

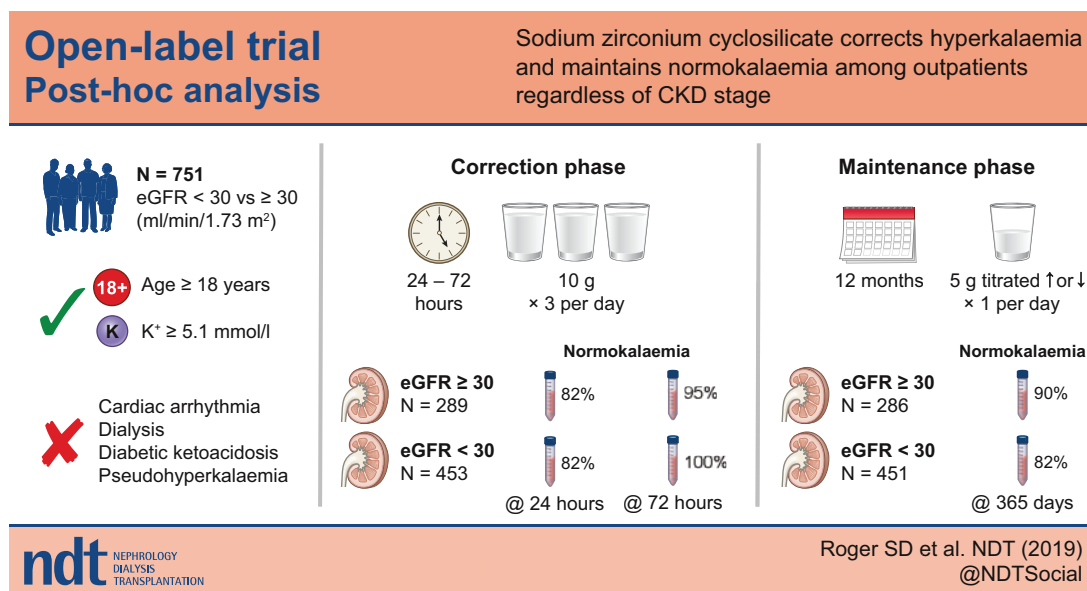
Long-term safety and efficacy of sodium zirconium cyclosilicate for hyperkalaemia in patients with mild/moderate versus severe/end-stage chronic kidney disease: comparative results from an open-label, Phase 3 study

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GRAPHICAL ABSTRACT



ABSTRACT

Background. Sodium zirconium cyclosilicate (SZC; formerly ZS-9) is a selective potassium (K^+) binder for the treatment of adults with hyperkalaemia. This *post hoc* analysis of an open-label, single-arm trial (NCT02163499) compared SZC efficacy and safety >12 months among outpatients with hyperkalaemia and Stages 4 and 5 chronic kidney disease (CKD) versus those with Stages 1–3 CKD.

Methods. Adults with serum $K^+ \geq 5.1$ mmol/L (measured by point-of-care i-STAT device) received SZC 10 g three times daily for 24–72 h until normokalaemia (i-STAT K^+ 3.5–5.0 mmol/L) was achieved [correction phase (CP)], followed by once daily SZC 5 g for <12 months [maintenance phase (MP)]. Here, patients were stratified by baseline estimated glomerular filtration rate (eGFR <30 or ≥ 30 mL/min/1.73 m²). Study endpoints included percent achieving normokalaemia during CP and MP, mean serum K^+ and bicarbonate during MP, and adverse events (AEs).

Results. Of 751 patients enrolled, 289 (39%), 453 (60%) and 9 (1%) had baseline eGFR values of <30, ≥ 30 mL/min/1.73 m² or missing, respectively. During the CP, 82% of patients achieved normokalaemia in both eGFR subgroups within 24 h, and 100 and 95% with baseline eGFR <30 and ≥ 30 mL/min/1.73 m², respectively, within 72 h. Corresponding proportions with normokalaemia during the MP were 82 and 90% at Day 365, respectively. Mean serum K^+ reduction from baseline during the CP was sustained throughout the MP and serum bicarbonate increased. AEs during the MP were more common in the eGFR <30 ≥ 30 mL/min/1.73 m² subgroup.

Conclusions. SZC corrects hyperkalaemia and maintains normokalaemia among outpatients regardless of the CKD stage.

Keywords: chronic kidney disease, estimated glomerular filtration rate, hyperkalaemia, potassium, sodium zirconium cyclosilicate

INTRODUCTION

Hyperkalaemia is a common electrolyte abnormality among patients with chronic kidney disease (CKD) [1–3] and is associated with increased morbidity and mortality [4]. The frequency and severity of hyperkalaemia are related to baseline estimated glomerular filtration rate (eGFR) level among those with CKD. Among these patients, hyperkalaemia prevalence defined as serum potassium (K^+) ≥ 5.0 mmol/L or ≥ 5.5 mmol/L is 14–20% or 3–8%, respectively [5]. Furthermore, for every 5 mL/min/1.73 m² decrease in eGFR, hyperkalaemia prevalence increased by 25% [5].

Although renin–angiotensin–aldosterone system inhibitors (RAASi) are mainstays of therapy among patients with proteinuric and diabetic CKD [6], use of maximum renoprotective RAASi dosages is limited due to RAASi-associated K^+ elevation risk [3]. Patients with severe CKD (Stages 4 and 5, eGFR <30 mL/min/1.73 m²) often have strict dietary requirements, including restricted intake of fluids, protein, sodium, phosphate and K^+ . These patients may benefit from medical management of hyperkalaemia, which may enable RAASi maintenance and fewer dietary restrictions.

Sodium zirconium cyclosilicate (SZC; formerly ZS-9) is a selective K^+ binder approved for use in the USA and the European Union for the treatment of adults with hyperkalaemia [7, 8]. SZC binds K^+ early as it transits through the gastrointestinal tract and is ultimately excreted in the faeces [7–9]. In the randomized, Phase 3 HARMONIZE study of SZC among outpatients with hyperkalaemia ($K^+ \geq 5.1$ mmol/L), SZC 10 g three times daily (TID) reduced serum K^+ to normal levels (K^+ 3.5–5.0 mmol/L) within a median of 2.2 h after the first administered dose, with 84% of patients achieving normokalaemia within 24 h [2]. Furthermore, normokalaemia was maintained by >71% of patients receiving once daily (QD) SZC dosing through Day 29 with no protocol-defined changes in diet or RAASi use [2].

The current open-label, single-arm study among ambulatory outpatients with hyperkalaemia demonstrated that SZC was associated with rapid correction and maintenance of normokalaemia up to 12 months [10]. Here, we compare the long-term efficacy and safety of SZC treatment for hyperkalaemia among outpatients with a baseline eGFR <30 versus ≥ 30 mL/min/1.73 m².

MATERIALS AND METHODS

Study design

We describe a *post hoc* analysis from a prospective, international, multicentre, single-arm, open-label Phase 3 trial (NCT02163499); the study design and primary results are previously described [10]. Briefly, adult (≥ 18 years) outpatients with hyperkalaemia ($K^+ \geq 5.1$ mmol/L), as measured by two consecutive readings with a point-of-care i-STAT device (Abbott Point of Care, Inc., Princeton, NJ, USA), were included. Patients with diabetic ketoacidosis, cardiac arrhythmias requiring immediate treatment, pseudohyperkalaemia and those on dialysis were excluded. The trial comprised two phases: the correction phase (CP), in which patients received 10 g SZC TID for 24–72 h until normokalaemia (3.5–5.0 mmol/L) was achieved; and the 12-month maintenance phase (MP), in which patients started treatment on a QD regimen of SZC 5 g to maintain normokalaemia [10]. During the MP, patients who did not maintain normokalaemia [i.e. having either hypokalaemia (i-STAT K^+ 3.0–3.4 mmol/L) or hyperkalaemia (i-STAT K^+ >5.0–6.5)] received protocol-mandated dose titrations in 5 g increments/decrements, with a minimum dose of 5 g once every other day (QoD) and a maximum dose of 15 g QD (Supplementary data, Table S1); patients who developed severe hypokalaemia (i-STAT K^+ <3.0 mmol/L) or severe hyperkalaemia (i-STAT K^+ >6.5 mmol/L) at any time discontinued the study. No protocol-mandated restrictions on diet or RAASi use were required. In this analysis, patients were stratified by baseline eGFR levels of <30 or ≥ 30 mL/min/1.73 m², corresponding to CKD Stages 4 and 5 and Stages 1–3, respectively. All participants gave their informed consent.

