIZE is a randomized, double-blind, placebo-controlled phase 3b study designed to investigate whether SZC provides clinically meaningful increases in serum HCO$_3^-$, in addition to correcting hyperkalemia and maintaining normokalemia, in patients with CKD-associated hyperkalemia and metabolic acidosis. This is the first known interventional study to prospectively evaluate a K$^+$ binder in patients with metabolic acidosis.
The standard of care for patients with CKD-associated metabolic acidosis is currently sodium bicarbonate therapy. Sodium bicarbonate increases serum $\text{HCO}_3^-$ and may lower serum $\text{K}^+$ while decreasing urinary $\text{NH}_4^+$ excretion in patients with CKD and metabolic acidosis [20, 21]. Gastrointestinal intolerance and the high pill burden needed to correct serum $\text{HCO}_3^-$ are limitations of sodium bicarbonate [22]. Moreover, treatment of metabolic acidosis with sodium bicarbonate- or citrate-containing liquids is often limited by poor palatability [23]. In patients with advanced CKD, adequate correction of metabolic acidosis (i.e., serum $\text{HCO}_3^-$ levels $>$22 mmol/L) with sodium bicarbonate or sodium citrate is associated with a significant increase in $\text{Na}^+$ load [24] and is often not achieved, most likely due to poor adherence [25]. Therefore, alternative therapeutic options for the management of CKD-associated metabolic acidosis with hyperkalemia would be useful.

SZC was shown to provide dose-dependent increases in serum $\text{HCO}_3^-$ in post hoc analyses of phase 3 studies of patients with hyperkalemia [17, 19] and may provide an alternative to sodium bicarbonate, or at least allow for a reduced dose, in patients with CKD-associated hyperkalemia and metabolic acidosis. Therefore, SZC has the potential to provide clinically meaningful improvements in serum $\text{HCO}_3^-$ in these patients.

Two general possible mechanisms are proposed to contribute to the serum $\text{HCO}_3^-$ increases observed with SZC: (1) SZC directly binding and removing $\text{NH}_4^+$ from the gastrointestinal tract (Fig. 2a) and (2) augmentation of renal ammoniagenesis and normalization of altered $\text{NH}_4^+$ transport as a result of hyperkalemia correction (Fig. 2b).

Under normal physiologic conditions, the main mechanism for increasing renal acid excretion is by augmenta-
HCO$_3^-$, an explanation of urea enterohepatic cycling is metabolized to urea by combining with HCO$_3^-$ [28, 29, 34]. Transported via the portal vein to the liver, where it is metabolized by proximal cells to glutamate, then α-ketoglutarate, producing two NH$_4^+$ and two HCO$_3^-$ ions per glutamate molecule [26]. HCO$_3^-$ is subsequently reabsorbed into the systemic circulation, whereas NH$_4^+$ is mostly excreted in the urine, with a small proportion undergoing metabolism to urea in the liver (consuming two HCO$_3^-$ ions) [28, 29]. NH$_4^+$ produced in proximal tubule is transported into the urinary space of the proximal tubule, either by the apical Na$^+$/H$^+$ exchanger (in place of H$^+$) or as NH$_3$ or both. Subsequently, NH$_4^+$ is reabsorbed by the thick ascending limb and is trapped in the interstitium, where NH$_3$ is then available to diffuse into the collecting tubule and interact with H$^+$, secreted mainly by H$^+$-ATPase, such that NH$_4^+$ is formed in the lumen of the collecting tubule and excreted in the urine [28]. However, in patients with CKD, NH$_4^+$ excretion is markedly diminished and hyperkalemia, when present, further decreases NH$_4^+$ excretion [28–30]. It is conceivable that SZC raises serum HCO$_3^-$ in part by directly binding and removing NH$_4^+$ in the gastrointestinal tract. The SZC binding site is similar in size to the ionic diameters of NH$_4^+$ and K$^+$ in an aqueous solution (both approximately 3 Å; Fig. 3). As such, it is postulated that SZC binds not only K$^+$ but also NH$_4^+$ in exchange for H$^+$ or Na$^+$ in the gastrointestinal tract [10, 11]. Direct removal of NH$_4^+$ from the gastrointestinal tract by SZC would additionally explain why dose-dependent decreases in BUN are also observed with SZC [17, 19].

