Supplemental Materials and Methods

Study Overview

Participants were recruited from nephrology, cardiology, and general medicine practices/clinics. Study sites were located in Australia, Germany, the Netherlands, Romania, South Africa, the United Kingdom, and the United States. This study was conducted according to US Title 21 Code of Federal Regulations and the International Conference on Harmonisation Good Clinical Practice guidelines, as well as with the principles of the Declaration of Helsinki and its most recent updates (Fortaleza, Brazil, October 2013). All participants provided written informed consent before study participation, and an institutional review board approved the study at each site. This study was approved by both central and local institutional review boards, and participants received compensation for expenses.

Study Design

Reasons for discontinuation from the study included expected progression of chronic kidney disease requiring dialysis, transplant, or other treatment and specific protocol-mandated reasons including development of serious arrhythmias, acute heart failure, or potential hyperkalemia-related electrocardiogram changes (eg, significant increase in PR interval, widening of the QRS complex or peaked T waves, or significant corrected QT interval changes) (1) during either phase of the study.

Study Drug Administration during the Maintenance Phase

Sodium zirconium cyclosilicate (SZC) is a tasteless, odorless, crystalline compound that was orally administered before breakfast as a powder suspension in 40 mL of water with no rinses or 180 mL of water with 2–30mL rinses. SZC dosing during the maintenance phase was initiated at 5g once-daily (QD) and titrated in 5g increments or decrements guided by the protocol-specified algorithm (Supplemental Figure 1B) to maintain K^+ 3.5–5.0 mmol/L

measured in plasma from whole blood with a point-of-care device (i-STAT, Abbott Point of Care, Princeton, NJ). The maximum dose permitted was 15gQD and the minimum dose was 5g every other day.

Clinical Laboratory Evaluations

Samples were collected under fasting conditions (with the exception of water, coffee or tea with or without milk or sugar, and essential medications only) for ≥8 hours before sample collection. Two separate whole blood samples were collected at the same time for different K^+ measurements: whole blood was collected in lithium heparin tubes for plasma K^+ measurements by i-STAT and in serum separator tubes for serum K^+ measurements, determined retrospectively by the central laboratory. The i-STAT K^+ measurement was used to determine study eligibility, continuation to the maintenance phase, and maintenance phase SZC dose titrations, while serum K^+ was used to assess treatment outcomes. During the maintenance phase, if the SZC dose was changed or stopped, or if renin–aldosterone–angiotensin system inhibitor or diuretic medications were adjusted/initiated, participants returned to the site 7 (± 1) days later for i-STAT and serum K^+ measurements. 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). Other assessments included serum chemistry parameters (calcium, magnesium, sodium, bicarbonate, and phosphate), urinalysis (sodium, pH, albumin, creatinine, and K^+; measured in 10 mL of urine), vital signs (pulse rate, weight, and systolic and diastolic blood pressure), and physical examinations, which were assessed at screening and follow-up visits (Figure 1A).

Study End Points

Additional post hoc exploratory i-STAT analyses included the proportions of participants who achieved mean i-STAT K^+ ≤5.1, ≤5.5, and 3.5–5.5 mmol/L over months 3–12, mean i-STAT K^+ over months 3–12, 6–9, and 9–12, and absolute and percent change from correction phase baseline in i-STAT K^+. For some outcomes, baseline measurements were taken only at the start of the correction phase but not repeated at initiation of the maintenance phase; therefore, correction phase baseline measurements may be used as a baseline for some maintenance phase outcomes.

Safety and tolerability were assessed by spontaneous investigator reports of adverse events (AEs) and serious AEs (categorized by Medical Dictionary for Regulatory Activities [MedDRA] version 17.0E preferred terms and standardized MedDRA queries [SMQ] for hemodynamic edema, effusions, and fluid overload), by vital signs, and by safety laboratory measurements. Resolution/recovery of SMQ events were collected from the AE case report form. Relatedness of AEs to SZC treatment was judged by the investigator.