Assessments

Blood K^+ was measured by two methods: whole-blood K^+ levels, measured by i-STAT, which determined study eligibility,

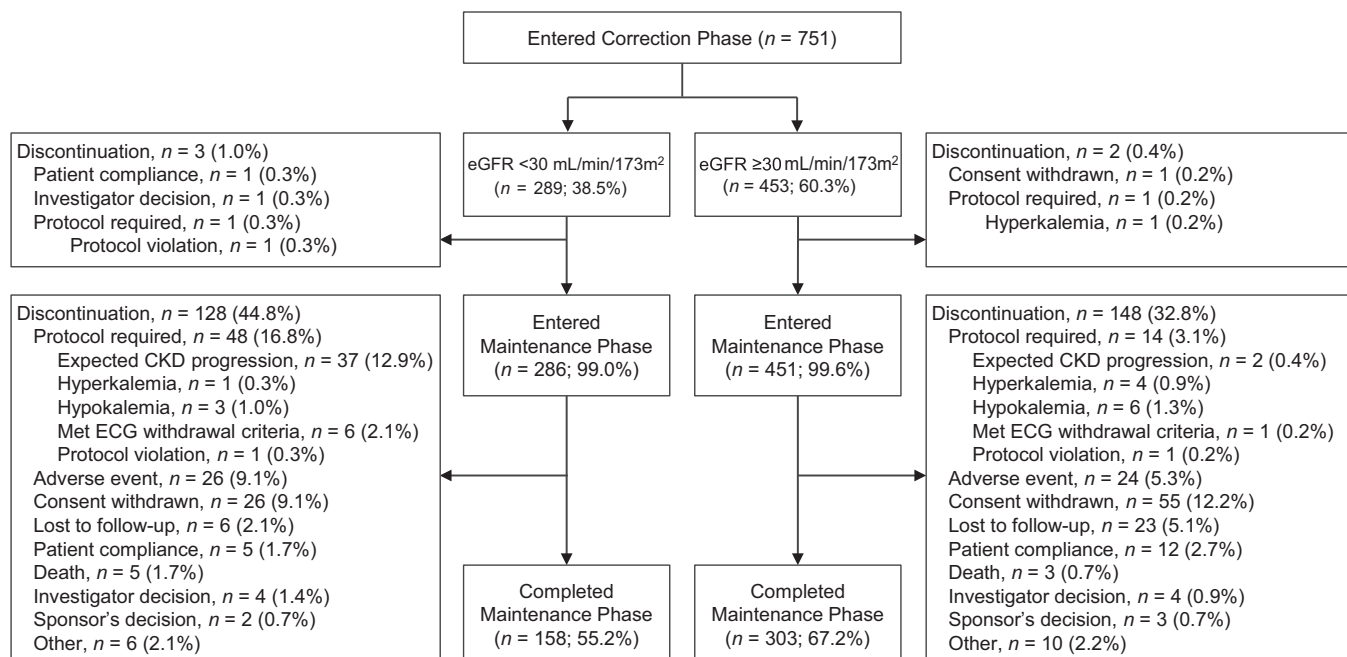


FIGURE 1: Patient disposition. Nine patients who entered the CP did not have a study baseline eGFR measurement. ECG, electrocardiogram.

entry into the MP and MP SZC dose titrations; and serum K^+ , measured by the central laboratory (consistent with usual clinical practice), which was used to analyse efficacy outcomes.

Study endpoints

Study endpoints were the proportion of patients achieving normokalaemia by i-STAT K^+ during the CP and MP and mean serum K^+ during the MP. Safety was assessed by spontaneous investigator reports of adverse events (AEs) and serious AEs, vital signs, change from baseline in serum bicarbonate and eGFR, incidence of hypokalaemia and change from CP baseline in selected serum chemistry levels. Oedema was evaluated by standardized Medical Dictionary for Regulatory Activities (MedDRA) standardized MedDRA query (SMQ oedema) for haemodynamic oedema, effusions and fluid overload. SMQs are collections of related MedDRA preferred terms that are used to screen for relevant safety signals in clinical trials [11].

Statistical considerations

Efficacy endpoints, drug exposure parameters and safety outcomes followed the pre-specified statistical analysis plan, with results described descriptively. Patients achieving defined i-STAT K^+ levels during the CP were calculated using the last observation carried forward approach. Mean changes from baseline in serum K^+ were evaluated with two-sided paired *t*-tests. A *post hoc* analysis compared Days 8–365 absolute mean and mean change from baseline in serum K^+ between the eGFR subgroups using two-sample two-sided *t*-tests. Analyses were based on the intention-to-treat (ITT) population, which included all patients who received SZC in a given study phase and had any post-baseline K^+ values measured. The safety population included patients who received one or more dose of SZC and had any post-baseline follow-up for safety.

RESULTS

Study population

Of the 751 patients enrolled in the CP, 9 (1%) patients did not have an eGFR measurement at study baseline, 289 (39%) had an $eGFR < 30 \text{ mL/min/1.73 m}^2$ and 453 (60%) had an $eGFR \geq 30 \text{ mL/min/1.73 m}^2$ (Figure 1). Among patients with an $eGFR < 30$ or $\geq 30 \text{ mL/min/1.73 m}^2$ who entered the MP, 45% ($n = 128$) and 33% ($n = 148$) of patients discontinued, respectively, and the largest proportions discontinuing the MP in each group were due to expected CKD progression [$n = 37$ (13%)] and withdrawn consent [$n = 55$ (12%)].

The majority of patients in both eGFR subgroups were male and white (Table 1). Among patients with $eGFR < 30 \text{ mL/min/1.73 m}^2$, 46 (16%) patients had CKD Stage 5 ($eGFR < 15 \text{ mL/min/1.73 m}^2$) and 243 (84%) had CKD Stage 4 ($eGFR 15$ to $< 30 \text{ mL/min/1.73 m}^2$). Comorbidities, including heart failure, diabetes and hypertension, were more frequent among patients with $eGFR < 30 \text{ mL/min/1.73 m}^2$ versus those with $eGFR \geq 30 \text{ mL/min/1.73 m}^2$. Furthermore, concomitant medications were taken by more patients with $eGFR < 30$ versus $\geq 30 \text{ mL/min/1.73 m}^2$, including calcium channel blockers, RAASi therapies and diuretics (Table 1).

Efficacy

At CP baseline, i-STAT K^+ was $> 6.0 \text{ mmol/L}$ in 22 (8%) and 29 (7%) patients in the $eGFR < 30$ and $\geq 30 \text{ mL/min/1.73 m}^2$ subgroups, respectively. During the CP, 82% of patients with baseline $eGFR < 30 \text{ mL/min/1.73 m}^2$ achieved normokalaemia (i-STAT K^+ 3.5–5.0 mmol/L) within 24 h of initiating SZC 10 g TID, and 100% achieved normokalaemia by 72 h (Figure 2A). In patients with baseline $eGFR \geq 30 \text{ mL/min/1.73 m}^2$, 82 and 95% achieved normokalaemia by 24 and 72 h, respectively (Figure 2B). Proportions of patients

Table 1. Baseline characteristics and demographics for patients with eGFR <30 and ≥30 mL/min/1.73 m² in the CP safety population^a

	eGFR <30mL/min/1.73m ² (n = 289)	eGFR ≥30mL/min/1.73m ² (n = 453)	P-value ^b
Age, mean (SD), years	64.8 (13.0)	62.9 (13.1)	0.057 ^c
Male, n (%)	164 (56.7)	277 (61.1)	0.250
Race, n (%)			
White	223 (77.2)	394 (87.0)	0.001
Black/African American	40 (13.8)	48 (10.6)	0.201
Asian	16 (5.5)	8 (1.8)	0.009
Other	10 (3.5)	3 (0.7)	0.007
Medical history, n (%)			
Heart failure ^d	55 (19.0)	54 (11.9)	0.010
Diabetes mellitus ^e	205 (70.9)	264 (58.3)	0.001
Hypertension (preferred term)	275 (95.2)	339 (74.8)	<0.001
Serum K ⁺ , mean (SD), mmol/L	5.7 (0.4)	5.6 (0.4)	<0.001 ^c
Serum K ⁺ , n (%), mmol/L			
<5.5	93 (32.2)	193 (42.6)	0.005
5.5 to <6.0	137 (47.4)	195 (43.0)	0.257
≥6.0	59 (20.4)	65 (14.3)	0.034
i-STAT K ⁺ , mean (range), mmol/L	5.5 (5.1–6.9)	5.5 (5.1–7.3)	0.082 ^c
i-STAT K ⁺ , n (%), mmol/L			
5.1 to <5.5	144 (49.8)	248 (54.7)	0.200
5.5 to <6.0	109 (37.7)	164 (36.2)	0.697
≥6.0	36 (12.5)	41 (9.1)	0.141
eGFR, mean (SD), mL/min/1.73 m ²	21.3 (5.7)	63.6 (30.6)	
eGFR, n (%), mL/min/1.73 m ²			
<15	46 (15.9)	0	
15 to <30	243 (84.1)	0	
30 to <60	0	263 (58.1)	
≥60	0	190 (41.9)	
Serum bicarbonate, mean (SD), mmol/L ^f	21.4 (3.6)	24.8 (3.3)	<0.001 ^c
Serum bicarbonate, n (%), mmol/L			
<22	137 (47.4)	73 (16.1)	
≥22	152 (52.6)	380 (83.9)	<0.001
Serum urea, mean (SD), mmol/L ^g	18.6 (5.6)	9.1 (5.0)	<0.001 ^c
Weight, mean (SD), kg	88.5 (23.0)	84.8 (21.2)	0.029 ^c
BP, mean (95% CI), mmHg			
Systolic	141.4 (139.1–143.8)	131.8 (130.2–133.4)	<0.001 ^c
Diastolic	76.5 (75.1–77.8)	77.5 (76.6–78.3)	0.231 ^c
Concomitant medication use, n (%)			
Any	288 (99.7)	435 (96.0)	
RAASi therapies	199 (68.9)	279 (61.6)	0.049
ACE inhibitors	122 (42.2)	212 (46.8)	0.227
ARBs	79 (27.3)	74 (16.3)	<0.001
MRAs	15 (5.2)	30 (6.6)	0.529
Diuretics	151 (52.2)	124 (27.4)	<0.001
Loop	133 (46.0)	95 (21.0)	<0.001
Thiazide	15 (5.2)	21 (4.6)	0.729
Other	12 (4.2)	13 (2.9)	0.405
Calcium channel blockers	142 (49.1)	111 (24.5)	<0.001
Dihydropyridine ^h	129 (44.6)	98 (21.6)	<0.001
Non-dihydropyridine ⁱ	16 (5.5)	15 (3.3)	0.099

^aSafety population included all patients who received one or more dose of SZC during the given study phase and had any post-baseline follow-up for safety.

