Safety and Efficacy of Sodium Zirconium Cyclosilicate for Long-Term Treatment of Hyperkalemia in Patients With Chronic Kidney Disease: Results From an Open-Label, Phase 3 Study

Simon D. Roger,[1] Philip T. Lavin,[2] Edgar V. Lerma,[3] Peter A. McCullough,[4] Javed Butler,[5] Bruce S. Spinowitz,[6] Stephan von Haehling,[7] Mikhail Kosiborod,[8] Steven Fishbane,[9] David K. Packham[10]

[1]Renal Research, Gosford, Australia; [2]Boston Biostatistics Research Foundation, Framingham, MA, USA; [3]University of Illinois at Chicago/Advocate Christ, Oak Lawn, IL, USA; [4]Baylor University Medical Center, Dallas, TX, USA; [5]University of Mississippi, Jackson, MS, USA; [6]New York Hospital Queens, New York, NY, USA; [7]University of Göttingen Medical School, Göttingen, Germany; [8]Saint Luke's Mid America Heart Institute, Kansas City, MO, USA; [9]Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY, USA; [10]Melbourne Renal Research Group, Melbourne, Australia

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Introduction

- Hyperkalemia (elevated serum potassium [K^+]) is a common electrolyte abnormality associated with increased morbidity and mortality[1]
- Patients with chronic kidney disease (CKD), particularly those who are treated with renin–angiotensin–aldosterone system inhibitor (RAASi) therapy, are at a greater risk for hyperkalemia[2,3] and may benefit from medical management of hyperkalemia
- Sodium zirconium cyclosilicate (SZC; formerly ZS-9) is a selective K^+ binder approved by the United States Food and Drug Administration and the European Medicines Agency for the treatment of adult patients with hyperkalemia
  - SZC is thought to initially bind K^+ in the small intestine and remains bound as it transits through the large intestine and is excreted from the body in the feces
  - SZC 10 g reduced serum K^+ within 2.2 hours of the first administered dose in most patients[4]
- In this post hoc analysis, we evaluated the efficacy and safety of outpatient SZC treatment for hyperkalemia among patients with a baseline estimated glomerular filtration rate (eGFR) <30 versus ≥30 mL/min/1.73 m^2 who were enrolled in the 12-month, international, prospective, multicenter, open-label, single-arm, phase 3 study (ZS-005; NCT02163499)

Methods

Study Design

- Adult outpatients (aged ≥18 years) with hyperkalemia (defined as K^+ ≥5.1 mmol/L; measured using a point-of-care i-STAT device [Abbott Point of Care, Inc., Princeton, NJ, USA]) were enrolled
  - Patients with pseudohyperkalemia, diabetic ketoacidosis, or cardiac arrhythmias requiring immediate treatment and those receiving dialysis were excluded
  - No protocol-mandated dietary restrictions or changes in RAASi therapy were required
- During the correction phase, SZC 10 g three times daily (TID) was taken orally (as an odorless, tasteless, white crystalline powder suspended in 40 mL of water with no rinses or in 180 mL of water with 2–30-mL rinses) before meals for 24–72 hours
- Patients who achieved i-STAT K^+ 3.5–5.0 mmol/L at any point during the correction phase immediately qualified to enter the 12-month maintenance phase during which patients received SZC 5 g once daily (QD) to start
- During the maintenance phase, the SZC dose was titrated to i-STAT K^+ ≤5.0 mmol/L according to **Table 1**

Table 1. SZC Dosing Algorithm

Correction Phase	Maintenance Phase				
	Observed K^+,[a] mmol/L	Current SZC Dose			
		5 g QoD	5 g QD	10 g QD	15 g QD
Patients received SZC 10 g TID until an i-STAT K^+ 3.5–5.0 mmol/L was achieved	3.0 to 3.4	Discontinue	Reduce to 5 g QoD	Reduce to 5 g QD	Reduce to 10 g QD
	3.5 to 5.0	No change	No change	No change	No change
	>5.0 to 6.5	Increase to 5 g QD	Increase to 10 g QD	Increase to 15 g QD[b]	No change

[a]Based on i-Stat K^+ value at visit.
[b]Increase to 15 g QD only occurred if K^+ >5.5 mmol/L.
Drug was discontinued if patients had a K^+ <3.0 or >6.5 mmol/L.
QoD, every other day.

