Sodium Zirconium Cyclosilicate among Individuals with Hyperkalemia

A 12-Month Phase 3 Study

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Abstract

Background and objectives Oral sodium zirconium cyclosilicate (formerly ZS-9) binds and removes potassium *via* the gastrointestinal tract. Sodium zirconium cyclosilicate–associated restoration and maintenance of normokalemia and adverse events were evaluated in a two-part, open label, phase 3 trial.

Design, setting, participants, & measurements In the correction phase, adult outpatients with plasma potassium ≥5.1 mmol/L (i-STAT Point-of-Care) received sodium zirconium cyclosilicate 10 g three times daily for 24–72 hours until normokalemic (potassium =3.5–5.0 mmol/L). Qualifying participants entered the ≤12-month maintenance phase and received sodium zirconium cyclosilicate 5 g once daily titrated to maintain normokalemia without dietary or medication restrictions. Prespecified primary end points were restoration of normal serum potassium values (3.5–5.0 mmol/L) during the correction phase and maintenance of serum potassium ≤5.1 mmol/L during the maintenance phase. Adverse events were assessed throughout.

Results Of 751 participants, 746 (99%) achieved normokalemia during the correction phase (mean serum potassium =4.8 mmol/L; 95% confidence interval, 4.7 to 4.8) and entered the maintenance phase; 466 (63%) participants completed the 12-month trial. Participants were predominantly white, men, and age ≥65 years old; 74% had an eGFR<60 ml/min per 1.73 m^2, and 65% used renin-angiotensin-aldosterone system inhibitors. Mean time on sodium zirconium cyclosilicate was 286 days. Mean daily sodium zirconium cyclosilicate dose was 7.2 g (SD=2.6). Over months 3–12, mean serum potassium was 4.7 mmol/L (95% confidence interval, 4.6 to 4.7); mean serum potassium values ≤5.1 and ≤5.5 mmol/L were achieved by 88% and 99% of participants, respectively. Of 483 renin-angiotensin-aldosterone system inhibitor users at baseline, 87% continued or had their dose increased; 11% discontinued. Among 263 renin-angiotensin-aldosterone system inhibitor–naïve participants, 14% initiated renin-angiotensin-aldosterone system inhibitor therapy. Overall, 489 (66%) participants experienced adverse events during the maintenance phase, and 22% experienced a serious adverse event. Of eight (1%) deaths, none were considered related to sodium zirconium cyclosilicate. Nine (1%) and 34 (5%) participants experienced serum potassium <3.0 and 3.0–3.4 mmol/L, respectively.

Conclusions After achieving normokalemia, individualized once daily sodium zirconium cyclosilicate was associated with maintenance of normokalemia without substantial renin-angiotensin-aldosterone system inhibitor changes for ≤12 months.

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Introduction

Potassium (K^+) homeostasis can be compromised among individuals with CKD, heart failure (HF), and diabetes mellitus and in those using renin-angiotensin-aldosterone system inhibitors (RAASis). Consequently, these individuals are at greater risk of persistent or recurrent hyperkalemia, and discontinuation of beneficial medications, such as RAASis, may be recommended (1–11). Despite potentially dangerous sequelae of hyperkalemia, no standard outpatient treatment paradigm exists (12). Individuals with severe hyperkalemia (K^+>6.0 mmol/L) are at increased risk of cardiac arrhythmias and sudden death, and they often require emergency treatment to rapidly normalize K^+ (13). Chronic hyperkalemia may be treated *via* dietary restrictions and nonspecific cation-binding organic polymers (*e.g.*, patiromer and sodium/calcium polystyrene sulfonate), but many of these are associated with limitations for long-term use (1,12,14–18).

Sodium zirconium cyclosilicate (SZC; formerly ZS-9) is an inorganic, insoluble, highly selective K^+ binder approved for the treatment of hyperkalemia in adults in the United States and the European Union. SZC

exchanges sodium and hydrogen ions for K^+ or ammonium ions in the gastrointestinal tract. The resulting K^+-bound complex is excreted in feces (19,20). Normokalemia is achieved within 4 hours of the first SZC 10-g dose in most individuals, and it is maintained for ≤28 days with once daily doses of 5–15 g; tolerability is generally comparable with placebo and consistent with populations with multiple comorbidities (21,22). Additionally, serum bicarbonate is increased (20,22), possibly through SZC binding of ammonium ions (19).

This two-part study in adult outpatients with hyperkalemia assessed SZC-associated correction of hyperkalemia over 24–72 hours, maintenance of normokalemia over 12 months, and adverse events (AEs).

Materials and Methods

Study Overview

This prospective, international, multicenter, open label, single-arm, phase 3 trial (ClinicalTrials.gov identifier: NCT02163499) was conducted between June 23, 2014 and November 4, 2016 at 56 global sites (Supplemental Table 1) in accordance with all local and international guidelines (Supplemental Material).

Study Design

Eligible outpatients (age ≥18 years old) had hyperkalemia (two consecutive K^+ plasma values ≥5.1 mmol/L measured in whole blood with a point-of-care device [i-STAT; Abbott Point of Care, Princeton, NJ]). Inclusion and exclusion criteria are described in Supplemental Table 2. In the initial 24- to 72-hour correction phase, participants received SZC 10 g three times daily. Participants who achieved normokalemia (K^+=3.5–5.0 mmol/L) were eligible for the subsequent 12-month maintenance phase (Figure 1A). No protocol-mandated dietary or RAASi restrictions were required. Participants were discontinued if normokalemia was not achieved during the correction phase or if CKD progressed such that dialysis, transplant, or other treatment was required; serious arrhythmias, acute HF, or potential hyperkalemia-related electrocardiogram changes occurred; or i-STAT K^+ was <3.0 or >6.5 mmol/L during the study or maintenance phase, respectively (Supplemental Material).

Study Drug Administration during the Maintenance Phase

Oral SZC therapy was initiated at 5 g once daily and titrated in 5-g increments or decrements guided by the protocol-specified algorithm (maximum 15 g once daily; minimum 5 g every other day) (Supplemental Figure 1) to maintain i-STAT K^+ pf 3.5–5.0 mmol/L.

Clinical Laboratory Evaluations

Two fasting blood samples were collected simultaneously for i-STAT and serum K^+ measurements. i-STAT K^+ determined overall study and maintenance-phase eligibility and SZC dose titrations. Serum K^+ determined treatment outcomes. K^+ measurements were taken on a weekly basis for the first month, every 4 weeks thereafter through day 365, and 7 (±1) days after cessation of study drug (Figure 1A).

Study End Points

The prespecified primary end points were restoration of normal serum K^+ (3.5–5.0 mmol/L) during the correction phase and maintenance of serum K^+ ≤5.1 and ≤5.5 mmol/L during the maintenance phase over months 3–12.