^bDetermined by Fisher's exact test, unless stated otherwise.

^cDetermined by two-sample *t*-test.

^dInvestigator defined in case report forms.

^eBased on standardized MedDRA query narrow terms.

^fNormal reference range 22–29 mmol/L.

^gNormal reference range 2.9–8.2 mmol/L.

^hIncludes amlodipine, nifedipine, lercanidipine and felodipine.

ⁱIncludes diltiazem and verapamil.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; CI, confidence interval; CRF, case report form.

achieving normokalaemia (i-STAT K⁺ 3.5–5.0 mmol/L) during the MP were 76 and 82% at Days 8 and 365, respectively, among patients with baseline eGFR <30 mL/min/1.73 m² (Figure 3A), and 88 and 90% at Days 8 and 365, respectively,

among patients with baseline eGFR ≥30 mL/min/1.73 m² (Figure 3B).

At CP baseline, the mean [standard deviation (SD)] baseline serum K⁺ level was 5.7 (0.4) and 5.6 (0.4) mmol/L for the eGFR

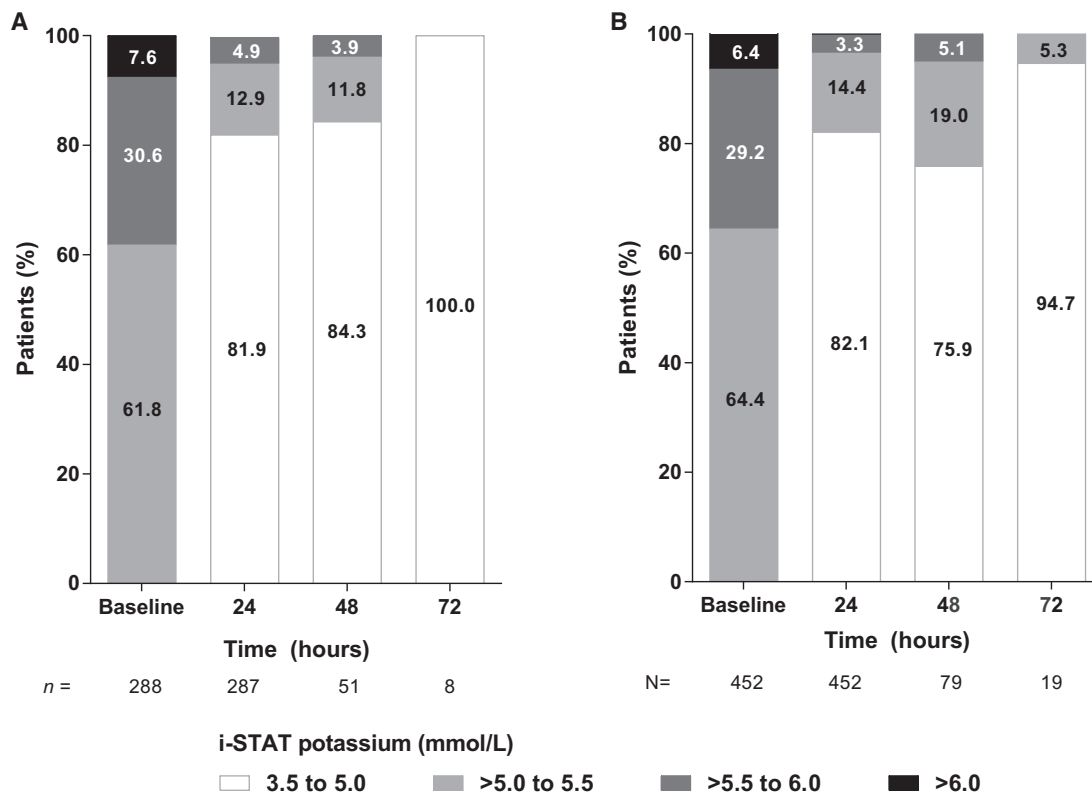


FIGURE 2: Proportion of patients with baseline eGFR (A) $<30\text{ mL/min/1.73 m}^2$ and (B) $\geq 30\text{ mL/min/1.73 m}^2$ achieving i-STAT K^+ levels in the CP ITT population. ITT population included all patients who received SZC and had any post-baseline K^+ values measured during the study phase. In (B), at 24 h, 0.2% of patients had i-STAT K^+ $>6.0\text{ mmol/L}$.

<30 and $\geq 30\text{ mL/min/1.73 m}^2$ subgroups, respectively. Reductions in mean serum K^+ achieved during the CP were maintained at all MP visits in both eGFR subgroups (Figure 4). Across study Days 8–365, mean (SD) serum K^+ levels were 4.8 (0.4) mmol/L in the eGFR $<30\text{ mL/min/1.73 m}^2$ subgroup and 4.7 (0.4) mmol/L in the eGFR $\geq 30\text{ mL/min/1.73 m}^2$ subgroup (P-value versus CP baseline <0.001 for both subgroups, P-value for difference between subgroups <0.001). Across study Days 8–365, mean changes from CP baseline (95% confidence interval) were -0.87 (-0.93 to -0.82) and -0.86 (-0.91 to -0.81), respectively (P-value versus CP baseline <0.001 for both subgroups, P-value for difference between subgroups = 0.765). Following cessation of SZC treatment, mean serum K^+ increased in the eGFR <30 and $\geq 30\text{ mL/min/1.73 m}^2$ subgroups from 4.7 to 5.1 mmol/L and from 4.5 to 4.9 mmol/L, respectively, yet remained decreased from CP baseline (mean change: -0.6 mmol/L , $P < 0.001$; and -0.7 mmol/L , $P < 0.001$, respectively, versus CP baseline).

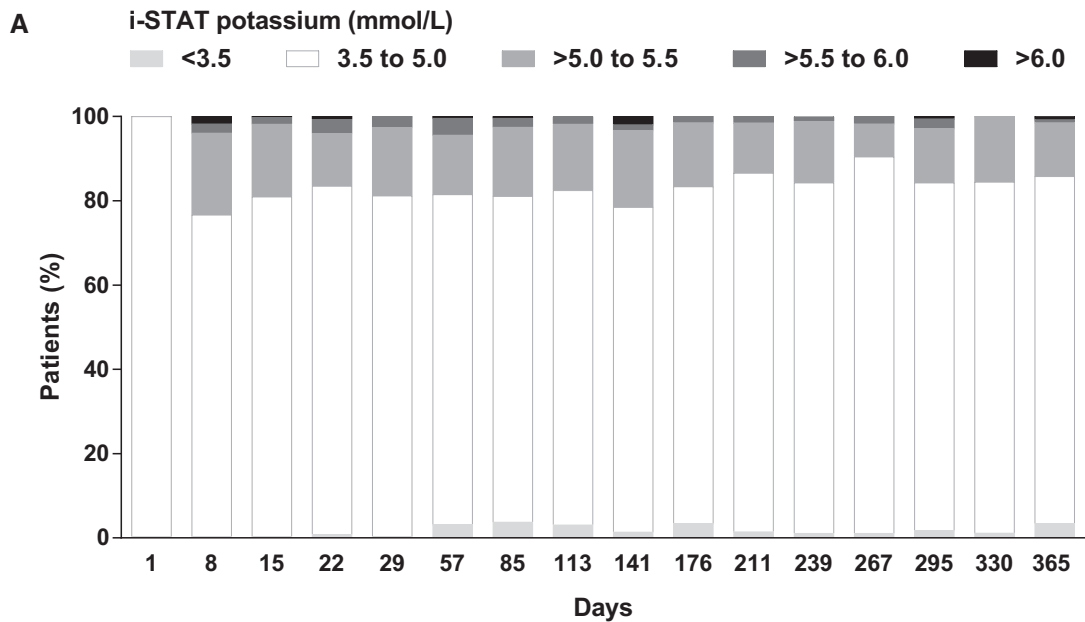
Dosing

The majority of patients in both eGFR subgroups (81–82%) achieved normokalaemia after receiving only 30 g of SZC (administered as three 10 g doses) $>24\text{ h}$ (Figure 5A). During the MP, the mean (SD) daily dose of SZC was 7.8 g (2.6) and 6.8 g (2.5) for the eGFR <30 and $\geq 30\text{ mL/min/1.73 m}^2$ subgroups, respectively ($P < 0.001$). In general, greater proportions of patients with baseline eGFR <30 versus $\geq 30\text{ mL/min/1.73 m}^2$ required doses of 10 or 15 g QD to maintain normokalaemia as