Statistical Considerations

For all K^+ goal end points, available K^+ assessments were averaged over the given time period for each participant and then compared to the goal cut-offs. Two-sided 95% confidence intervals (CIs) for the proportion of participants achieving a specific goal were computed using an exact binomial test, while two-sided 95% CIs for mean changes from baseline were computed using a paired *t* test at each visit. Incidences of SMQ edema were summarized by the mean SZC dose that each participant received during the entire maintenance phase, categorized as ≤5 g, >5 to ≤10 g, and >10 g. No imputation for missing data was performed. The intention-to-treat population for the maintenance phase included all participants who received SZC and had any postbaseline K^+ values measured. The safety

population included all participants who received ≥1 dose of SZC and had any postbaseline follow-up for safety.

Supplemental Results

Additional Description of Adverse Events During the Maintenance Phase

Of the 113 participants with SMQ edema, 106 (97%) had comorbid hypertension, 96 (85%) chronic kidney disease, and 86 diabetes mellitus (76%) at baseline; 84 (74%) participants were taking RAASis, 66 (58%) calcium channel blockers, and 62 (55%) loop diuretics. The incidence of SMQ edema appeared to be less common in participants with total mean SZC exposures of ≤5 g SZC (9% [32/351]) than >5 to ≤10 g SZC (18% [58/320]) or >10 g SZC (31% [23/75]) for up to 12 months.

Overall, 1% of participants were hospitalized for an SMQ edema event (hospitalization rate: 1.72 per 100 participant-years). Of the SMQ edema events, 60% (68 participants; 80 events) were recorded as resolved, with another 10% (11 participants; 12 events) recorded as recovering/resolving. SMQ edema events resolved with no medication change in 4% of participants. Among participants experiencing SMQ edema events, 67/113 participants (59% of those with edema; 67/746 [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 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 ≥1 increase in loop diuretic dose/dosing frequency to treat the event. Two participants discontinued SZC, and one discontinued the study due to an SMQ edema event. Further interpretation of the safety data for edema may be confounded due to the lack of a placebo or active comparator

arm. However, in the previously reported 28-day, placebo-controlled HARMONIZE study, the incidence of edema (including generalized and peripheral edema) was low in participants receiving SZC 5 g (2% [1/45]), 10 g (6% [3/51]), and 15 g (14% [8/56]) and placebo (2% [2/85]) (2).

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.

Nine participants each experienced AEs of hypomagnesemia and hypocalcemia, while four participants experienced hyponatremia. Of these, one incidence of hypocalcemia was considered to be potentially clinically significant (<1.75 mmol/L) (Supplemental Table 11). There were eight incidences of potentially clinically significant high values of calcium (>2.75 mmol/L) and one of magnesium (>1.64 mmol/L). Potentially clinically significant high serum phosphate values were observed in 23 participants (3%; Supplemental Table 11). Of these, 22 (96%) had stage 4–5 CKD at baseline; 14 participants had baseline eGFR <15 min/mL/1.73 m^2 and 8 (35%) had baseline eGFR of 15–<30 min/mL/1.73 m^2.

References

1. Rossignol P, Legrand M, Kosiborod M, Hollenberg SM, Peacock WF, Emmett M, Epstein M, Kovesdy CP, Yilmaz MB, Stough WG, Gayat E, Pitt B, Zannad F, Mebazaa A: Emergency management of severe hyperkalemia: guideline for best practice and opportunities for the future. *Pharmacol Res* 113: 585–591, 2016.
2. Kosiborod M, Rasmussen HS, Lavin P, Qunibi WY, Spinowitz B, Packham D, Roger SD, Yang A, Lerma E, Singh B: Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA,* 312**:** 2223–2233, 2014.