- Two K^+ assessments were performed concurrently at each study visit:
  - i-STAT K^+ (immediately available) was used to determine study eligibility, duration of corrective treatment, and SZC dose titrations during the maintenance phase
  - Serum K^+ measurements from the central laboratory were used to evaluate efficacy outcomes
- K^+ levels were measured daily during the 24–72-hour correction phase, weekly through the first month, and every 4 weeks thereafter during the maintenance phase
- This post hoc analysis evaluated the efficacy and safety of SZC among patients with a baseline eGFR <30 versus ≥30 mL/min/1.73 m^2
  - Study end points were the proportion of patients achieving normokalemia by i-STAT K^+ during the correction phase, mean serum K^+ during the maintenance phase, change from baseline in sodium bicarbonate level, and adverse events (AEs)

Results

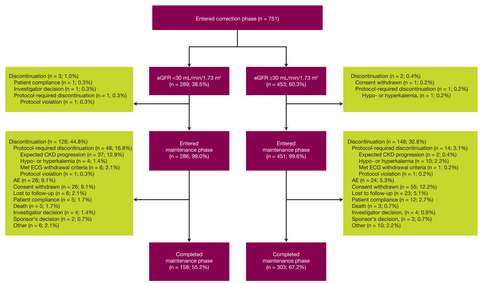
- Of the 751 patients enrolled in the study, 742 had a baseline eGFR measurement; of these, 289 had a baseline eGFR <30 mL/min/1.73 m^2 (**Table 2**; **Figure 1**)

Table 2. Patient Demographics and Baseline Characteristics

	eGFR <30 mL/min/1.73 m^2 (n = 289)	eGFR ≥30 mL/min/1.73 m^2 (n = 453)	*P* Value
Age, years, mean ± SD	64.8 ± 13.0	62.9 ± 13.1	>0.05
Male, n (%)	164 (56.7)	277 (61.1)	>0.05
Race, n (%)			
White	223 (77.2)	394 (87.0)	<0.001
Black/African American	40 (13.8)	48 (10.6)	>0.05
Asian	16 (5.5)	8 (1.8)	<0.01
Other	10 (3.5)	3 (0.7)	<0.01
Geographic region, n (%)			
United States	225 (77.9)	408 (90.1)	<0.001
Other countries[a]	64 (22.1)	45 (9.9)	
Weight, kg, mean ± SD	88.5 ± 23.0	84.8 ± 21.2	<0.05
Serum K^+, mmol/L, mean (range)[b]	5.7 (4.8–7.3)	5.6 (4.0–7.6)	<0.001
Serum K^+, mmol/L, n (%)			
<5.5	93 (32.2)	193 (42.6)	<0.01
5.5 to <6.0	137 (47.4)	195 (43.0)	>0.05
≥6.0	59 (20.4)	65 (14.3)	<0.05
i-STAT K^+, mmol/L, mean (range)[b]	5.5 (5.1–6.9)	5.5 (5.1–7.3)	<0.05
i-STAT K^+, mmol/L, n (%)			
<5.5	144 (49.8)	248 (54.7)	>0.05
5.5 to <6.0	109 (37.7)	164 (36.2)	>0.05
≥6.0	36 (12.5)	41 (9.1)	>0.05
eGFR, mL/min/1.73 m^2, mean (range)	21.3 (4.3–29.8)	63.6 (30.0–178.5)	
eGFR, mL/min/1.73 m^2, n (%)			
<15	46 (15.9)	0 (0.0)	
15 to <30	243 (84.1)	0 (0.0)	
30 to <45	0 (0.0)	173 (38.2)	
45 to <60	0 (0.0)	33 (7.3)	
50 to <60	0 (0.0)	57 (12.6)	
Comorbidity, n (%)			
Heart failure[c]	55 (19.0)	54 (11.9)	<0.05
Diabetes mellitus	201 (69.6)	262 (57.8)	<0.01
Hypertension	275 (95.2)	339 (74.8)	<0.001
Concomitant medication use, n (%)			
RAASi therapy	199 (68.9)	279 (61.6)	<0.05
ACE inhibitors	122 (42.2)	212 (46.8)	>0.05
ARBs	79 (27.3)	74 (16.3)	<0.001
MRAs	15 (5.2)	30 (6.6)	>0.05
Diuretics	158 (54.7)	140 (30.9)	<0.001
Loop	132 (45.7)	95 (21.0)	<0.001
Thiazide	13 (4.5)	21 (4.6)	<0.001
Other[d]	11 (3.8)	13 (2.9)	>0.05
Combined medication[e]	14 (4.8)	23 (5.1)	>0.05
Calcium channel blockers	142 (49.1)	111 (24.5)	<0.001
Dihydropyridine	126 (43.6)	98 (21.6)	<0.001
Non-dihydropyridine	17 (5.9)	15 (3.3)	>0.05