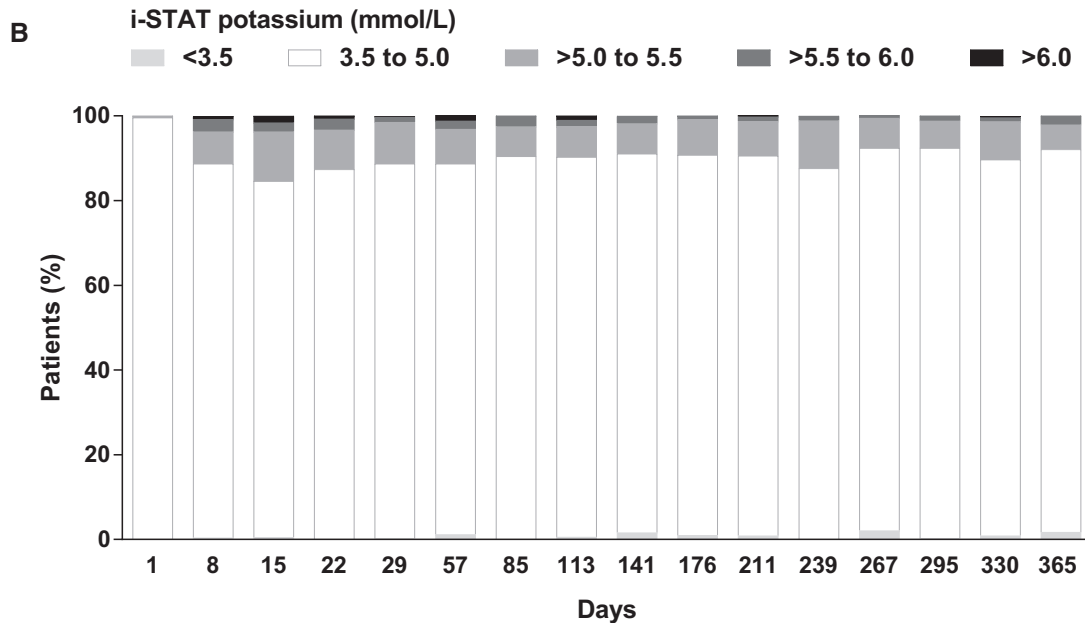
the MP progressed; and ≥ 26 and $\geq 56\%$, respectively, maintained normokalaemia at a dose of 5 g QD throughout the MP (Figure 5B and C). Person-time exposure to each dose of SZC was 2% for the 5 g QoD dose, 57% for the 5 g QD dose, 34% for the 10 g dose and 7% for the 15 g dose relative to the total person-time exposure to all SZC doses.

Safety

Greater proportions of patients with baseline eGFR $<30\text{ mL/min/1.73 m}^2$ experienced AEs during the MP versus patients with eGFR $\geq 30\text{ mL/min/1.73 m}^2$ (83% versus 54%, respectively; Table 2). Gastrointestinal disorders were more common in patients with eGFR $<30\text{ mL/min/1.73 m}^2$ (34%; $n = 96$) compared with patients with an eGFR of $\geq 30\text{ mL/min/1.73 m}^2$ (16%; $n = 70$), with the most common being nausea (11 and 6%, respectively) and constipation (11 and 4%, respectively). The three most common individual AEs experienced by patients in the eGFR $<30\text{ mL/min/1.73 m}^2$ subgroup were hypertension (15%), peripheral oedema (13%) and urinary tract infection (12%), all of which occurred more frequently when compared with the eGFR $\geq 30\text{ mL/min/1.73 m}^2$ subgroup (8, 8 and 6%, respectively). The most common treatment-related individual AEs in both the eGFR <30 and $\geq 30\text{ mL/min/1.73 m}^2$ subgroups were constipation (4 and 3%, respectively), nausea (2% in both) and peripheral oedema (2% in both). During the CP, only one AE of peripheral oedema occurred. During the MP, SMQ oedema events occurred more frequently in the



Day	1	8	15	22	29	57	85	113	141	176	211	239	267	295	330	365
<i>n</i>	279	278	268	266	265	249	238	223	214	210	194	185	179	171	168	141
Patients (%)																
<3.5	0.4	0.4	0.4	0.8	0.4	3.2	3.8	3.1	1.4	3.4	1.5	1.1	1.1	1.8	1.2	3.5
3.5 to 5	99.6	76.3	80.6	82.7	80.8	78.3	77.3	79.4	77.1	80.0	85.1	83.2	89.4	82.5	83.3	82.3
>5 to 5.5	0	19.4	17.2	12.4	16.2	14.1	16.4	15.7	18.2	15.2	11.9	14.6	7.8	12.9	15.5	12.8
>5.5 to 6	0	2.2	1.5	3.4	2.6	4	2.1	1.8	1.4	1.4	1.5	1.1	1.7	2.3	0	0.7
≥ 6	0	1.8	0.4	0.8	0	0.4	0.4	0	1.9	0	0	0	0	0.6	0	0.7



Day	1	8	15	22	29	57	85	113	141	176	211	239	267	295	330	365
<i>n</i>	446	446	435	430	427	417	398	390	381	371	359	355	339	330	321	291
Patients (%)																
<3.5	0	0.4	0.5	0	0.2	1.2	0	0.6	1.6	1	0.9	0	2.1	0.3	0.9	1.7
3.5 to 5	99.6	88.3	84.1	87.4	88.5	87.5	90.5	89.7	89.5	89.8	89.7	87.6	90.3	92.1	88.8	90.4
>5 to 5.5	0.4	7.6	11.7	9.3	9.8	8.2	7.0	7.2	7.1	8.4	8.1	11.3	7.1	6.4	9.0	5.8
>5.5 to 6	0	2.9	2.1	2.6	1.2	1.9	2.5	1.5	1.8	0.8	1.1	1.1	0.6	1.2	0.9	2.1
≥ 6	0	0.7	1.6	0.7	0.2	1.2	0	1.0	0	0	0.3	0	0	0	0.3	0

FIGURE 3: Proportion of patients with baseline eGFR (A) <30 mL/min/1.73 m² and (B) ≥ 30 mL/min/1.73 m² achieving i-STAT K⁺ levels in the MP ITT population. ITT population included all patients who received SZC and had any post-baseline K⁺ values measured during the study phase.