Secondary end points included the proportions of participants with mean serum K^+ =3.5–5.5 mmol/L over months 3–12; mean serum K^+ over months 3–12, 6–9, and 9–12; and change from baseline in serum K^+ and bicarbonate (all participants and those with baseline bicarbonate <22 mmol/L and normal bicarbonate levels [19–34 mmol/L]). A prespecified exploratory analysis examined change in RAASi dose, whereas *post hoc* exploratory analyses examined i-STAT K^+ measures. Safety was assessed by spontaneous investigator reports of AEs and serious AEs, vital signs, and laboratory measures. Edema was evaluated by standardized Medical Dictionary for Regulatory Activities query (SMQ edema) for hemodynamic edema, effusions, and fluid overload.

Statistical Considerations

The power calculation was performed on the primary end points of restoring normokalemia (serum K^+ =3.5–5.0 mmol/L) and maintaining serum K^+ ≤5.1 or ≤5.5 mmol/L. Enrollment of 700 participants would provide >90% power to rule out an 80% achievement rate of each serum K^+ goal (null hypothesis) from an 85% achievement rate (alternative) using a two-sided exact test at an α-level of 0.05. For analyses using continuous end points, this sample size would detect a 0.07-mmol/L difference in serum K^+ from baseline to day 365 with 90% power and two-sided 5% type 1 error assuming an SD of 0.5 on the basis of data from a previous trial (21).

Results

Study Population

Of 1561 participants screened, 751 entered the correction phase, and 746 entered the maintenance phase (Figure 1B). Most participants had multiple comorbidities, required concomitant RAASi therapy, and had a history of hyperkalemia (Table 1). At correction-phase baseline, 65% of participants received concomitant RAASis, and 38% received diuretics (Supplemental Table 3).

Three participants were excluded from serum K^+ analyses for the correction phase, and 280 discontinued therapy before completing the maintenance phase (Figure 1B). Discontinuations were distributed evenly during follow-up (Supplemental Figure 2).

SZC-Associated Changes in K^+ and Bicarbonate

Correction Phase. At baseline, mean i-STAT K^+ and serum K^+ values were 5.5 mmol/L (minimum to maximum, 5.1–7.3) and 5.6 mmol/L (minimum to maximum, 4.0–7.6), respectively (Supplemental Figures 3 and 4). Within 24 hours, 613 (82%) and 494 (66%) participants achieved K^+ 3.5–5.0 mmol/L by i-STAT and serum K^+, respectively; 104 additional participants (14%; mean baseline serum K^+ =5.8 mmol/L; minimum to maximum, 4.7–7.3) required 48 hours of treatment, and 28 (4%; mean baseline serum K^+ =5.9 mmol/L; minimum to maximum, 4.6–7.2) required 72 hours of treatment. At completion of the correction phase, 99.5% (95% confidence interval [95% CI], 98.6% to 99.9%) and 99.9% (95% CI, 99.3% to 100.0%) of participants had i-STAT K^+ values of 3.5–5.0 and

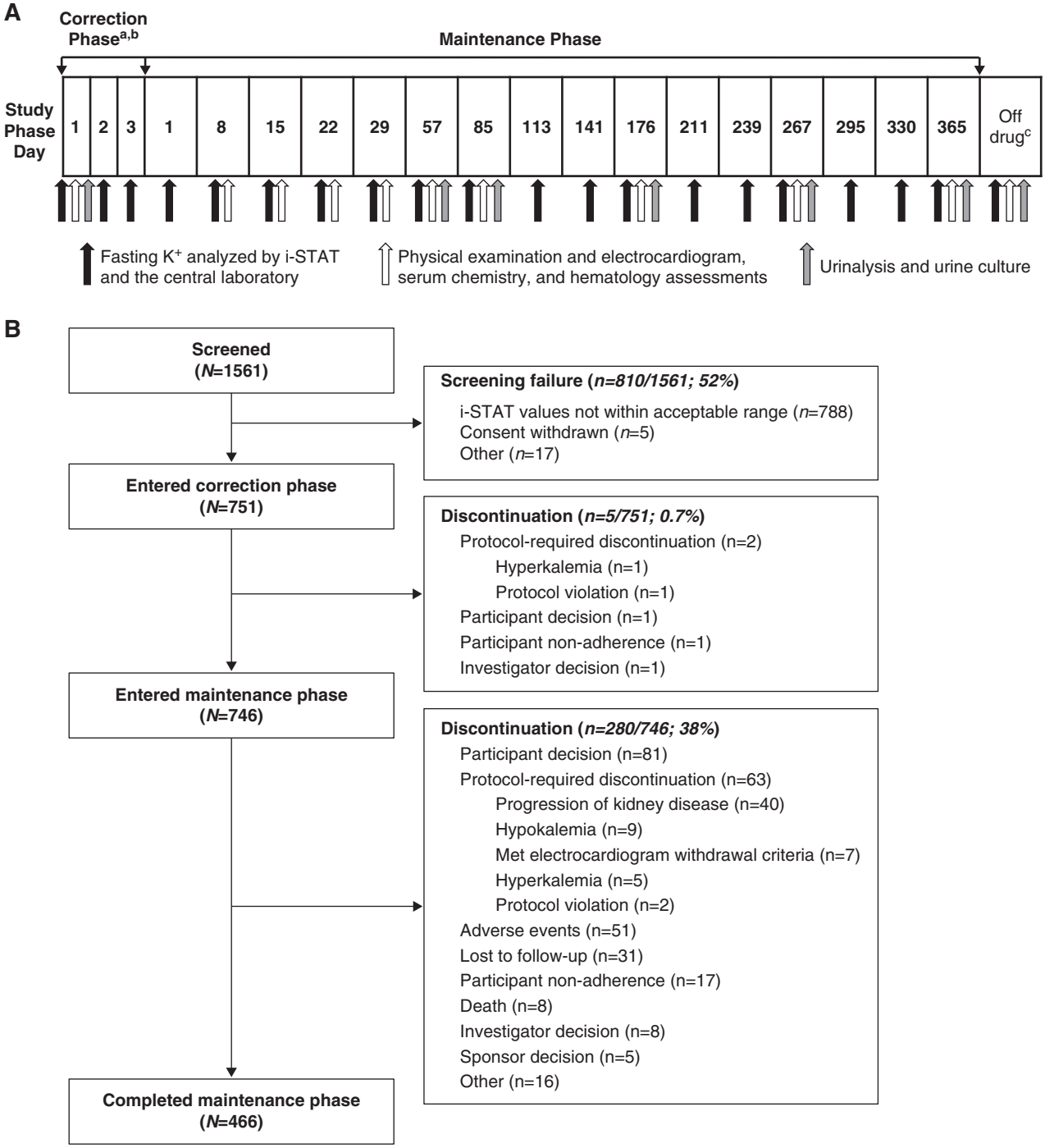


Figure 1. | **(A) Study design and (B) participant disposition.** [a]Participants who achieved normokalemia (potassium [K^+] =3.5–5.0 mmol/L) as measured by the i-STAT Point-of-Care device at any point during the correction phase were immediately eligible to enter the 12-month maintenance phase and received once daily treatment with sodium zirconium cyclosilicate (SZC; provided in 40 ml of water [no rinse] or 180 ml with 2×30-ml rinses). [b]K^+ was only measured on days when SZC was administered. [c]Off-drug values were collected 7 (±1) days after the last administration of SZC. Three participants were excluded from serum K+ analyses for the correction phase: two did not have at least one serum K^+ measurement, and one had a missing K^+ measurement during active dosing; however, this participant had a postdose K^+ measurement and was eligible for entry into the maintenance phase.