Supplemental Table 1. Study sites and principal investigators by country

Investigator Name	Affiliation	Location
United States		
Idalia Acosta	San Marcus Clinical Research Clinic, Inc.	Miami, FL
Ravindra Agarwal	Agarwal Nephrology and Hypertension	Columbus, GA
Rajesh Ailani	Riverside Clinical Research, Creekside Medical Research	Edgewater, FL Deland, FL
Sreedhara Alla	Northwest Louisiana Nephrology	Shreveport, LA
German Alvarez	Clinical Research of Brandon	Brandon, FL
Naveen Atray	Capital Nephrology Medical Group	Sacramento, CA
Diogo Belo	California Institute of Renal Research	Chula Vista, CA
Geoffrey Block	Denver Nephrologists	Denver, CO
Suzan Buxton	Arizona Kidney Disease & Hypertension Centers Medical Research Service, LLC	Peoria, AZ
Robert Cohen	Southwest Clinical Research Institute	Tempe, AZ
Daniel Coyne	Chromalloy American Kidney Center Washington University Center for Advanced Medicine & School of Medicine	St. Louis, MO St. Louis, MO
Paul Crawford	Research by Design	Chicago, IL
Mohamed El-Shahawy	Academic Medical Research Institute	Los Angeles, CA
George Fadda	California Institute of Renal Research	Camesa, CA
Steven Fishbane	North Shore University Hospital	Great Neck, NY
Claude Galphin	Southeast Renal Research Institute	Chattanooga, TN
Nirav Gandhi	Southern California Medical Research Center	La Palma, CA
Srinivas Hariachar	Outcomes Research	Hudson, FL
Mohammad Ismail	Mohammad Ismail, MD, Inc.	Paramount, CA
Younus Ismail	Scottsboro Quick Care Clinic	Scottsboro, AL
Mikhail Kosiborod	Saint Luke's Hospital of Kansas City	Kansas City, MO
Jorge Kusnir	Florida Premier Research Institute	Winter Park, FL
Carlos Leon-Forero	Southern Utah Kidney and Hypertension	St. George, UT
Edouard Martin	South Florida Research Institute	Lauderdale Lakes, FL
Moustafa	South Carolina Nephrology & Hypertension Center	Orangeburg, SC
Jesus Navarro	Genesis Clinical Research	Tampa, FL
Pablo Pergola	Clinical Advancement Center	San Antonio, TX
Raymond Petrillo	Northwest Renal Clinic	Portland, OR

Christopher Phillips	Four Rivers Clinical Research, Inc.	Paducah, KY
Wajeh Qunibi	University of Texas Health Science Center at San Antonio University Health System Dialysis Northwest	San Antonio, TX San Antonio, TX
Javier Ricardo	Empire Clinical Research	Miami Lakes, FL
John Robertson	Apex Research of Riverside	Riverside, CA
Douglas Shemin	Rhode Island Hospital	Providence, RI
Kenneth Smith	Clinical Research Trials of Michigan	Chesterfield, MI
Bruce Spinowitz	Nephrology Associates	Flushing, NY
Pusadee Suchinda	Carolina Diabetes and Kidney Center	Sumter, SC
Jalal Taslimi	Dr Jalal Taslimi Medical Center	Miami, FL
Bijin Thajudeen	University of Arizona Sarver Heart Center Banner – University Medical Center –South Campus	Tucson, AZ Tucson, AZ
Joel Topf	St. Clair Nephrology Research	Roseville, MI
Theodossis Zacharis	Creekside Clinical Research	Deland, FL
Australia		
Steve Holt	Royal Melbourne Hospital	Parkville
Peter Mount	Austin Hospital	Heidelberg
David Mudge	Princess Alexandra Hospital	Woolloongabba
David Packham	Melbourne Medical Research Group	Melbourne
Simon Roger	Renal Research	Gosford
Europe		
Johnathan Barratt	Leicester General Hospital	Leicester, UK
Frank Dellanna	Davita Clinical Research Deutschland GmbH	Dusseldorf, Germany
Wolfram Döhner	Charité Campus Virchow-Klinikum	Berlin, Germany
Liffert Vogt	Amsterdam Medical Center	Amsterdam, Netherlands
Stephan von Haehling	Universitätsmedizin Göttingen	Göttingen, Germany
South Africa		
Graham Ellis	Synexus Helderberg Clinical Trials Centre	Somerset West
Zelda Punt	Phoenix Pharma	Port Elizabeth
Brian Rayner	University of Cape Town	Cape Town
Elane van Nieuwenhuizen	Synexus Watermeyer Clinical Research	Pretoria