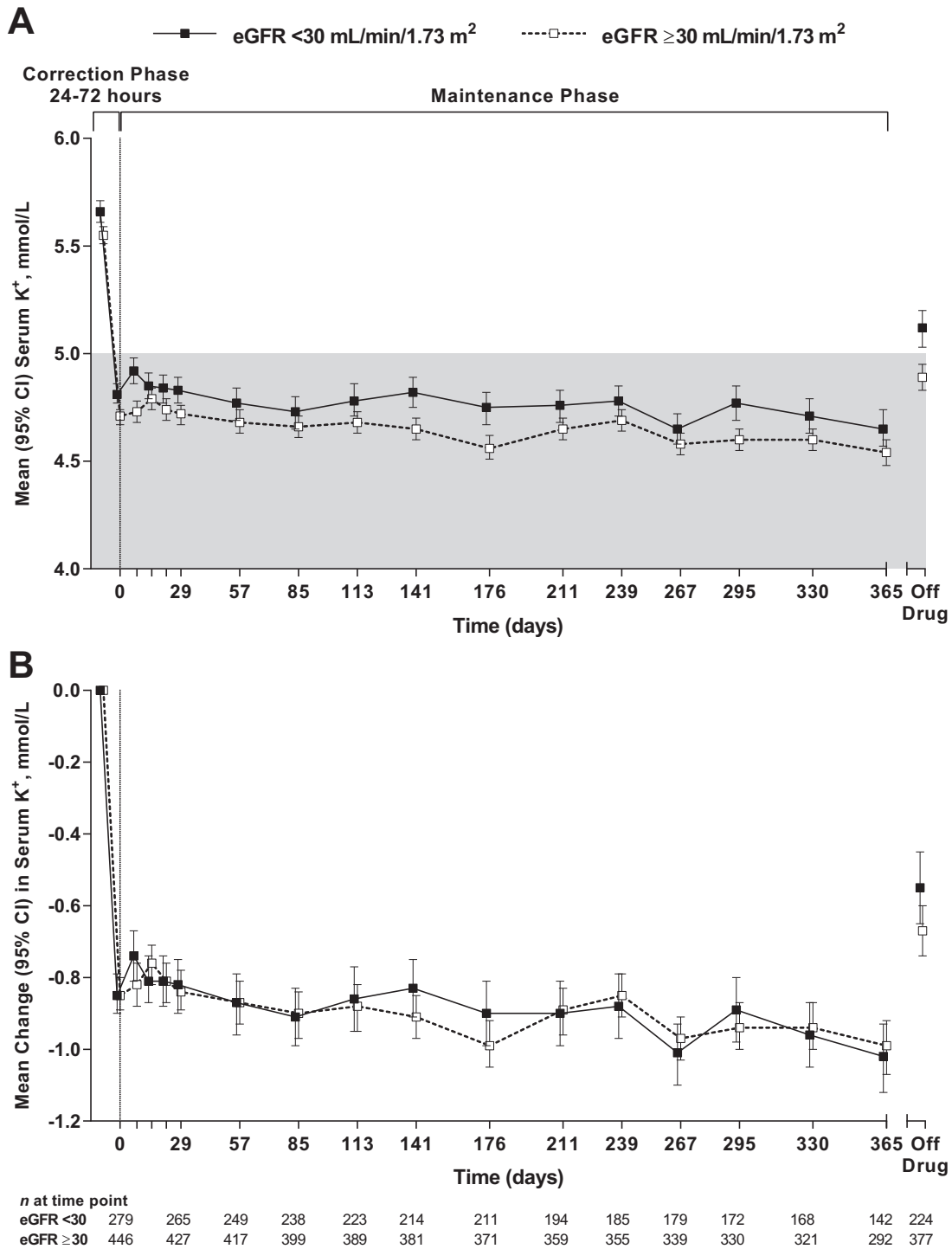


FIGURE 4: Mean absolute serum K⁺ (A) and mean change in serum K⁺ (B) over time in the MP ITT population. ITT population included all patients who received SZC and had any post-baseline K⁺ values measured during the study phase. Across study Days 8–365, absolute mean (SD) serum K⁺ levels were 4.8 (0.4) mmol/L in the eGFR <30 mL/min/1.73 m² subgroup and 4.7 (0.4) mmol/L in the eGFR ≥30 mL/min/1.73 m² subgroup (P-value for difference <0.001); corresponding values for mean (95% CI) change from CP baseline were −0.87 (−0.93 to −0.82) and −0.86 (−0.91 to −0.81), respectively (P-value for difference = 0.765). Off-drug values were recorded within 7 (±1) days following the last dose of SZC in 75 and 86% of patients with baseline eGFR <30 and ≥30 mL/min/1.73 m², respectively. Off-drug values were recorded outside of the 7 (±1)-day window in 25 and 14% of patients with baseline eGFR <30 and ≥30 mL/min/1.73 m², respectively. Sensitivity analyses showed that mean off-drug serum K⁺ values within versus outside of the 7 (±1)-day window were similar (P = 0.459 and 0.914 for patients with baseline eGFR <30 and ≥30 mL/min/1.73 m², respectively). All bars P < 0.001 versus CP baseline. CI, confidence interval.

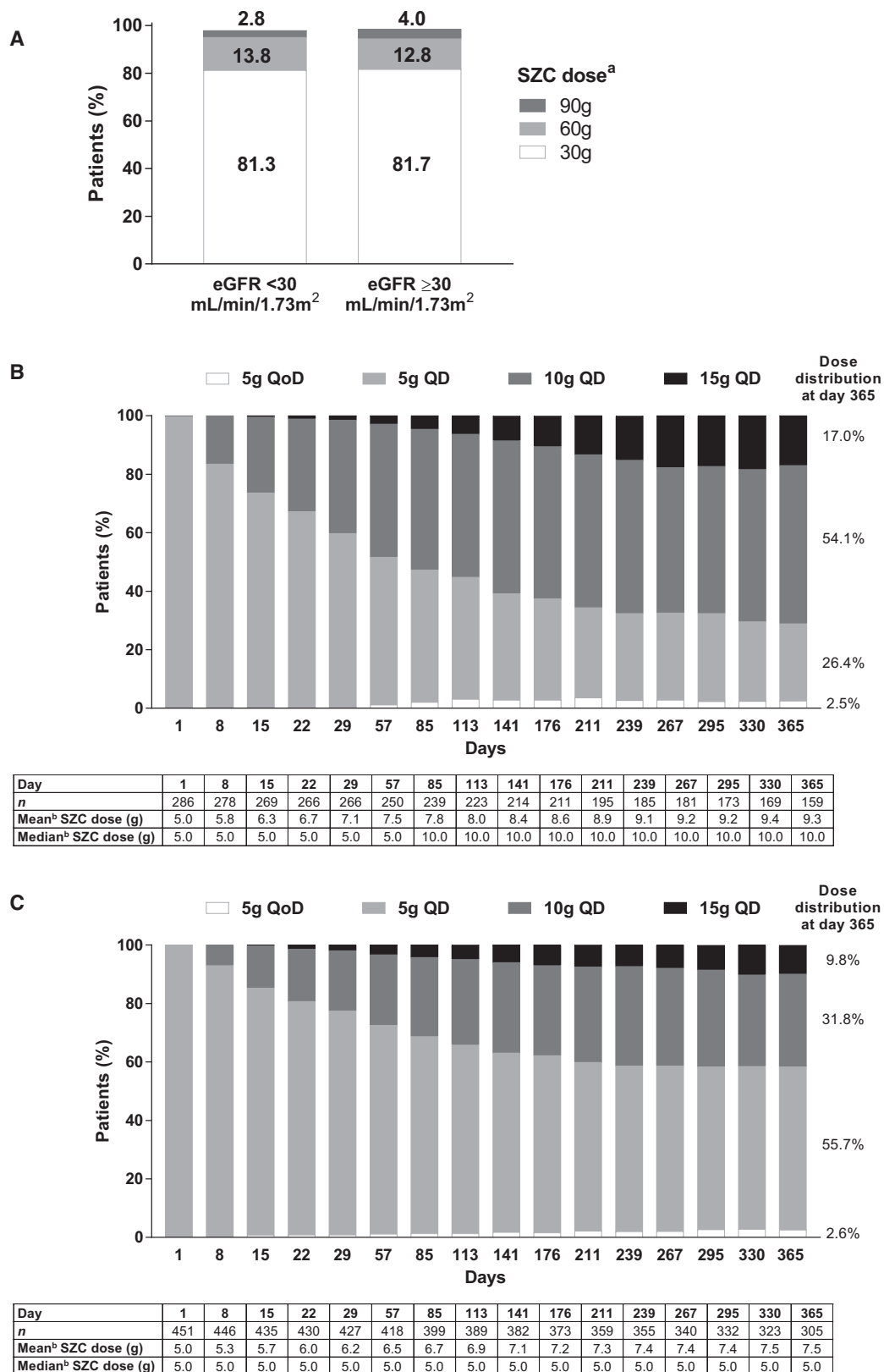


FIGURE 5: Distribution of SZC dosing in the safety populations of each study phase (safety population included all patients who received one or more dose of SZC during the given study phase and had any post-baseline follow-up for safety). (A) Total dose required to achieve normokalaemia during the CP^a; and distribution of SZC dosing per study visit in patients with baseline eGFR B) < 30 , and C) ≥ 30 mL/min/1.73m² in the maintenance phase. ^aDuring the CP, one, two and three patients in the eGFR < 30 mL/min/1.73m² subgroup received SZC 10, 20 and 50 g, respectively, while one, three, two and one patient in the eGFR ≥ 30 mL/min/1.73m² subgroup received SZC 10, 20, 50 and 70 g, respectively). ^bMean and median dose reported are for last dose administered prior to that MP day's endpoint measurements.