[a]Centres in Australia, Europe, and South Africa.
[b]Based on patients in the correction phase intention-to-treat population.
[c]Defined based on case report form.
[d]Included thiazide-like diuretics.
[e]Included both thiazide and thiazide-like diuretics in combination with other medications.
Statistical significance was determined using the Fisher exact test with the exception of age, weight, and serum and i-STAT K^+, which was determined by *t* test.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; SD, standard deviation.

Figure 1. Patient Disposition

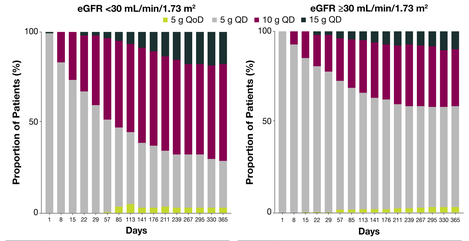


Nine patients who entered the correction phase did not have a baseline eGFR measurement.
ECG, electrocardiogram.

SZC Dosing

- The majority of patients with a baseline eGFR <30 (n = 235; 81.3%) and ≥30 mL/min/1.73 m^2 (n = 370; 81.7%) only required a total of SZC 30 g (administered as 10 g TID over 1 day) to achieve normokalemia and qualify for entry into the maintenance phase
- During the maintenance phase, patients with a baseline eGFR <30 mL/min/1.73 m^2 generally required a higher SZC dose than those with a baseline eGFR ≥30 mL/min/1.73 m^2 (**Figure 2**)

Figure 2. Dosing by Visit During the First 3 Months of the Maintenance Phase



	Day														
	1	8	15	22	29	57	85	113	141	176	211	239	267	295	330	365
n	286	278	269	266	266	250	239	223	214	211	195	185	181	173	169	159
Mean SZC dose (g)	5.0	5.8	6.3	6.7	7.1	7.5	7.8	8.0	8.4	8.6	8.8	9.1	9.2	9.2	9.4	9.3
Median SZC dose (g)	5.0	5.0	5.0	5.0	5.0	5.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0

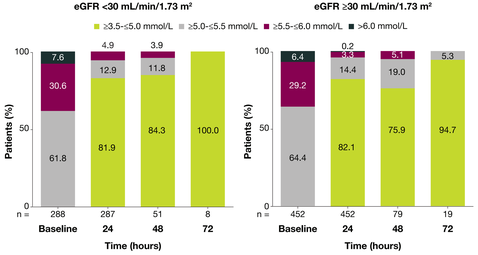
	Day														
	1	8	15	22	29	57	85	113	141	176	211	239	267	295	330	365
n	451	446	435	430	427	418	399	389	382	373	359	355	340	332	323	305
Mean SZC dose (g)	5.0	5.3	5.7	6.0	6.2	6.5	6.7	6.9	7.1	7.2	7.3	7.4	7.4	7.4	7.5	7.5
Median SZC dose (g)	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0