Supplemental Table 2. Inclusion and exclusion criteria

Inclusion Criteria	**Exclusion Criteria**
• Provision of written informed consent • Age ≥18 years • For participants outside Germany: 2 consecutive i-STAT K^+ values, measured 60 (± 15) minutes apart, both ≥5.1 mmol/L and measured within 1 day before the first dose of SZC on correction phase day 1 • For participants in Germany: 2 consecutive i-STAT K^+ values, measured 60 (± 15) minutes apart, both ≥5.1 mmol/L and ≤6.5 mmol/L and measured within 1 day before the first dose of SZC on correction phase day 1 • Ability to have repeated blood draws or effective venous catheterization • For participants outside the European Union: Women of childbearing potential must have had a negative pregnancy test within 1 day before the first dose of SZC on correction phase day 1 and sexually active women of childbearing potential must have been using 2 forms of medically acceptable contraception, with ≥1 being a barrier method • For participants in the European Union: Women of childbearing potential must have had a negative pregnancy test within 1 day before the first dose of SZC on correction phase day 1 and sexually active women of childbearing potential must have been using a highly effective medically acceptable contraception	• Signs and symptoms of pseudohyperkalemia • Treatment with lactulose, rifaximin, or other nonabsorbed antibiotics for hyperammonemia within 7 days before the first dose of SZC on correction phase day 1 • Treatment with sodium polystyrene sulfonate or calcium polystyrene sulfonate within 3 days before the first dose of SZC on correction phase day 1 • Life expectancy of <12 months • Severely physically or mentally incapacitated and, in the opinion of the investigator, unable to perform the tasks associated with the protocol • Women who were pregnant, lactating, or planning to become pregnant • Diabetic ketoacidosis • Presence of any condition which, in the opinion of the investigator, placed the participant at undue risk or potentially jeopardized the quality of the data to be generated • Known hypersensitivity or previous anaphylaxis to SZC or to any of its components • Treatment with a drug or device within the last 30 days that had not received regulatory approval at the time of study entry • Cardiac arrhythmias that required immediate treatment • Undergoing dialysis • Randomization/enrollment in the previous ZS-002, ZS-003, ZS-004, or ZS-004E studies • Documented glomerular filtration rate <15 mL/min/1.73 m^2 within 90 days before study entry • For participants in Germany: – Participants presenting with a heart-rate corrected QT interval of 450 msec and additional risk factors for torsade de pointes (eg, heart failure or family history of long QT syndrome) and taking concomitant medications causing QT prolongation – Participants who were committed to an institution by virtue of an order issued either by judicial or administrative authorities – Participants who were dependents of the sponsor, investigator, or institution

K^+, potassium; SZC, sodium zirconium cyclosilicate.

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

ATC Class, *n* (%)	Correction Phase (*N*=751)
Any medication	732 (98)
Agents acting on the renin–angiotensin system	476 (63)
Lipid-modifying agents	459 (61)
Drugs used in diabetes	423 (56)
β-blocking agents	336 (45)
Antithrombotic agents	330 (44)
Vitamins	302 (40)
Diuretics	296 (39)
Analgesics	218 (29)
Drugs for acid-related disorders	265 (35)
Calcium channel blockers	256 (34)
Antianemic preparations	185 (25)
Psychoanaleptics	136 (18)
Antihypertensives (other)	120 (16)
Antigout preparations	116 (15)
Drugs for obstructive airway diseases	115 (15)

Note: Only agents acting on the renin–angiotensin system and diuretics during dosing with SZC are included. Diuretic use is specifically limited to ATC Level 2.
ATC, Anatomical Therapeutic Chemical; SZC, sodium zirconium cyclosilicate.
[a]The safety population comprised all participants who received ≥1 dose of SZC during the given study phase and had any postbaseline follow-up for safety.