3.5–5.5 mmol/L, respectively. Likewise, 78% (95% CI, 75% to 81%) and 99% (95% CI, 98% to 99.4%) of participants achieved serum K^+ values of 3.5–5.0 or 3.5–5.5 mmol/L, respectively (Figure 2, Supplemental Figure 5).

Maintenance Phase. Mean serum K^+ at maintenance-phase baseline was 4.8 mmol/L, a mean reduction of 0.9 mmol/L (−15%) from correction-phase baseline. Mean serum K^+ values of ≤5.1, ≤5.5, and 3.5–5.5 mmol/L were achieved by 88%, 99%, and 99% of participants, respectively, over months 3–12 (Figure 3, A–C).

Between days 8 and 365, mean serum K^+ was 4.8 mmol/L (95% CI, 4.7 to 4.8). Median serum K^+ values during months 3–12, 6–9, and 9–12 are presented in Figure 3D. After discontinuation of SZC (7 [±1] days after drug cessation), mean serum K^+ increased by 0.4 from 4.6 mmol/L (95% CI, 4.53 to 4.63) at day 365 to 5.0 mmol/L (95% CI, 4.9 to 5.0). A significant change in mean serum K^+ from correction-phase baseline was observed at all time points ($P<0.001$ for all; minimum to maximum, −0.8 to −1.0 mmol/L; mean percentage change, −14% to −18%) (Figure 3E).

During the maintenance phase, mean increases from correction-phase baseline in bicarbonate ranged from 0.8 to 1.2 mmol/L (mean percentage change, 4%–6%), a trend observed even among participants with bicarbonate <22 mmol/L (Supplemental Table 4) and in participants who did not initiate or require a change in sodium bicarbonate therapy during the study (Supplemental Figure 6). The proportion of participants with normal bicarbonate levels increased from 74% at baseline to 86% at day 365 (Figure 4A); conversely, those with bicarbonate <22 mmol/L decreased from 28% at baseline to 17% at day 365 (Figure 4B). During the maintenance phase, 81 (11%) participants took sodium bicarbonate therapy: 61 (75%) existing prescriptions and 20 (25%) new prescriptions.

Of the 483 participants who received RAASis at the start of the correction phase, 74% maintained the same RAASi dose. Overall, 13% had a dose increase, and 14% had a dose decrease (nonmutually exclusive); 11% discontinued RAASis. Among RAASi-naïve participants at baseline (n=263), 37 (14%) initiated RAASis.

Correlation of i-STAT and Serum K^+. Linear regressions of serum K^+ against i-STAT K^+ were strongly correlated in the correction and maintenance phases (Supplemental Figure 7). Serum K^+ values were generally slightly higher than i-STAT K^+ values. Trends in SZC-associated changes in serum K^+ values (reported previously) were consistent with i-STAT K^+ values (Supplemental Figures 8 and 9).

Dosing

Correction Phase. The median number of doses required to achieve i-STAT K^+ =3.5–5.0 mmol/L was three doses (interquartile range, 3–3 doses), and the median treatment duration was 1 day (interquartile range, 1–1 day). Most participants (n=612 [82%]) achieved normokalemia by i-STAT after administration of SZC 30 g (three 10-g doses) over 24 hours, 99 (13%) participants required 60 g (six 10-g doses) over 48 hours, and 27 (4%) participants required 90 g (nine 10-g doses) over 72 hours. The remaining 13 (2%) participants required 10 g (n=2), 20 g (n=5), 50 g (n=5), or 70 g (n=1) to achieve normokalemia.

Maintenance Phase. All but one participant (who started on SZC 10 g and downtitrated to 5 g once daily) started treatment with SZC at 5 g once daily. Mean and median times to the first dose titration were 70 days (SD=79) and 29 days, respectively. Mean daily SZC dose received was 7.2 g (SD=2.6) administered over a mean of 286 days. Most participants (minimum to maximum, 85%–100%) received either SZC 5 or 10 g once daily during the maintenance phase (Supplemental Figure 10A). The maximum dose for 47% of participants was 5 g once daily, with a mean exposure duration of 269 days (95% CI, 255 to 284). The next most common maximum dose was 10 g once daily (41%), with a mean total duration of exposure for these participants of 290 days (95% CI, 278 to 303). Only 87 (12%) participants received 15 g once daily, with a mean exposure duration of 338 days (95% CI, 325 to 351). Most participants (84%) had less than or equal to one SZC dose modification during the maintenance phase (Supplemental Figure 10B). The most common dose modification was uptitration from the starting dose of 5 g once daily to 10 g once daily (37%). The mean time to the last SZC dose modification was 107 days (95% CI, 98 to 116).

Safety

During the correction phase, 31 (4%) participants experienced an AE: most commonly nausea and urinary tract infection (Supplemental Table 5). One participant experienced a peripheral edema event.

During the maintenance phase, 66% of participants experienced an AE. Overall, 12% experienced an investigator-adjudged AE related to SZC, and 17% experienced a severe event. Gastrointestinal disorders were reported in 22% of participants: most commonly nausea (8%), constipation (6%), vomiting (5%), and diarrhea (4%). The most common specific AEs were hypertension (11%), peripheral edema (10%), and urinary tract infection (8%) (Supplemental Table 6, Table 2).

Hypertension was reported as an AE in 82 participants; of these, 76 had a history of hypertension, and 73 required treatment for the event. Hypertension was rated as mild to moderate in most participants, and only one event was considered related to SZC by the investigator.