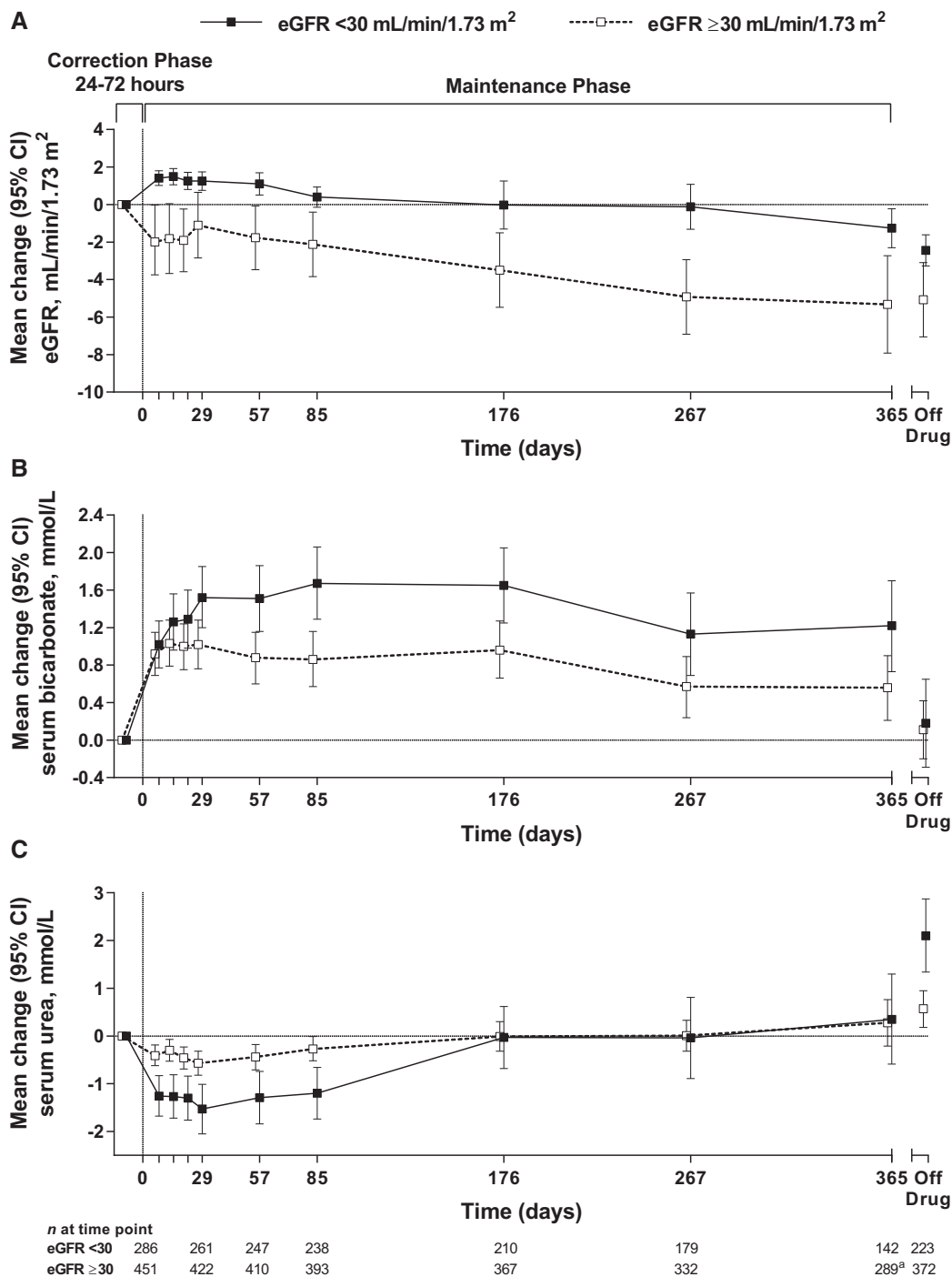


FIGURE 6: Change from CP baseline in (A) eGFR, (B) serum bicarbonate and (C) serum urea over time in the MP safety population. Safety population included all patients who received one or more dose of SZC during the given study phase and had any post-baseline follow-up for safety. ^aTwo hundred and ninety for eGFR and serum bicarbonate data. Off-drug values were recorded within 7 (± 1) days following the last dose of SZC in 75 and 87% of patients with baseline eGFR <30 and ≥ 30 mL/min/1.73 m², respectively. Off-drug values were recorded outside of the 7 (± 1)-day window in 25 and 13% of patients with baseline eGFR <30 and ≥ 30 mL/min/1.73 m², respectively. Sensitivity analyses showed that mean off-drug eGFR values within versus outside of the 7 (± 1)-day window were similar ($P = 0.121$ and $P = 0.085$ for patients with baseline eGFR <30 and ≥ 30 mL/min/1.73 m², respectively).

eGFR <30 mL/min/1.73 m² versus the eGFR ≥ 30 mL/min/1.73 m² subgroup (21 versus 11%, respectively; [Table 2](#); see [Supplementary data, Table S2](#) for the full description of these events and their management with loop diuretics).

During the MP, serious AEs were experienced by 31 and 16% of patients in the eGFR <30 and ≥ 30 mL/min/1.73 m² subgroups, respectively ([Table 2](#)). Of these, pneumonia and acute renal failure were the most common serious AEs among

Table 2. AEs, laboratory values and RAASi use in the MP safety population^a

	eGFR <3030mL/min/173m ² (n = 286)	eGFR ≥30mL/min/173m ² (n = 451)
AEs (≥5% of patients)	237 (82.9)	245 (54.3)
SMQ oedema ^b	60 (21.0)	51 (11.3)
Hypertension ^c	42 (14.7)	36 (8.0)
Peripheral oedema	36 (12.6)	35 (7.8)
Urinary tract infection	33 (11.5)	25 (5.5)
Constipation	30 (10.5)	17 (3.8)
Nausea	30 (10.5)	26 (5.8)
Anaemia	27 (9.4)	16 (3.5)
Acute renal failure	23 (8.0)	10 (2.2)
Upper respiratory tract infection	18 (6.3)	19 (4.2)
Vomiting	16 (5.6)	20 (4.4)
Headache	15 (5.2)	8 (1.8)
Treatment-related AEs (≥1% of patients)	43 (14.9)	50 (11.0)
Constipation	12 (4.2)	12 (2.6)
Nausea	5 (1.7)	9 (2.0)
Peripheral oedema	5 (1.7)	9 (2.0)
Serious AEs (≥1% of patients)	88 (30.8)	70 (15.5)
Pneumonia	10 (3.5)	4 (0.9)
Acute renal failure	7 (2.4)	1 (0.2)
Acute respiratory failure	5 (1.7)	0
Chest pain	5 (1.7)	6 (1.3)
Acute myocardial infarction	4 (1.4)	1 (0.2)
Congestive cardiac failure	4 (1.4)	6 (1.3)
Cellulitis	4 (1.4)	3 (0.7)
Cardiac failure	3 (1.0)	1 (0.2)
Urinary tract infection	3 (1.0)	1 (0.2)
Hypoglycaemia	3 (1.0)	1 (0.2)
Hyperkalaemia	3 (1.0)	1 (0.2)
Pulmonary oedema	3 (1.0)	0
Chronic renal failure	3 (1.0)	1 (0.2)
Osteomyelitis	2 (0.7)	6 (1.3)
AEs leading to discontinuation ^d (≥3 patients)	58 (20.3)	42 (9.3)
Acute renal failure	8 (2.8)	1 (0.2)
Congestive cardiac failure	5 (1.7)	6 (1.3)
Chronic renal failure	5 (1.7)	0
Acute myocardial infarction	3 (1.0)	0
Atrial fibrillation	3 (1.0)	1 (0.2)
Cardiac failure	3 (1.0)	1 (0.2)
Dyspnoea	3 (1.0)	2 (0.4)
Chest pain	0	3 (0.7)
Osteomyelitis	0	4 (0.9)
eGFR, mean (SD), mL/min/1.73 m ²		
CP baseline	21.4 (5.7)	63.4 (30.6)
MP Day 8	22.9 (6.9)	61.7 (25.8)
MP Day 365	21.4 (7.7)	60.5 (25.6)
MP Day 8, mean (95% CI) change	1.41 (1.02 to 1.80)***	-1.99 (-3.75 to -0.22)*
Mean (95% CI) change at MP Day 365	-1.26 (-2.30 to -0.23)*	-5.32 (-7.92 to -2.73)***
Serum bicarbonate, mean (SD), mmol/L		
CP baseline	21.5 (3.6)	24.8 (3.3)
MP Day 8	22.5 (3.8)	25.7 (3.1)
MP Day 365	22.9 (3.3)	25.5 (3.1)
Mean (95% CI) change at MP Day 8	1.02 (0.77 to 1.27)***	0.92 (0.69 to 1.15)***
Mean (95% CI) change at MP Day 365	1.22 (0.73 to 1.70)***	0.56 (0.21 to 0.90)**
Serum urea, mmol/L		
CP baseline	18.6 (5.6)	9.1 (5.0)
MP Day 8	17.2 (5.8)	8.6 (4.5)
MP Day 365	18.5 (6.6)	9.0 (5.9)
Mean (95% CI) change at MP Day 8	-1.26 (-1.68 to -0.83)***	-0.41 (-0.62 to -0.19)***
Mean (95% CI) change at MP Day 365	0.35 (-0.59 to 1.30)	0.28 (-0.21 to 0.76)
RAASi usage during the study		
RAASi-naïve at CP baseline	88/286 (30.8)	173/451 (38.4)
Initiated RAASi	24/88 (27.3)	13/173 (7.5)
MRA-containing RAASi regimen	1/88 (1.1)	1/173 (0.6)
Non-MRA-containing RAASi regimen	23/88 (26.1)	12/173 (6.9)

Continued

Table 2. Continued

	eGFR <30 mL/min/1.73 m ² (n = 286)	eGFR ≥30 mL/min/1.73 m ² (n = 451)
RAASi therapy at CP baseline	198/286 (69.2)	278/451 (61.6)
Stable dose	138/198 (69.7)	217/278 (78.1)
MRA-containing RAASi regimen	10/198 (5.1)	13/278 (4.7)
Non-MRA-containing RAASi regimen	128/198 (64.6)	204/278 (73.4)
Increased dose ^e	25/198 (12.6)	35/278 (12.6)
MRA-containing RAASi regimen	5/198 (2.5)	12/278 (4.3)
Non-MRA-containing RAASi regimen	20/198 (10.1)	23/278 (8.3)
Decreased dose ^e	38/198 (19.2)	29/278 (10.4)
MRA-containing RAASi regimen	5/198 (2.5)	10/278 (3.6)
Non-MRA-containing RAASi regimen	33/198 (16.7)	19/278 (6.8)
Discontinued	28/198 (14.1)	21/278 (7.6)
MRA-containing RAASi regimen	2/198 (1.0)	6/278 (2.2)
Non-MRA-containing RAASi regimen	26/198 (13.1)	15/278 (5.4)

Data are presented as n (%) or n/N (%) unless otherwise indicated.