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

	Overall Safety Population (*N*=746)			Participants With Bicarbonate Level <22 mmol/L (*n*=207)		
	n	**Mean (95% CI) Change, mmol/L**	**Mean (95% CI) Percent Change**	***n***	**Mean (95% CI) Change, mmol/L**	**Mean (95% CI) Percent Change**
CP baseline	737	23.48 (23.21–23.76)	—	207	18.80 (18.49–19.10)	—
MP day 8	711	0.96 (0.79–1.13)[c]	4.73 (3.95–5.52)[c]	199	1.70 (1.39– 2.02)[c]	9.42 (7.63–11.20)[c]
MP day 15	701	1.12 (0.93–1.31)[c]	5.64 (4.74–6.55)[c]	198	2.20 (1.82–2.58)[c]	12.15 (10.03–14.28)[c]
MP day 22	688	1.11 (0.92–1.30)[c]	5.64 (4.72–6.56)[c]	190	2.40 (2.02–2.77)[c]	13.13 (10.97–15.30)[c]
MP day 29	683	1.21 (1.01–1.42)[c]	6.17 (5.20–7.14)[c]	192	2.51 (2.13–2.88)[c]	13.90 (11.71–16.08)[c]
MP day 57	657	1.11 (0.90–1.33)[c]	5.76 (4.75–6.76)[c]	182	2.49 (2.07–2.91)[c]	13.61 (11.32–15.91)[c]
MP day 85	631	1.17 (0.93–1.40)[c]	6.06 (4.94–7.18)[c]	169	2.77 (2.29–3.25)[c]	15.12 (12.37–17.87)[c]
MP day 176	577	1.22 (0.97–1.46)[c]	6.21 (5.08–7.33)[c]	147	2.82 (2.37–3.28)[c]	15.49 (12.90–18.08)[c]
MP day 267	511	0.76 (0.50–1.03)[c]	4.13 (2.96–5.31)[c]	122	2.28 (1.77–2.79)[c]	12.38 (9.57–15.19)[c]
MP day 365	432	0.77 (0.49–1.06)[c]	4.29 (2.99–5.59)[c]	100	2.57 (1.98–3.16)[c]	14.35 (10.99–17.71)[c]
MP day 365/EOS[b]	725	0.96 (0.73–1.18)[c]	5.20 (4.13–6.26)[c]	203	2.63 (2.18–3.07)[c]	14.47 (12.03–16.90)[c]

CI, confidence interval; CP, correction phase; EOS, end of study; MP, maintenance phase.

[a]The safety population comprised all participants who received ≥1 dose 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]$P \leq 0.001$ vs CP baseline.

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

MedDRA Preferred Term, *n* (%)	**Correction Phase (*N*=751)**
Any adverse event	31 (4)
Abdominal distension	1 (0.1)
Abdominal pain upper	1 (0.1)
Alcohol abuse	1 (0.1)
Arthropod bite	1 (0.1)
Back pain	1 (0.1)
Cellulitis	1 (0.1)
Constipation	2 (0.3)
Diarrhea	2 (0.3)
Edema peripheral	1 (0.1)
Flank pain	1 (0.1)
Flatulence	1 (0.1)
Foreign body sensation in eyes	1 (0.1)
Headache	1 (0.1)
Hyperesthesia	1 (0.1)
Hyperglycemia	1 (0.1)
Hypertension	1 (0.1)
Infection	1 (0.1)
Keratitis	1 (0.1)
Malaise	1 (0.1)
Migraine	1 (0.1)
Muscle spasms	1 (0.1)
Myopia	1 (0.1)
Nasal congestion	1 (0.1)
Nausea	4 (0.5)
Pain	1 (0.1)

MedDRA Preferred Term, *n* (%)	Correction Phase (*N*=751)
Pain in extremity	1 (0.1)
Palpitations	1 (0.1)
Pruritus	1 (0.1)
Renal failure acute	1 (0.1)
Sinusitis	1 (0.1)
Skin ulcer	1 (0.1)
Type 2 diabetes mellitus	1 (0.1)
Urinary incontinence	1 (0.1)
Urinary tract infection	4 (0.5)

MedDRA, Medical Dictionary for Regulatory Activities.
[a]The safety population comprised all participants who received ≥1 dose of sodium zirconium cyclosilicate during the given study phase and had any postbaseline follow-up for safety.

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

MedDRA Preferred Term, *n* (%)	Maintenance Phase (*N*=746)
Any adverse event	489 (66)
Anemia	44 (6)
Arthralgia	19 (3)
Atrial fibrillation	12 (2)
Back pain	11 (2)
Blood creatinine increased	9 (1)
Bronchitis	18 (2)
Cardiac failure congestive	24 (3)
Cardiac murmur	16 (2)
Cellulitis	21 (3)
Chest pain	28 (4)
Constipation	48 (6)
Cough	22 (3)
Diarrhea	33 (4)
Dizziness	17 (2)
Dyspnea	31 (4)
Edema	15 (2)
Edema peripheral	72 (10)
Fall	22 (3)
Fatigue	14 (2)
Fluid overload	12 (2)
Gout	18 (2)
Headache	23 (3)
Hyperglycemia	10 (1)
Hyperkalemia	19 (3)
Hyperphosphatemia	14 (2)
Hypertension	82 (11)
Hypocalcemia	9 (1)
Hypoglycemia	14 (2)