SMQ edema was reported by 113 (15%) participants (Table 2) and considered related to SZC in 18 (2%) participants (Supplemental Material, Supplemental Table 7), and it was more frequent in the first few months of treatment (Supplemental Figure 11) and with high SZC doses (Supplemental Material). Most SMQ edema events were of mild (55%) or moderate (35%) severity. Participants with SMQ edema events during the maintenance phase were older; more likely to have an eGFR<45 ml/min per 1.73 m^2, HF, and K^+>5.5 mmol/L; and more likely to have used a calcium channel blocker or diuretic at correction-phase baseline than those without SMQ edema events (Supplemental Table 8). Ten events were serious (pulmonary edema [n=3], fluid overload [n=3], ascites, local swelling, pleural effusion, and generalized edema [n=1 each]); one was considered related to SZC. Among participants experiencing SMQ edema events, 67 of 113 participants (59% of those with edema; 67 of 746 [9%] of the study population) required loop diuretics. Of these, 30 (27% of those with edema; 4% of the study population) were diuretic naïve at baseline

Table 1. Baseline characteristics and demographics for participants in the correction-phase safety population who entered the maintenance phase

Characteristic[a]	Overall Population, *n*=746
Age, yr, mean (SD)	64 (13)
Sex	
Men	446 (60)
Women	300 (40)
Race	
White	620 (83)
Black	88 (12)
Asian	25 (3)
Other	13 (5)
Ethnicity	
Hispanic	317 (43)
Non-Hispanic	429 (58)
Geographic region	
United States	634 (85)
Other countries[b]	112 (15)
Weight, kg, mean (SD)	86 (22)
BP, mm Hg, mean (95% CI)[c]	
Systolic	136 (134 to 137)
Diastolic	77 (76 to 78)
Serum potassium, mmol/L, mean (minimum to maximum)[d]	4.8 (3.3–6.6)
Serum potassium, mmol/L	
<3.5	1 (0.1)
3.5–5.0	582 (78)
5.1– <5.5	146 (20)
5.5 to <6.0	16 (2)
≥6.0	1 (0.1)
i-STAT potassium, mmol/L, mean (minimum to maximum)[d]	4.5 (3.4–5.4)
i-STAT potassium, mmol/L	
<3.5	1 (0.1)
3.5–5.0	731 (98)
5.1 to <5.5	2 (0.3)
5.5 to <6.0	0 (0.0)
≥6.0	0 (0.0)
Missing	12 (2)
eGFR, ml/min per 1.73 m^2, mean (SD)[d]	47 (32)
eGFR, ml/min per 1.73 m^2	
<15	43 (6)
15 to <30	243 (33)
30 to <45	173 (23)
45 to <60	90 (12)
≥60	188 (25)
Not reported	9 (1)
Aldosterone, nmol/L[e]	
<0.11	30 (4)
0.11–0.86	303 (41)
>0.86	18 (2)
Comorbidity	
CKD[f]	483 (65)
Diabetes mellitus[f]	474 (64)
Heart failure[g]	111 (15)
Hyperkalemia[h]	421 (56)
Hypertension	618 (83)
Organ transplant	11 (2)
Liver	2 (0.3)
Pancreas	2 (0.3)
Kidney	9 (1)
Concomitant medication use	
RAASi therapy	483 (65)
ACE inhibitors	336 (45)
ARBs	157 (21)
Mineralocorticoid receptor antagonists	44 (6)
Diuretics[i]	282 (38)
Loop	236 (32)
Thiazide	35 (5)
Other[j]	25 (3)
Calcium channel blockers[k]	257 (34)
β-blockers[d]	357 (48)
Furosemide equivalent units[l]	
Mean (95% CI)	1.4 (1.2 to 1.5)
Minimum to maximum	0.01–6
n, %	
0 to <1 unit	81/236 (34)
1 to <2 units	81/236 (34)
2 to <3 units	45/236 (19)
≥3 units	29/236 (12)

Values are *n* (%) unless otherwise specified. 95% CI, 95% confidence interval; RAASi, renin-angiotensin-aldosterone system inhibitor; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

[a]The safety population comprised all participants who received one or more doses of sodium zirconium cyclosilicate during the given study phase and had any postbaseline follow-up for safety.

[b]Centers in Australia, Europe, and South Africa.

[c]Collected at correction-phase baseline for 746 participants in the maintenance-phase safety population.

[d]Collected at maintenance-phase baseline for 746 participants in the maintenance-phase safety population.

[e]Collected at correction-phase baseline for 351 participants with evaluated aldosterone levels in the maintenance-phase safety population.

[f]On the basis of standardized Medical Dictionary for Regulatory Activities query narrow terms.

[g]On the basis of patient report form.

[h]Represents 418 participants with "hyperkalemia" and three participants with "blood potassium increased" collected at correction-phase baseline among the 751 participants in the correction-phase safety population.

[i]Subcategories are not mutually exclusive.

[j]The "other" category consisted of nonthiazide low-ceiling diuretics and potassium-sparing diuretics.

[k]Collected at correction-phase baseline for 751 participants in the correction-phase safety population.

[l]Furosemide 40 mg/d=1 furosemide equivalent unit per day, bumetanide 1 mg/d=1 furosemide equivalent unit per day, and torasemide 20 mg/d=1 furosemide equivalent unit per day.

and initiated a loop diuretic to treat the event, 36 (32% of those with edema; 5% of the study population) were using loop diuretics at baseline, and for one, usage at baseline was undetermined. Of the 36 participants using diuretics at baseline who experienced an SMQ edema event, 28 (25% of those with edema; 4% of the study population) required one or more increases in loop diuretic dose/dosing frequency to treat the event. Two participants discontinued SZC and one discontinued the study due to SMQ edema.

Serious AEs were experienced by 22% of participants during the maintenance phase (Supplemental Table 9, Table 2). AEs led to discontinuation of SZC in 14% of participants (Supplemental Table 10, Table 2). Of eight deaths, none