^aSafety population included all patients who received one or more dose of SZC during the given study phase and had any post-baseline follow-up for safety.

^bPreferred terms included in the oedema SMQ were ascites, fluid overload, fluid retention, generalized oedema, local swelling, oedema, oedema peripheral, pericardial effusion, pleural effusion and pulmonary oedema.

^cAs reported by site with no specific threshold.

^dDiscontinuation may be due to one or more AE.

^eNot mutually exclusive—some patients had both dose increases and decreases during the course of therapy.

*P < 0.05, **P < 0.01, ***P < 0.001 versus CP baseline (paired t-test).

patients in the eGFR <30 mL/min/1.73 m² subgroup. AEs led to discontinuation in 20% of patients in the eGFR <30 mL/min/1.73 m² subgroup versus 9% in the eGFR ≥30 mL/min/1.73 m² subgroup (Table 2).

During the MP, hypokalaemia (i-STAT K⁺ <3.0 mmol/L or ≤3.4 mmol/L if on SZC 5 g QoD) at any one visit was as high as 3.8 and 2.1% in the eGFR <30 and ≥30 mL/min/1.73 m² subgroups, respectively (Figure 3); study discontinuation due to hypokalaemia occurred in three (1%) and six (1%) patients, respectively; and study discontinuation due to hyperkalaemia (i-STAT K⁺ >6.5 mmol/L) occurred in one (<1%) and four (1%) patients, respectively.

Overall, eGFR decreased over time in both eGFR subgroups, but appeared to decline less among patients with eGFR <30 mL/min/1.73 m² for whom eGFR initially increased (Table 2 and Figure 6A). Following SZC cessation, eGFR fell further among patients with eGFR <30 mL/min/1.73 m² (to 19.6 mL/min/1.73 m²) and remained unchanged among patients with eGFR ≥30 mL/min/1.73 m² (Figure 6A).

As expected for patients with impaired kidney function, CP baseline mean serum bicarbonate was lower and serum urea was higher in the eGFR <30 versus ≥30 mL/min/1.73 m² subgroup (Table 1). During SZC treatment, mean serum bicarbonate increased from CP baseline to MP Day 8 by 1.0 and 0.9 mmol/L in the eGFR <30 and ≥30 mL/min/1.73 m² subgroups, respectively (P < 0.001 versus CP baseline for both; Table 2). These increases were maintained over time, returning to pre-treatment levels following SZC cessation (Figure 6B). Of note, greater proportions of patients in the eGFR <30 versus ≥30 mL/min/1.73 m² subgroup were using oral sodium bicarbonate therapy at CP baseline (16 versus 4%, respectively), and more patients in the <30 versus ≥30 mL/min/1.73 m² subgroup initiated oral bicarbonate during the study (8% versus 1%). In both subgroups, serum urea initially decreased

at Day 8 but returned to pre-treatment levels by Day 365 (Table 2 and Figure 6C).

RAASi use during the study is presented in Table 2. Among participants who were receiving RAASi at CP baseline, 70 and 78% maintained the same RAASi dose in the eGFR <30 mL/min/1.73 m² and ≥30 mL/min/1.73 m² subgroups, respectively. Corresponding proportions with a dose increase were 13 and 13% in both subgroups, with a dose decrease (not mutually exclusive with respect to dose increases) 19 and 10% and with RAASi discontinuation 14 and 8%. Of note, the proportion of patients continuing on the same dose of mineralocorticoid receptor antagonist (MRA)-containing RAASi regimen was 5% in both eGFR subgroups (Table 2). Among RAASi-naïve participants at CP baseline, 27 and 8% initiated RAASi in the eGFR <30 mL/min/1.73 m² and ≥30 mL/min/1.73 m² subgroups, respectively.

DISCUSSION

In this long-term study of outpatients with hyperkalaemia, serum K⁺ levels were normalized within 72 h of SZC initiation, and normokalaemia (i-STAT K⁺ 3.5–5.0 mmol/L) was maintained for up to 12 months, regardless of CKD stage. Administration of SZC appeared to similarly maintain normokalaemia in those above and below an eGFR of 30 mL/min/1.73 m². After initiating SZC 10 g TID, normokalaemia was achieved by 82% in both eGFR subgroups within 24 h, and by 100 and 95% of patients with baseline eGFR <30 and ≥30 mL/min/1.73 m², respectively, within 72 h during the CP. Corresponding proportions with normokalaemia during the MP were 76 and 88% at Day 8, respectively, and 82 and 90% at Day 365, respectively. CP baseline and Days 8–365 absolute mean serum K⁺ levels were 0.1 mmol/L higher (both P < 0.001) in the baseline eGFR <30 versus ≥30 mL/min/1.73 m² subgroup. In contrast, Days 8–365 mean changes from CP baseline of −0.87 and −0.86 in the baseline eGFR <30 and

≥ 30 mL/min/1.73 m² subgroups, respectively, were not significantly different ($P = 0.765$). Thus, as expected from its gastrointestinal site of action, SZC lowered serum K⁺ equally among patients with mild/moderate and severe/end-stage CKD.

These findings are consistent with previous SZC studies that included patients with impaired renal function. In a randomized, double-blind, placebo-controlled Phase 2 study of 90 patients with hyperkalaemia and Stage 3 CKD (eGFR 30–60 mL/min/1.73 m²), SZC 3 g or 10 g TID rapidly and significantly decreased serum K⁺ levels within 48 h compared with placebo [12]. In the HARMONIZE study of outpatients with hyperkalaemia, of whom 66% of patients had CKD (eGFR <60 mL/min/1.73 m²), 98% of patients achieved normokalaemia within 48 h of initiating SZC 10 g TID [2].

Other K⁺-binding agents also decrease serum K⁺ levels in patients with CKD. In randomized studies of patients with Stage 3 or 4 diabetic kidney disease [13] or CKD receiving RAASi therapy [14], patiromer significantly reduced serum K⁺ levels after 4 weeks of therapy. In a retrospective study among adults with Stage 4/5 CKD or end-stage renal disease, single-dose sodium polystyrene sulfonate therapy significantly decreased serum K⁺ levels within 24 h, although serious gastrointestinal AEs, including ulceration and rectal haemorrhage, were reported in 5% of patients [15].

In the current study, following discontinuation of SZC, serum K⁺ levels increased among patients in both eGFR subgroups at 1 week, but remained below pre-treatment levels. This may reflect a gradual return to increased serum K⁺ levels without the reduction in K⁺ absorption from the gastrointestinal tract, as well as possible K⁺ release from body intracellular stores. Thus, SZC therapy may have a potential safety window for patients missing doses of up to 1 week, during which time mean serum K⁺ would be expected to increase by 0.4–0.5 mmol/L.

In addition to the serum K⁺-lowering effects of SZC, serum bicarbonate levels increased by the second week of treatment and were maintained for 12 months in both eGFR subgroups. Low bicarbonate levels are commonly observed among patients with reduced renal function and are thought to be caused by decreases in ammonia synthesis, bicarbonate regeneration and hydrogen excretion in the kidneys [16]. When combined with other acid excretion tubular defects, low bicarbonate leads to metabolic acidosis, which is associated with multiple musculoskeletal complications, progression of CKD and increased mortality [16, 17]. Therefore, the observed increases in serum bicarbonate with SZC treatment, which are not due to changes in oral sodium bicarbonate administration [10], may provide potential benefits in terms of decreasing the risk of metabolic acidosis, as well as reducing the need for alkali supplementation with sodium bicarbonate.

During the initial weeks of SZC treatment, serum urea decreased in both subgroups but returned to pre-treatment levels at 12 months (Figure 6C), consistent with the expected gradual decline in eGFR over time (Figure 6A). Reductions in serum urea and increases in serum bicarbonate have been observed in other SZC studies [12, 18], and are thought to occur via a separate mechanism by which SZC traps ammonium ions in the gut

[12, 19, 20]. Whether these changes in urea and bicarbonate with SZC might reduce the rate of decline among patients with more advanced CKD should be further evaluated, especially since eGFR appeared relatively preserved during SZC treatment among these patients and dropped further on SZC cessation (Figure 6A), an effect not explained by changes in blood pressure (Supplementary data, Figure S1).

To maintain normokalaemia over the 12-month study period, higher mean daily doses of SZC were required among patients with baseline eGFR <30 mL/min/1.73 m² versus those with eGFR ≥ 30 mL/min/1.73 m². Over time, greater proportions of patients in the lower versus higher eGFR subgroup required SZC doses of 10 or 15 g QD to maintain normokalaemia, while the majority of patients in the higher eGFR subgroup required a dose of 5 g QD (Figure 5). This suggests that, although SZC can normalize serum K⁺ levels in patients with moderate-to-severe renal impairment, dose titration may be required for long-term maintenance of normokalaemia. This is most likely due to their higher serum K⁺ levels and a greater requirement for medications that elevate serum K⁺, such as RAASis.