MedDRA Preferred Term, *n* (%)	Maintenance Phase (*N*=746)
Hypokalemia	11 (2)
Hypomagnesemia	9 (1)
Hypotension	10 (1)
Influenza	10 (1)
Insomnia	8 (1)
Local swelling	12 (2)
Metabolic acidosis	11 (2)
Muscle spasms	23 (3)
Musculoskeletal pain	9 (1)
Nasopharyngitis	19 (3)
Nausea	56 (8)
Osteomyelitis	12 (2)
Pain	14 (2)
Pain in extremity	17 (2)
Pneumonia	24 (3)
Pruritus	8 (1)
Pyrexia	8 (1)
Rales	12 (2)
Rash	10 (1)
Renal failure acute	33 (4)
Renal failure chronic	12 (2)
Sinusitis	15 (2)
Skin ulcer	19 (3)
Upper respiratory tract infection	37 (5)
Urinary tract infection	59 (8)
Vertigo	8 (1)
Vitamin D deficiency	8 (1)
Vomiting	36 (5)

MedDRA, Medical Dictionary for Regulatory Activities.
[a]The safety population comprised all participants who received ≥1 dose of sodium zirconium cyclosilicate during the given study phase and had any postbaseline follow-up for safety.

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

Hemodynamic Edema, Effusions, and Fluid Overload SMQ Preferred Term	Participants, n (%)	Number of Events
Any adverse event[b]	**113 (15)c**	**139**
Ascites	1 (0.1)	1
Edema	15 (2)	16
Fluid overload	12 (2)	13
Fluid retention	1 (0.1)	1
Generalized edema	4 (0.5)	4
Local swelling	12 (2)	13
Pericardial effusion	1 (0.1)	1
Peripheral edema	72 (10)	84
Pleural effusion	3 (0.4)	3
Pulmonary edema	3 (0.4)	3

SMQ, standardized Medical Dictionary for Regulatory Activities query.
[a]The safety population comprised all participants who received ≥1 dose of sodium zirconium cyclosilicate during the given study phase and had any postbaseline follow-up for safety. [b]Individual preferred term adverse events were not mutually exclusive.
[c]Participants who reported more than 1 event during the maintenance phase were counted only once in the total number of participants reporting any event.

Supplemental Table 8. Correction phase[a] 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

Characteristic	Edema SMQ Population[b] (*n*=113)	Non-Edema Population (*n*=638)
Age, years, mean (SD)	67 (12)	63 (13)
Age category, years		
<65	47 (42)	331 (52)
≥65	66 (58)	307 (48)
Sex		
Male	70 (62)	378 (59)
Female	43 (38)	260 (41)
Race		
White	85 (75)	539 (85)
Black/African American	20 (18)	69 (11)
Asian	4 (4)	21 (3)
Other	4 (4)	9 (1)
Ethnicity		
Hispanic	24 (21)	296 (46)
Non-Hispanic	89 (79)	342 (54)
Geographic region		
United States	88 (80)	551 (86)
Other countries[c]	25 (22)	87 (14)
Weight, kg		
<85	52 (46)	354 (56)
≥85	59 (52)	283 (44)
Missing	2 (2)	1 (0.2)
Blood pressure, mm Hg, mean (95% CI)		
Systolic	144.7 (140.7–148.6)	133.9 (132.5–135.4)
Diastolic	76.4 (74.1–78.7)	77.2 (76.4–78.0)
Serum K^+, mmol/L, mean (min–max)[d]	5.7 (4.6–7.6)	5.6 (4.0–7.3)
Serum K^+, mmol/L		

Characteristic	Edema SMQ Population[b] (*n*=113)	Non-Edema Population (*n*=638)
5.1 to <5.5	23 (20)	214 (34)
5.5 to <6.0	62 (55)	276 (43)
≥6.0	25 (22)	101 (16)
i-STAT K^+, mmol/L, mean (min–max)[d]	5.6 (5.1–6.5)	5.5 (5.1–7.3)
i-STAT K^+, mmol/L		
5.1 to <5.5	48 (43)	349 (55)
5.5 to <6.0	52 (46)	224 (35)
≥6.0	13 (12)	65 (10)
eGFR, mL/min/1.73 m^2, mean (SD)	31 (14)	50 (33)
eGFR, mL/min/1.73 m^2		
<15	7 (6)	39 (6)
15 to <30	53 (50)	190 (30)
30 to <45	40 (35)	133 (21)
45 to <60	7 (6)	83 (13)
≥60	4 (4)	186 (29)
Not reported	2 (2)	7 (1)
Comorbidity		
Chronic kidney disease	96 (85)	390 (61)
Diabetes mellitus	86 (76)	391 (61)
Heart failure	28 (25)	84 (13)
Hyperkalemia[e]	69 (61)	352 (55)
Hypertension	106 (94)	516 (81)
Concomitant medication use		
RAASi therapy	84 (74)	401 (63)
ACE inhibitors	49 (43)	289 (45)
ARBs	37 (33)	119 (19)
MRAs	10 (9)	35 (6)
Diuretics	72 (64)	225 (35)
Calcium channel blockers	66 (58)	191 (30)
β-blockers	78 (69)	279 (44)