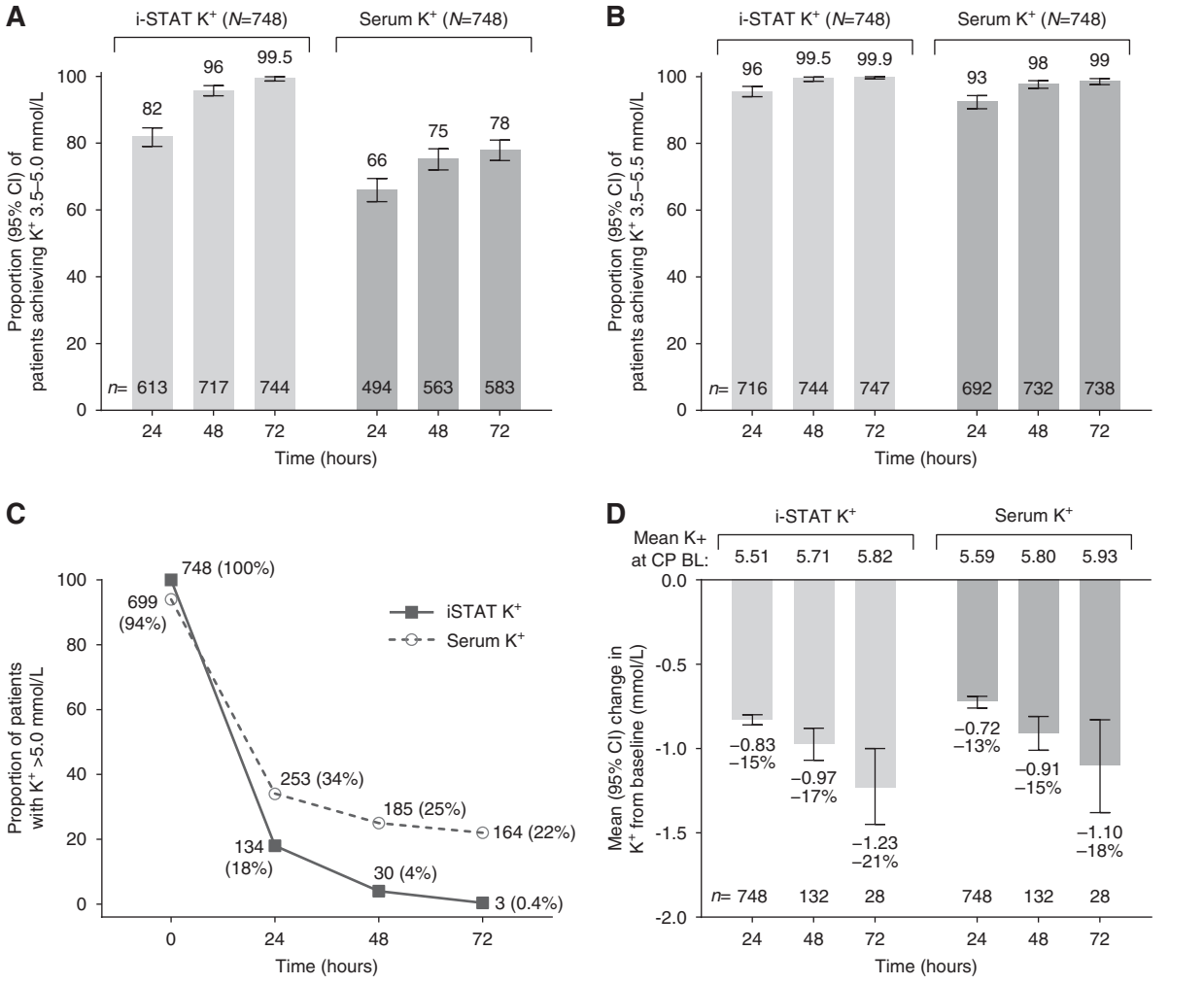


Figure 2. | **Proportion of participants who achieved a potassium (K^+) value of (A) 3.5–5.0, (B) 3.5–5.5, or (C) >5.0 mmol/L by i-STAT and serum K^+ during the correction phase (CP) and (D) change in K^+ from baseline (with annotated mean change and percentage change values) by i-STAT and serum K^+ during the CP**. Data in A and B were calculated using the last observation carried forward method. BL, baseline; 95% CI, 95% confidence interval.

were considered related to SZC. HF was experienced by 5% of participants; 3% experienced HF as a serious AE and required hospitalization for the event, resulting in a hospitalization rate of 3.6 per 100 participant-years.

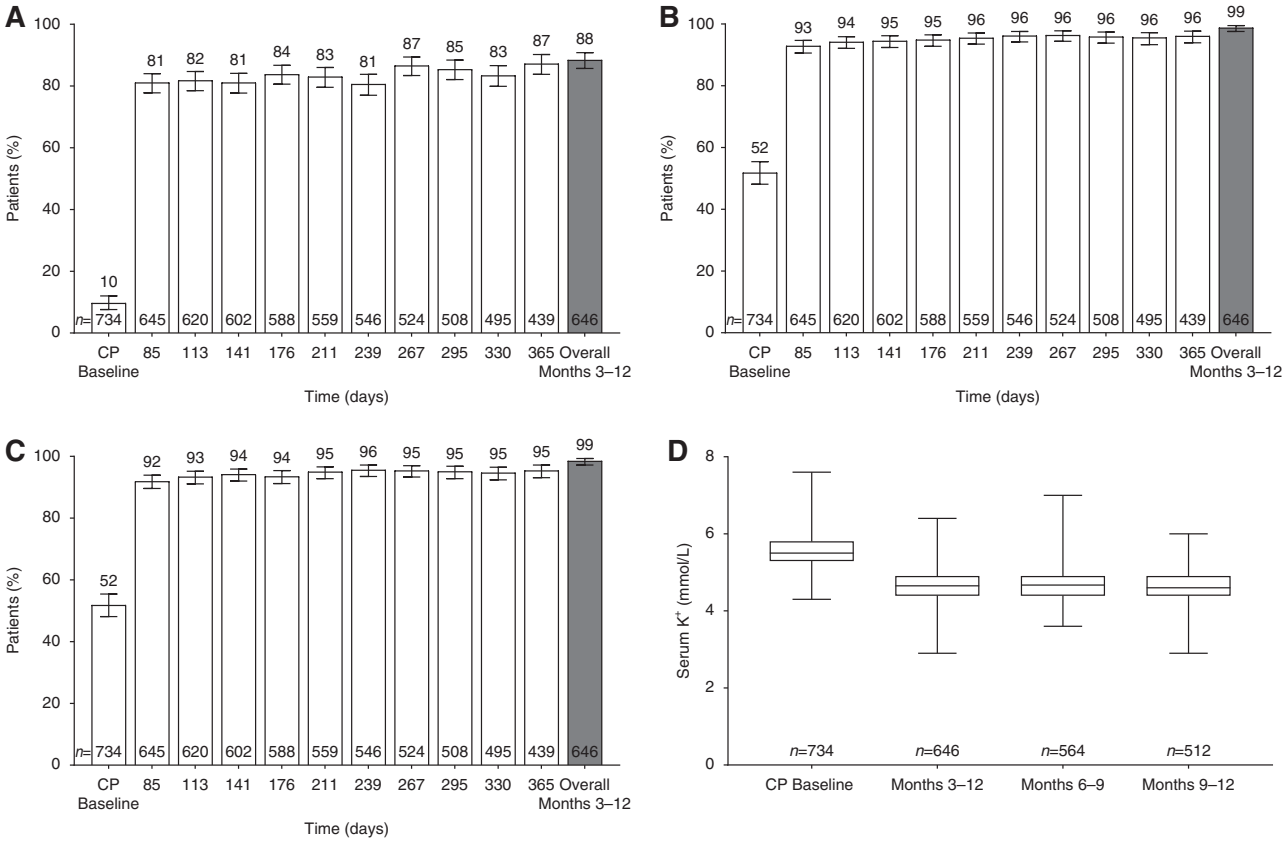
No participants had severe hypokalemia (serum K^+ <2.5 mmol/L) during the maintenance phase, nine had serum K^+ of 2.5–2.9 mmol/L (one event each), and 34 had serum K^+ of 3.0–3.4 mmol/L (42 events). Serum K^+ =5.5–6.0 and >6.0 mmol/L occurred in 194 (417 events) and 72 (90 events) participants, respectively.