To understand how direct binding of NH$_4^+$ by SZC in the gastrointestinal tract may result in increased serum HCO$_3^-$, an explanation of urea enterohepatic cycling is warranted. Urea is synthesized in the liver following the breakdown of amino acids from protein-rich foods [29]. Although urea is mostly removed from the body via urinary excretion, a fraction (approximately 25%) passes from the systemic circulation into the gastrointestinal tract, most likely by passive diffusion [31, 32]. As patients with CKD have elevated BUN levels [33], diffusion of urea from the systemic circulation into the gastrointestinal tract is likely to be proportionately increased compared with that of healthy individuals. In the gastrointestinal tract, urea is hydrolyzed by bacterial ureases to release NH$_4^+$ and HCO$_3^-$, which are normally absorbed through the gastrointestinal epithelium [34]. NH$_4^+$ is transported via the portal vein to the liver, where it is metabolized to urea by combining with HCO$_3^-$ [28, 29, 34].

The binding of NH$_4^+$ by SZC in exchange for Na$^+$ and subsequent increased removal of NH$_4^+$ in the feces likely interrupt this enterohepatic loop of urea nitrogen salvage, allowing HCO$_3^-$ in the portal vein to bypass the liver, and decreasing urea resynthesis in the liver. Because dose-dependent decreases in BUN have been observed with SZC [17, 19], the overall expected effect is an increase in serum HCO$_3^-$ and a reduction in BUN [35]. This effect would be additive and independent of any K$^+$-lowering effect of SZC on renal ammoniagenesis (described in the following paragraphs).

The second hypothesized mechanism by which SZC increases serum HCO$_3^-$ is that the normalization of serum K$^+$ with SZC leads to the correction of metabolic acidosis. An early case study by Szy lamin et al. [36] showed that normalization of hyperkalemia with sodium polystyrene sulfonate in a patient with isolated hyperaldosteronism led to resolution of acidosis and restored urinary NH$_3$ excretion. Correction of hyperkalemia could lead to increased NH$_3$ production in the renal proximal tubule and increased final excretion as NH$_4^+$, which subsequently leads to increased serum HCO$_3^-$. Renal ammoniagenesis is decreased during hyperkalemia [37, 38], as indicated by an in vitro study showing reduced ammoniagenesis with elevated K$^+$ concentrations [39]. Moreover, an inverse relationship between plasma K$^+$ and NH$_4^+$ excretion was demonstrated using in vivo experimental models [37, 40]. In addition, hyperkalemia can alter NH$_4^+$ transport within the nephron, causing reduced medullary accumulation of NH$_4^+$ in the collecting duct [40], as demonstrated in an animal model of chronic hyperkalemia [41]. Based on an animal model of selective aldosterone deficiency, aldosterone enhances H$^+$ secretion and increases ammoniagenesis directly and indirectly by lowering serum K$^+$ [42]. Therefore, patients with CKD and aldosterone deficiency often develop hyperkalemic metabolic acidosis [43].

The exploratory path analysis using data from three phase 3 studies of SZC in patients with hyperkalemia strongly suggested that the SZC-associated rise in serum HCO$_3^-$ is the result of NH$_4^+$ binding in the gastrointestinal tract, based on the association of the increase in HCO$_3^-$ with the serum urea reduction path but not with the pathways via reduction in serum K$^+$ or increases in urine pH [17]. The NEUTRALIZE study may provide further data to support this hypothesis as study assessments will include serum urea, spot urine pH measurement, and urine NH$_4^+$-to-creatinine and citrate-to-creatinine ratio calculations, as well as assessment of serum HCO$_3^-$ and serum K$^+$. 