Values are *n* (%) unless otherwise specified.

ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; CI, confidence interval; eGFR, estimated glomerular filtration rate; K^+, potassium; MRAs, mineralocorticoid receptor antagonists; RAASi, renin–angiotensin–aldosterone system inhibitor; SD, standard deviation; SMQ, standardized Medical Dictionary for Regulatory Activities query.

[a]The safety population comprised all participants who received ≥1 dose of sodium zirconium cyclosilicate during the given study phase and had any postbaseline follow-up for safety.

[b]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.

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

[d]At correction phase baseline where K^+ was the mean of 2 different pretreatment K^+ values, recorded 60 (± 15) minutes apart on correction phase day 1.

[e]Includes participants with "hyperkalemia" or "blood potassium increased."

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

MedDRA Preferred Term, *n* (%)	Maintenance Phase (*N*=746)
Any serious adverse event	161 (22)
Acute myocardial infarction	6 (0.8)
Acute respiratory failure	5 (0.7)
Anemia	2 (0.3)
Angina unstable	3 (0.4)
Asthenia	2 (0.3)
Atrial fibrillation	3 (0.4)
Bronchitis	3 (0.4)
Cardiac failure	4 (0.5)
Cardiac failure congestive	11 (2)
Cellulitis	7 (0.9)
Cerebrovascular accident	3 (0.4)
Chest pain	11 (2)
Cholecystitis	2 (0.3)
Chronic obstructive pulmonary disease	3 (0.4)
Constipation	2 (0.3)
Dehydration	2 (0.3)
Diabetic foot	2 (0.3)
Dyspnea	5 (0.7)
Fluid overload	3 (0.4)
Gangrene	2 (0.3)
Hyperkalemia	4 (0.5)
Hypertension	4 (0.5)
Hypoglycemia	4 (0.5)
Lobar pneumonia	3 (0.4)
Myocardial infarction	3 (0.4)
Osteomyelitis	8 (1)
Peptic ulcer	2 (0.3)
Pneumonia	14 (2)
Pulmonary edema	3 (0.4)

MedDRA Preferred Term, *n* (%)	Maintenance Phase (*N*=746)
Renal failure acute	8 (1)
Renal failure chronic	4 (0.5)
Respiratory failure	3 (0.4)
Sepsis	3 (0.4)
Skin ulcer	4 (0.5)
Syncope	2 (0.3)
Transient ischemic attack	2 (0.3)
Troponin increased	2 (0.3)
Urinary tract infection	4 (0.5)
Ventricular tachycardia	2 (0.3)

MedDRA, Medical Dictionary for Regulatory Activities.
[a]The safety population comprised all participants who received ≥1 dose of sodium zirconium cyclosilicate during the given study phase and had any postbaseline follow-up for safety.

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

MedDRA Preferred Term, *n* (%)	**Maintenance Phase (*N*=746)**
Any adverse event leading to discontinuation	102 (14)
Acute myocardial infarction	3 (0.4)
Acute respiratory failure	1 (0.1)
Ankle fracture	1 (0.1)
Arthralgia	1 (0.1)
Atrial fibrillation	4 (0.5)
Atrial flutter	1 (0.1)
Azotemia	1 (0.1)
Breast cancer	1 (0.1)
Cardiac arrest	1 (0.1)
Cardiac failure	4 (0.5)
Cardiac failure acute	1 (0.1)
Cardiac failure congestive	11 (2)
Cardiomyopathy	1 (0.1)
Chest pain	3 (0.4)
Chondrocalcinosis pyrophosphate	1 (0.1)
Constipation	2 (0.3)
Cystitis hemorrhagic	1 (0.1)
Dehydration	1 (0.1)
Delirium	1 (0.1)
Dependence on enabling machine or device	1 (0.1)
Diarrhea	2 (0.3)
Dizziness	1 (0.1)
Drug dose omission	1 (0.1)
Dyspnea	5 (0.7)
Electrocardiogram abnormal	2 (0.3)
Eosinophil count increased	1 (0.1)
Fluid overload	2 (0.3)
Gastric ulcer	1 (0.1)
Gastritis	1 (0.1)