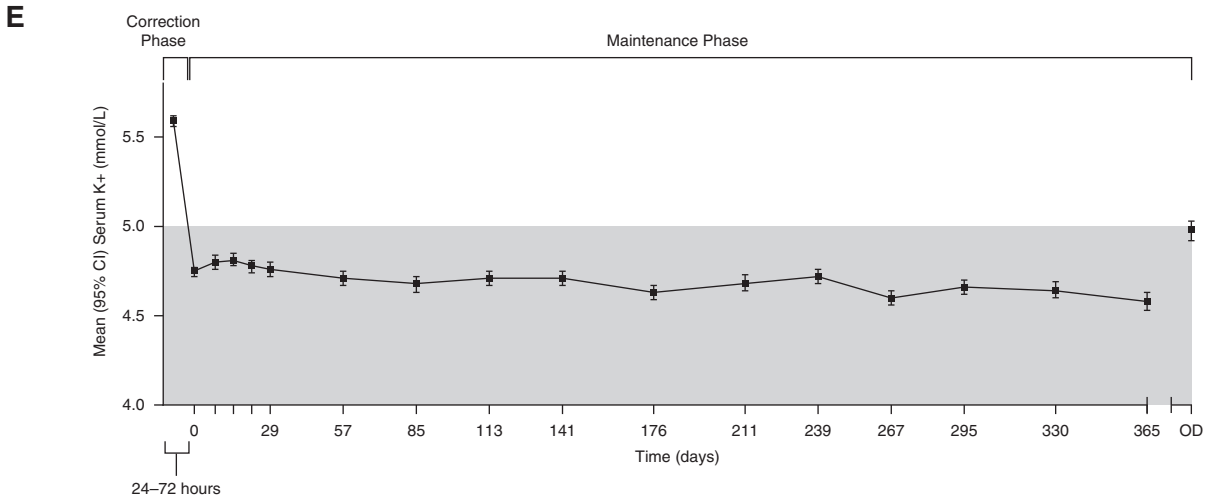
No clinically meaningful changes were observed in vital signs, and there were only minimal changes in serum and urinary parameters (Supplemental Tables 11 and 12, Table 3).

Discussion

The results from this study are consistent with prior smaller and shorter clinical studies of SZC (20–22), and they further show that SZC use is associated with both rapid correction of hyperkalemia and long-term maintenance of normokalemia up to 12 months. Here, the observed mean reduction in baseline serum K^+ of −0.72 mmol/L at 24 hours is consistent with previous reports of −0.11 mmol/L within 1 hour of administering a single 10-g dose of SZC (20) and −0.7 and −1.1 mmol/L after 48-hour treatment with SZC 10 g three times daily (21,22).

Our study also demonstrated that short-term three times daily SZC dosing restored normokalemia in >99% of outpatients within 24–72 hours and that once daily dosing with SZC, starting from 5 g once daily and subsequently individualized, provided maintenance of normokalemia for up to 12 months, with 87% of participants achieving serum K^+ ≤5.1 mmol/L at day 365. Nearly all participants who continued treatment maintained serum K^+ ≤5.5 mmol/L at regularly scheduled visits. Importantly, SZC-associated serum K^+ reduction was achieved with no protocol-mandated changes to diet or RAASi therapy. In fact, many participants maintained (74%) or increased (13%) their baseline RAASi dosing. Although lack of a control group





	Day																
	1	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**176**	**211**	**239**	**267**	**295**	**330**	**365**	**OD**
n	734	733	713	705	701	674	645	620	602	588	559	546	524	508	495	439	597
Nominal Δ, mmol/L	−0.85	−0.79	−0.78	−0.81	−0.83	−0.87	−0.91	−0.88	−0.88	−0.96	−0.90	−0.87	−0.99	−0.93	−0.94	−1.00	−0.63
Percent Δ, %	−15	−14	−14	−14	−15	−15	−16	−15	−15	−17	−16	−15	−17	−16	−17	8	−11

Figure 3. | Proportion of participants with mean serum potassium (K^+) values (A) ≤5.1, (B) ≤5.5, and (C) 3.5–5.5 mmol/L by visit in the maintenance-phase intention-to-treat (ITT) population; (D) box and whisker plots of median, interquartile range, minimum, and maximum serum K^+ values at months 3–12, 6–9, and 9–12 in the maintenance-phase ITT population; and (E) mean serum K^+ over time in the maintenance-phase ITT population. The ITT population included all participants who received sodium zirconium cyclosilicate (SZC) and had any postbaseline K^+ values measured during the study phase. Gray bars in A–C represent means of all visits occurring over months 3–12. In D, the median serum K^+ was 5.5 mmol/L at correction-phase (CP) baseline, 4.7 mmol/L from months 3–12 and months 6–9, and 4.6 mmol/L from months 9–12. For all bars in E, $P<0.001$ versus CP baseline. Off-drug (OD) values were recorded at 7 (±1) days after the last dose of SZC. Δ indicates change; 95% CI, 95% confidence interval.