Efficacy

Correction Phase

- More than 80% of patients, regardless of their eGFR levels, achieved an i-STAT K^+ 3.5–5.0 mmol/L within 24 hours (**Figure 3**)

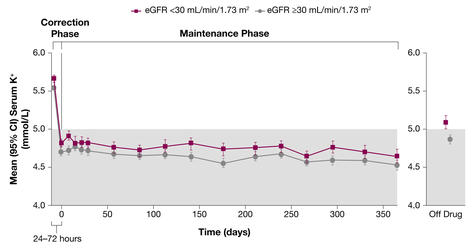
Figure 3. Proportion of Patients Achieving i-STAT K^+ During the Correction Phase



Maintenance Phase

- For both eGFR groups, mean serum K^+ decreased by 0.85 mmol/L from the correction phase baseline to the start of the maintenance phase; this change was maintained over 12 months (**Figure 4**)

Figure 4. Serum K^+ Over Time During the Maintenance Phase



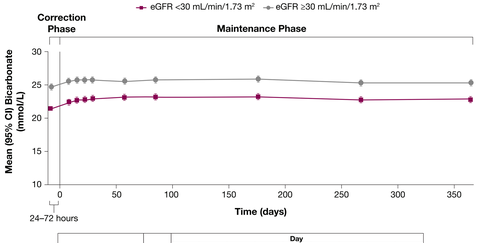
		Day														
eGFR, mL/min/1.73 m^2	CP	0	8	15	22	29	57	85	113	141	176	211	239	267	295	330	365	OD
<30, n	279	279	278	269	266	265	249	238	223	214	211	194	185	179	172	168	142	217
<30, mean SZC dose	10.0	5.0	5.0	5.9	6.4	6.7	7.1	7.6	7.9	8.1	8.5	8.8	9.0	9.1	9.2	9.2	9.4	–
≥30, n	446	446	446	435	430	427	417	399	389	381	371	359	355	339	330	321	292	373
≥30, mean SZC dose	10.0	5.0	5.0	5.3	5.7	6.0	6.3	6.5	6.8	7.0	7.2	7.3	7.3	7.4	7.4	7.4	7.5	–

OD values were collected 7 ± 1 day after the last administration of drug.
CI, confidence interval; CP, correction phase; OD, off drug.

Safety

- Serum bicarbonate levels increased from baseline to day 8, and the change was maintained during the maintenance phase for both eGFR subgroups on SZC (**Figure 5**)

Figure 5. Bicarbonate Level Over Time During the Maintenance Phase



		Day							
eGFR, mL/min/1.73 m^2	CP	8	15	22	29	57	85	176	267	365
<30, n	286	276	268	264	261	247	238	210	179	142
≥30, n	451	435	433	424	422	410	393	367	332	290

Bicarbonate, mmol/L, mean (95% CI)	eGFR <30 mL/min/1.73 m^2	eGFR ≥30 mL/min/1.73 m^2
CP baseline	21.5 (21.1–21.9)	24.8 (24.5–25.1)
MP Day 8	22.5 (22.1–23.0)*	25.7 (25.4–26.0)*
MP Day 365	22.9 (22.3–23.4)*	25.5 (25.1–25.8)†

*P < 0.001 vs CP baseline; †P = 0.0018 vs CP baseline.
At baseline, oral bicarbonate therapy was used by 45 (15.6%) and 17 (3.8%) patients in the eGFR <30 and ≥30 mL/min/1.73 m^2 groups, respectively, and was subsequently initiated by 22 (7.6%) and 5 (1.1%) patients, respectively, during the study period.
CI, confidence interval; CP, correction phase; MP, maintenance phase.