Despite the benefits of optimal RAASi dosing for slowing cardiovascular and kidney disease progression, many patients received suboptimal dosing or discontinued RAASis, often due to hyperkalaemia [21, 22]. Moreover, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are often not able to adequately reduce aldosterone levels, requiring the addition of an MRA [23]. However, in cardiovascular treatment guidelines, MRAs are contraindicated among patients with an eGFR <30 mL/min/1.73 m² [24], despite possible beneficial effects of MRA in patients with advanced kidney disease [25]. In the current study, long-term control of hyperkalaemia was achieved on the background of stable RAASi use (including MRAs) in the majority of patients, regardless of the level of renal impairment. In addition, although RAASi dose reductions and discontinuations were more frequent in the eGFR <30 mL/min/1.73 m² subgroup, RAASis were also initiated more frequently in the eGFR <30 mL/min/1.73 m² versus the ≥ 30 mL/min/1.73 m² subgroup.

The overall incidence of AEs, serious AEs and AEs leading to discontinuation was higher among patients in the eGFR <30 versus ≥ 30 mL/min/1.73 m² subgroup. The greater incidence of AEs among patients with moderate-to-severe or end-stage CKD, particularly SMQ oedema, may be associated with these patients having more comorbidities (19% versus 12% had a history of heart failure), use of other medications (45% versus 22% used dihydropyridine calcium channel blockers; 52% versus 27% used diuretics) or level of renal impairment as patients with more severe CKD lose the ability to excrete salt and water.

This analysis has several strengths, including its long duration of follow-up (up to 12 months) and an outpatient study population in which ~40% of patients had Stage 4 or 5 CKD, allowing for the assessment of SZC efficacy and safety in this patient subgroup.

The limitations of this analysis include its *post hoc* nature, and open-label and single-arm study design with no placebo control, which does not permit causal associations to be

made between treatment and outcomes. In addition, the generalizability of these findings may be limited as this study was not designed exclusively to evaluate the efficacy and safety of SZC in a CKD population.

In conclusion, this analysis suggests that SZC corrects hyperkalaemia and maintains normokalaemia in outpatients with moderate-to-severe or end-stage CKD (eGFR <30 mL/min/1.73 m²), with similar efficacy to that observed in those with mild or moderate CKD or normal renal function (eGFR ≥30 mL/min/1.73 m²).

SUPPLEMENTARY DATA

Supplementary data are available at [ndt online](http://ndt.online).

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AUTHORS' CONTRIBUTIONS

J.B., M.K. and S.F. were involved in the conceptualization and design of the study. S.D.R., B.S.S., S.v.H., M.K., D.K.P. were involved in the conduct of the study. P.T.L., J.B. were responsible for the statistical analysis of the data. S.D.R., E.V.L., P.A.M., J.B., B.S.S., M.K., J.Z., D.K.P. were responsible for the interpretation of the data. S.D.R., P.T.L., E.V.L., P.A.M., J.B., B.S.S., S.v.H., M.K., J.Z., S.F., D.K.P. contributed to writing and critically reviewing the manuscript.

CONFLICT OF INTEREST STATEMENT

S.D.R. has received travel fees for investigator meetings and honoraria for serving on advisory boards for AstraZeneca, Vifor Pharma and ZS Pharma. P.T.L. is an employee of Boston Biostatistics Research Foundation, which has a contract from ZS Pharma to support biostatistics activities. E.V.L. is a subinvestigator with Research by Design and has received grant support from ZS Pharma. P.A.M. reports no disclosures. J.B. has received research support from the National Institutes of Health, European Union and Patient-centered Outcomes Research Institute, and has served as a consultant to Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CVRx, Janssen, Luitpold Pharmaceuticals, Inc., Medtronic, Novartis, Relypsa, Inc., Vifor Pharma and ZS Pharma. B.S.S. has received grant support and has served as a consultant for ZS Pharma. S.v.H. has served as an investigator for clinical trials sponsored by ZS Pharma and as a paid consultant for Vifor Pharma. M.K. has served as a consultant and advisory board member to AstraZeneca and ZS Pharma, was an investigator for clinical

trials sponsored by ZS Pharma and has received research grants from AstraZeneca. J.Z. is an employee of and holds ownership interest in AstraZeneca, PLC. S.F. has received research funding from ZS Pharma. D.K.P. has received travel fees and honorarium for serving on advisory boards from AstraZeneca and ZS Pharma and has served as an investigator on the SZC clinical trials.

REFERENCES

1. Einhorn LM, Zhan M, Hsu VD *et al*. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med* 2009; 169: 1156–1162
2. Kosiborod M, Rasmussen HS, Lavin P *et al*. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA* 2014; 312: 2223–2233
3. Tandukar S, Fried LF. Dyskalemia in chronic kidney disease: how concerned should we be? *Nephron* 2018; 140: 58–62
4. An JN, Lee JP, Jeon HJ *et al*. Severe hyperkalemia requiring hospitalization: predictors of mortality. *Crit Care* 2012; 16: R225
5. Gilligan S, Raphael KL. Hyperkalemia and hypokalemia in CKD: prevalence, risk factors, and clinical outcomes. *Adv Chronic Kidney Dis* 2017; 24: 315–318
6. Turner JM, Bauer C, Abramowitz MK *et al*. Treatment of chronic kidney disease. *Kidney Int* 2012; 81: 351–362
7. European Medicines Agency. *Lokelma™ (Sodium Zirconium Cyclosilicate): Summary of Product Characteristics*. 2018. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004029/WC500246774.pdf (7 August 2018, date last accessed)
8. US Food and Drug Administration. *Lokelma™ (Sodium Zirconium Cyclosilicate) for Oral Suspension: Prescribing Information*. 2018. http://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207078s000lbl.pdf (19 December 2019, date last accessed)
9. Stavros F, Yang A, Leon A *et al*. Characterization of structure and function of ZS-9, a K⁺ selective ion trap. *PLoS One* 2014; 9: e114686
10. Spinowitz BS, Fishbane S, Pergola PE *et al*. Sodium zirconium cyclosilicate among individuals with hyperkalemia: a 12-month Phase 3 Study. *Clin J Am Soc Nephrol* 2019; 14: 798–809
11. Chang LC, Mahmood R, Qureshi S *et al*. Patterns of use and impact of standardised MedDRA query analyses on the safety evaluation and review of new drug and biologics license applications. *PLoS One* 2017; 12: e0178104
12. Ash SR, Singh B, Lavin PT *et al*. A phase 2 study on the treatment of hyperkalemia in patients with chronic kidney disease suggests that the selective potassium trap, ZS-9, is safe and efficient. *Kidney Int* 2015; 88: 404–411
13. Bakris GL, Pitt B, Weir MR *et al*. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. *JAMA* 2015; 314: 151–161
14. Weir MR, Bakris GL, Bushinsky DA *et al*. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 2015; 372: 211–221
15. Hunt TV, DeMott JM, Ackerbauer KA *et al*. Single-dose sodium polystyrene sulfonate for hyperkalemia in chronic kidney disease or end-stage renal disease. *Clin Kidney J* 2018; 12: 408–413
16. Dobre M, Rahman M, Hostetter TH. Current status of bicarbonate in CKD. *J Am Soc Nephrol* 2015; 26: 515–523
17. Chen W, Abramowitz MK. Metabolic acidosis and the progression of chronic kidney disease. *BMC Nephrol* 2014; 15: 55
18. Packham DK, Rasmussen HS, Lavin PT *et al*. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med* 2015; 372: 222–231
19. McCullough PA, Costanzo MR, Silver M *et al*. Novel agents for the prevention and management of hyperkalemia. *Rev Cardiovasc Med* 2015; 16: 140–155
20. Rafique Z, Peacock WF, LoVecchio F *et al*. Sodium zirconium cyclosilicate (ZS-9) for the treatment of hyperkalemia. *Expert Opin Pharmacother* 2015; 16: 1727–1734

21. Epstein M, Reaven NL, Funk SE *et al.* Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care* 2015; 21: S212–S220
22. Garlo KG, Bates DW, Seger DL *et al.* Association of changes in creatinine and potassium levels after initiation of renin angiotensin aldosterone system inhibitors with emergency department visits, hospitalizations, and mortality in individuals with chronic kidney disease. *JAMA Netw Open* 2018; 1: e183874
23. Bomback AS. Mineralocorticoid receptor antagonists in end-stage renal disease: efficacy and safety. *Blood Purif* 2016; 41: 166–170
24. Yancy CW, Jessup M, Bozkurt B *et al.* 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *JACC* 2013; 62: e147–e239
25. Zeng Q, Zhou X, Xu G. Safety evaluation and cardiovascular effect of additional use of spironolactone in hemodialysis patients: a meta-analysis. *Drug Des Devel Ther* 2019; 13: 1487–1499

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