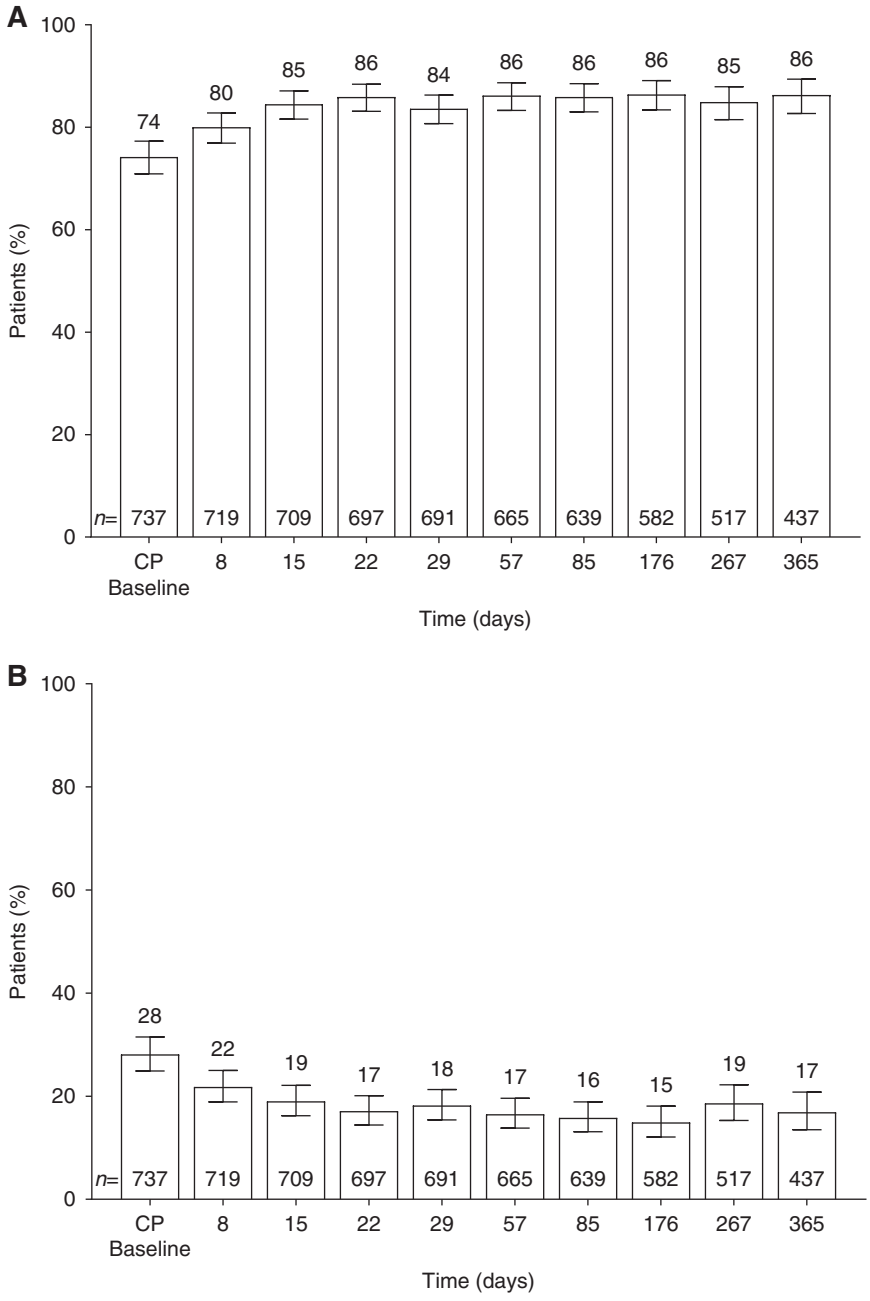


Figure 4. | **Proportion of participants with (A) normal bicarbonate levels and (B) a bicarbonate level <22 mmol/L in the maintenance-phase safety population**. Normal bicarbonate levels were defined as 19–34 mmol/L as determined by individual laboratories on the basis of age/sex. The safety population comprised all participants who received one or more doses of sodium zirconium cyclosilicate during the given study phase and had any postbaseline follow-up for safety. CP, correction phase.

confounds the interpretation of safety data, the common occurrence of gastrointestinal AEs was consistent with other short-term placebo-controlled studies (21,22). In this study, reported AEs were generally mild to moderate in severity and manageable without interruption of SZC treatment. After cessation of SZC treatment, K^+ levels increased, highlighting the need for chronic treatment in this population. Our findings also suggest that SZC is associated with good tolerability during 12 months of treatment, supporting the utility of SZC in the long-term management of individuals with hyperkalemia, including those who would benefit from continuation and optimization of concomitant RAASi therapy. The observed increase in serum bicarbonate levels with SZC is of much interest, because it may have a protective effect among individuals with CKD; however, potential improvement in acidosis could not be determined and warrants additional investigation. Because SZC contains sodium, the incidence of edema is of particular clinical importance. Because of the lack of a control group in our study, we explored

Table 2. Adverse events and deaths in the maintenance-phase safety population

MedDRA Preferred Term, *n* (%)[a]	Maintenance Phase, *n*=746
Adverse events (≥5% of participants)	489 (66)
Anemia	44 (6)
Constipation	48 (6)
Hypertension[b]	82 (11)
Nausea	56 (8)
Peripheral edema	72 (10)
SMQ edema[c]	113 (15)
Upper respiratory tract infection	37 (5)
Urinary tract infection[d]	59 (8)
Serious adverse events (≥0.5% of participants)	161 (22)
Acute myocardial infarction	6 (0.8)
Acute respiratory failure	5 (0.7)
Cardiac failure	4 (0.5)
Cardiac failure congestive	11 (2)
Cellulitis	7 (0.9)
Chest pain	11 (2)
Dyspnea	5 (0.7)
Hyperkalemia	4 (0.5)
Hypertension	4 (0.5)
Hypoglycemia	4 (0.5)
Osteomyelitis	8 (1)
Pneumonia	14 (2)
Renal failure acute	8 (1)
Renal failure chronic	4 (0.5)
Skin ulcer	4 (0.5)
Urinary tract infection[d]	4 (0.5)
Adverse events leading to treatment discontinuation (≥0.5% of participants)	102 (14)
Atrial fibrillation	4 (0.5)
Cardiac failure	4 (0.5)
Cardiac failure congestive	11 (2)
Dyspnea	5 (0.7)
Osteomyelitis	4 (0.5)
Renal failure acute	9 (1)
Renal failure chronic	6 (0.8)
Reasons for death	8 (1)
Cardiac arrest/methamphetamine intoxication	1 (0.1)
Cystitis hemorrhagic	1 (0.1)
Dyspnea/electrocardiogram abnormal	1 (0.1)
Heart injury	1 (0.1)
Hypercapnia/respiratory failure	1 (0.1)
Interstitial lung disease	1 (0.1)
Myocardial infarction	1 (0.1)
Renal failure chronic	1 (0.1)

MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized Medical Dictionary for Regulatory Activities query.
[a]The safety population comprised all participants who received one or more doses of sodium zirconium cyclosilicate during the given study phase and had any postbaseline follow-up for safety.
[b]As reported by site with no specific threshold.
[c]Preferred terms included in the edema SMQ were ascites, fluid overload, fluid retention, generalized edema, local swelling, edema, edema peripheral, pericardial effusion, pleural effusion, and pulmonary edema.
[d]As determined by the investigator.

edema incidence in comparable populations in previous reports. In one 20-week study in participants with diabetic nephropathy and a mean eGFR of 33 ml/min per 1.73 m^2, edema was reported in 17% of participants given placebo (23). In longer-term (52-week) studies, peripheral edema was reported in 7% of participants with diabetes and mild kidney insufficiency who received placebo (24) and 10%–11% of participants with diabetes and severe kidney insufficiency, of whom 25%–30% had hyperkalemia (25). A previous SZC trial showed edema incidence to be higher among participants administered SZC 15 g versus placebo (21). In this study, a maximum dose of SZC 5 or 10 g was sufficient to maintain normokalemia in 88% of participants. Given that this study included high proportions of participants with eGFRs of 15 to <30 (33%) or <15 ml/min per 1.73 m^2 (6%) and HF (15%), the observed peripheral edema rate (10%) seems to be consistent with expectations for this population, although once again, lack of placebo control precludes firm conclusions being drawn. Moreover, an apparent association between higher SZC exposure and development of edema events is likely to be confounded by the fact that those participants requiring higher SZC doses are also more likely to have multiple comorbidities (including lower eGFR) or be receiving treatments that inherently increase the risk of volume overload (*e.g.*, calcium channel blockers or β-blockers). Here, a conservative approach involved reporting AEs occurring within the SMQ edema category, which included terms potentially independent of sodium intake (for example, "local swelling").