- AEs were more frequent among patients with a baseline eGFR <30 versus ≥30 mL/min/1.73 m^2 (**Table 3**)
- Hypokalemia (serum K^+ <3.5 mmol/L) was reported in 20 (6.9%) and 23 (5.1%) patients in the eGFR <30 and ≥30 mL/min/1.73 m^2 groups, respectively

Table 3. AEs, Serious AEs, and AEs Leading to Discontinuation in ≥5%, ≥1.0%, and ≥1.0% of Patients, Respectively, Over 12 Months

MedDRA Preferred Team, n (%)	eGFR <30 mL/min/1.73 m^2 (n = 286)	eGFR ≥30 mL/min/1.73 m^2 (n = 451)	*P* Value
AEs	**237 (82.9)**	**245 (54.3)**	**<0.001**
Anemia	27 (9.4)	16 (3.5)	<0.01
Constipation	30 (10.5)	17 (3.8)	<0.001
Diarrhea	12 (4.2)	21 (4.7)	>0.05
Headache	15 (5.2)	8 (1.8)	<0.05
Hypertension	42 (14.7)	36 (8.0)	<0.01
Nausea	30 (10.5)	26 (5.8)	<0.05
Peripheral edema	36 (12.6)	35 (7.8)	<0.05
Renal failure acute	23 (8.0)	10 (2.2)	<0.001
Upper respiratory tract infection	18 (6.3)	19 (4.2)	>0.05
Urinary tract infection	33 (11.5)	25 (5.5)	<0.01
Vomiting	16 (5.6)	20 (4.4)	>0.05
Serious AEs	**88 (30.8)**	**70 (15.5)**	**<0.001**
Acute renal failure	7 (2.4)	1 (0.2)	<0.01
Acute respiratory failure	5 (1.7)	0 (0.0)	<0.01
Cellulitis	4 (1.4)	3 (0.7)	>0.05
Chest pain	5 (1.7)	6 (1.3)	>0.05
Congestive cardiac failure	4 (1.4)	6 (1.3)	>0.05
Osteomyelitis	2 (0.7)	6 (1.3)	>0.05
Pneumonia	10 (3.5)	4 (0.9)	<0.05
AEs leading to discontinuation	**58 (20.3)**	**42 (9.3)**	**<0.001**
Acute myocardial infarction	3 (1.0)	0 (0.0)	>0.05
Acute renal failure	8 (2.8)	1 (0.2)	<0.01
Atrial fibrillation	3 (1.0)	1 (0.2)	>0.05
Cardiac failure	3 (1.0)	1 (0.2)	>0.05
Chronic renal failure	5 (1.7)	0 (0.0)	<0.01
Congestive cardiac failure	5 (1.7)	6 (1.3)	>0.05
Dyspnea	3 (1.0)	2 (0.4)	>0.05

As reported by site with no specific threshold.
MedDRA, Medical Dictionary for Regulatory Activities.

Limitations

- This is a post hoc analysis of a single-arm, open-label study with no placebo arm
- The generalizability of these findings may be limited as the ZS-005 study was not designed to evaluate the efficacy and safety of SZC in the CKD population

Conclusions

- Outpatient SZC treatment normalized K^+ levels within 72 hours and maintained normokalemia for up to 12 months in patients with a range of eGFR values
- The AEs observed appeared consistent with the patients' underlying conditions
  - The greater incidence of AEs among patients with a baseline eGFR <30 versus ≥30 mL/min/1.73 m^2 may be related to more comorbidities, level of renal dysfunction, or use of other medications
- Serum bicarbonate levels increased by the second week of SZC treatment and were maintained for 12 months in both eGFR subgroups
- This analysis suggests that SZC effectively corrects hyperkalemia and maintains normokalemia on an outpatient basis even in patients with moderate to severe CKD (eGFR <30 mL/min/1.73 m^2)

References

1. An JN, et al. *Crit Care*. 2012;16(6):R225.
2. Einhorn LM. *Arch Intern Med*. 2009;169(12):1156–1162.
3. Luo J, et al. *Clin J Am Soc Nephrol*. 2016;11(1):90–100.
4. Kosiborod M, et al. *JAMA*. 2014;312(21):2223–2233.

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