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Given that SZC is proposed to bind $\text{NH}_4^+$ (as well as $\text{K}^+$) in exchange for $\text{Na}^+$, there is some concern that SZC treatment may be associated with $\text{Na}^+$ release and systemic absorption. A phase 1 study in healthy volunteers on a high $\text{K}^+$/low $\text{Na}^+$ diet previously showed no significant changes in urinary or fecal $\text{Na}^+$ excretion with SZC administration [44], and a phase 2 study in patients with CKD and hyperkalemia showed no increase in 24-h urinary $\text{Na}^+$ excretion with SZC compared with placebo [18], suggesting that SZC is not associated with significant release and systemic absorption of $\text{Na}^+$. In clinical trials, mild-to-moderate edema was observed in patients, not on dialysis, primarily with the 15 g QD SZC dose [10]. In a clinical trial in patients on chronic hemodialysis, most of whom received SZC doses of 5 g–10 g QD on non-dialysis days, there was no difference in interdialytic weight gain between the SZC and placebo groups, suggesting fluid retention was similar [10, 45].

There are several potential limitations of this study. Assessment of 24-h urinary $\text{Na}^+$, $\text{K}^+$, urea, and $\text{NH}_4^+$ would have provided better insights regarding the effects of SZC on their urinary excretion than spot urinary analyses, while the amount of $\text{NH}_4^+$ that is bound by SZC would require 24-h fecal measurements. However, these tests were not included in the study protocol because of practical considerations. Further studies may be needed to examine these parameters in more detail. In addition, SZC will be administered without the requirement for fasting; therefore, acid-base status may be affected in those who receive SZC with meals.

Conclusions

NEUTRALIZE is the first study to prospectively explore the potential benefits and risks of using SZC in patients with CKD-associated hyperkalemia and metabolic acidosis. This study will determine if SZC can provide sustained increases in serum $\text{HCO}_3^-$ while maintaining normokalemia in this patient population. The study will also provide additional evidence for the efficacy and safety of SZC administration in these patients and may provide further information on the mechanism by which SZC increases serum $\text{HCO}_3^-$ concentrations.

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Statement of Ethics

This study protocol was reviewed and approved by the central Institutional Review Board (Advarra®, approval number PRO00048231) or local IRBs where applicable. The clinical study protocol is publicly registered (NCT04727528) and the results will be disclosed according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations. All procedures will be in accordance with the Declaration of Helsinki and informed consent will be obtained from all individuals included in the study.

Conflict of Interest Statement

S.R.A. has received honoraria from AstraZeneca for participation in corporate-sponsored programs but has no current financial ties to AstraZeneca. D.B. has received an investigator-initiated grant from AstraZeneca to study the effect of SZC on fecal $\text{NH}_4^+$ and has received consulting fees from Tricida, Astra Zeneca, and Relypsa, is the founder and main stakeholder of Angiotensin Therapeutics Inc. and is coinventor of patents entitled “Active Low Molecular Weight Variants of Angiotensin Converting Enzyme 2,” “Active Low Molecular Weight Variants of Angiotensin Converting Enzyme 2 (ACE2) for the Treatment of Diseases and Conditions of the Eye,” and “Shorter Soluble Forms of Angiotensin Converting Enzyme 2 (ACE2) for Treating and Preventing Coronavirus Infection.” J.K. is an advisory board member for AstraZeneca and has received grants from Fresenius Renal Therapies and consulting fees from Tricida and Nephcentric. Y.O., W.P., Y.B., and E.G. are employees of AstraZeneca. L.F. has no conflicts of interest to declare, and as a Veterans Affairs employee, does not receive compensation.

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Author Contributions

Yemisi Oluwatosin led the study conception and design and protocol development. Stephen R. Ash, Daniel Batlle, William Pottorf, and Linda Fried contributed to the study design and protocol development. Linda Fried and Daniel Batlle are on the study steering committee, and Linda Fried is a national principal investigator for the study. Jessica Kendrick, Yasmin Brahmbhatt, and Emily Guerrieri have contributed to the study conduct. Stephen R. Ash provided the study hypothesis that the direct binding of $\text{NH}_4^+$ by SZC in the gastrointestinal tract is the reason for the increase in serum $\text{HCO}_3^-$ during SZC treatment. Stephen R. Ash, Daniel Batlle, Jessica Kendrick, Yemisi Oluwatosin, William Pottorf, Yasmin Brahmbhatt, Emily Guerrieri, and Linda Fried meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, contributed to manuscript drafting and critical review/revision, and have read and approved the final manuscript.
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