The binding selectivity of SZC differs from polymeric K^+-binding compounds, such as sodium/calcium polystyrene sulfonate and patiromer (18,19,26). Unlike other K^+ binders, SZC binds to K^+ and similarly sized ammonium cations with high selectivity, but it binds poorly to calcium and magnesium ions (19). This study supports this in showing that SZC treatment provided a sustained reduction in serum K^+, with only a single patient with clinically significant hypocalcemia and no instances of clinically significant hypomagnesemia (Supplemental Table 11).

Several potential limitations of this study should be considered. First, because this was an open label study, it did not control for disease severity, comorbidities, and medication use. Second, participants who discontinued treatment were not followed prospectively. Third, treatment decisions were made on the basis of point-of-care i-STAT K^+ testing, whereas analyses of treatment associations were performed using serum K^+ values. Because serum K^+ was generally higher than i-STAT K^+, dose titration decisions may have been different if on the basis of serum K^+, potentially further decreasing achieved K^+. Fourth, follow-up beyond 7 days after the last SZC treatment may have provided additional information on hyperkalemia rates after cessation of therapy.

Data from this long-term, single-arm, open label study demonstrated that outpatient treatment of hyperkalemia with SZC was associated with rapid correction of hyperkalemia and maintenance of normokalemia among participants who continued therapy for up to 12 months without dietary or RAASi medication restrictions. Tolerability in this population with multiple comorbidities was generally consistent with that reported previously for SZC in shorter-term controlled clinical trials.

Table 3. Vital signs for the maintenance-phase safety population

Vital Sign	Mean (95% CI) Value at CP Baseline, *n*=746	Mean (95% CI) Change from CP Baseline[a]	
		Day 29, *n*=701	Day 365/EOS, *n*=731[b]
Systolic BP, mm Hg	135.6 (134.2 to 137.0)	−1.1 (–2.4 to 0.2)	0.0 (–1.4 to 1.4)
Diastolic BP, mm Hg	77.1 (76.3 to 77.8)	−0.3 (–1.0 to 0.4)	−0.6 (–1.4 to 0.2)
Pulse rate, beats per minute	69.0 (68.2 to 69.8)	0.1 (–0.6 to 0.7)	1.3 (0.5 to 2.0)
Weight, kg[c]	86.25 (84.66 to 87.84)	0.28 (–0.06 to 0.62)	0.32 (–0.10 to 0.74)

95% CI, 95% confidence interval; CP, correction phase; EOS, end of study.
[a]The safety population comprised all participants who received one or more doses of sodium zirconium cyclosilicate during the given study phase and had any postbaseline follow-up for safety.
[b]Day 365/EOS represents the last scheduled study visit day (±1 day) while on study drug.
[c]The numbers of participants with available weight measure were 743, 690, and 426 for CP baseline and days 29 and 365/EOS of the maintenance phase, respectively.

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Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.12651018/-/DCSupplemental.

Supplemental Materials and Methods.

Supplemental Results.

Supplemental Table 1. Study sites and principal investigators by country.

Supplemental Table 2. Inclusion and exclusion criteria.

Supplemental Table 3. Concomitant medications reported by ≥15% of participants in the correction phase safety population.

Supplemental Table 4. Change from correction phase baseline in serum bicarbonate levels in the maintenance phase safety population.

Supplemental Table 5. Adverse events that occurred in any participant in the correction phase safety population.

Supplemental Table 6. Adverse events that occurred in ≥1% of participants in the maintenance phase safety population.

Supplemental Table 7. Adverse events that occurred within the hemodynamic edema, effusions, and fluid overload SMQ in the maintenance phase safety population (N=746).

Supplemental Table 8. Correction phase baseline characteristics and demographics stratified by participants who did or did not experience an adverse event within the hemodynamic edema, effusions, and fluid overload SMQ during the maintenance phase.

Supplemental Table 9. Serious adverse events that occurred in ≥2 participants in the maintenance phase safety population.

Supplemental Table 10. Adverse events that led to treatment discontinuation during the maintenance phase safety population.

Supplemental Table 11. Serum laboratory values in the maintenance phase safety population (N=746).

Supplemental Table 12. Urine laboratory parameters in the maintenance phase safety population.

Supplemental Figure 1. Dose titration algorithm.

Supplemental Figure 2. Time from baseline to study discontinuation for any reason in the maintenance phase safety population.

Supplemental Figure 3. Proportion of participants with an i-STAT K^+ measurement at (A) baseline (n=749) and at (B) 24 (n=748), (C) 48 (n=132), and (D) 72 hours (n=28) during the correction phase.

Supplemental Figure 4. Proportion of participants with a serum K^+ measurement at (A) baseline (n=749) and at (B) 24 (n=748), (C) 48 (n=132), and (D) 72 hours (n=28) during the correction phase.

Supplemental Figure 5. Proportion of participants (N=751) who achieved a mean change in (A) i-STAT K^+ and (B) serum K^+. BL, baseline; CI, confidence interval; CP, correction phase; K^+, potassium.

Supplemental Figure 6. Mean serum bicarbonate levels of participants excluding those who either initiated or had a change (dose/frequency) in sodium bicarbonate therapy during the study.

Supplemental Figure 7. Correlation between i-STAT and serum K^+ measurements in the (A) correction and (B) maintenance phases ITT population.

Supplemental Figure 8. Proportion of participants with i-STAT K^+ of (A) ≤5.1 mmol/L, (B) ≤5.5 mmol/L, and (C) 3.5–5.5 mmol/L by visit in the maintenance phase ITT population.

Supplemental Figure 9. i-STAT K^+ (A) over time and (B) at months 3–12, 6–9, and 9–12 in the maintenance phase ITT population.

Supplemental Figure 10. (A) Distribution of SZC dosing per study visit and (B) number of SZC dose modifications (increases or decreases) needed in the maintenance phase safety population.

Supplemental Figure 11. Kaplan-Meier curve for time to events in the hemodynamic edema, effusions, and fluid overload SMQ after SZC dosing in the maintenance phase safety population.

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