Gastrointestinal necrosis	1 (0.1)
Gout	1 (0.1)
Headache	1 (0.1)
Heart injury	1 (0.1)
Hematuria	1 (0.1)
Hypercapnia	1 (0.1)
Hyperkalemia	3 (0.4)
Hypokalemia	1 (0.1)
Interstitial lung disease	1 (0.1)
Libido decreased	1 (0.1)
Lobar pneumonia	1 (0.1)
Mental status changes	1 (0.1)
Monocyte count increased	1 (0.1)
Multiple sclerosis	1 (0.1)
Muscle spasms	1 (0.1)
Myocardial infarction	3 (0.4)
Nausea	1 (0.1)
Neutrophil count decreased	1 (0.1)
Osteomyelitis	4 (0.5)
Palpitations	1 (0.1)
Pancreatitis acute	1 (0.1)
Pancreatitis chronic	1 (0.1)
Peptic ulcer	1 (0.1)
Pericarditis uremic	1 (0.1)
Peripheral edema	1 (0.1)
Pharyngitis	1 (0.1)
Pneumonia	2 (0.3)
Pneumonia cryptococcal	1 (0.1)
Presyncope	1 (0.1)
Prostatic-specific antigen increased	1 (0.1)
Pulmonary mass	2 (0.3)
Pulmonary physical examination abnormal	1 (0.1)
Rash	1 (0.1)
Renal failure acute	9 (1)

Renal failure chronic	6 (0.8)
Renal transplant	1 (0.1)
Respiratory failure	1 (0.1)
Sciatica	1 (0.1)
Staphylococcal sepsis	1 (0.1)
Toxicity to various agents	1 (0.1)
Troponin increased	1 (0.1)
Urosepsis	1 (0.1)
Venous insufficiency	1 (0.1)
Ventricular tachycardia	2 (0.3)
Vomiting	4 (0.5)
White blood cell decreased	1 (0.1)

MedDRA, Medical Dictionary for Regulatory Activities.
[a]The safety population comprised all participants who received ≥1 dose of sodium zirconium cyclosilicate during the given study phase and had any postbaseline follow-up for safety.

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

	Mean (95% CI) at CP Baseline	Mean (95% CI) Change From CP Baseline		Potentially Clinically Significant Values, *n* (%)[c,d]		
		Day 29	Day 365/EOS[b]	Low	High	Total
Magnesium, mmol/L	0.81 (0.80–0.82)	–0.01 (–0.01 to 0.00)	0.01 (0.00–0.01)	0 (0.0)	1 (0.1)	727 (98)
Calcium, mmol/L	2.31 (2.30–2.33)	0.02 (0.01–0.04)	–0.01 (–0.02 to 0.01)	1 (0.1)	8 (1)	726 (97)
Sodium, mmol/L	138.4 (138.1–138.7)	0.7 (0.4–1.0)	0.2 (–0.1 to 0.5)	0 (0.0)	0 (0.0)	727 (98)
Phosphate, mmol/L	1.18 (1.16–1.20)	0.03 (0.02–0.05)	0.07 (0.05–0.09)	0 (0.0)	23 (3)	727 (98)

CI, confidence interval; CP, correction phase; EOS, end of study.
[a]The safety population comprised all participants who received ≥1 dose 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]Potentially clinically significant shifts from CP baseline to maximum follow-up.
[d]Magnesium (low <0.37 mmol/L; high >1.64 mmol/L); calcium (low <1.75 mmol/L; high >2.75 mmol/L); sodium (low <120 mmol/L; high >160 mmol/L); phosphate (low <0.65 mmol/L; high >2.10 mmol/L).

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

	CP Baseline	MP Day 85	MP Day 176	MP Day 365
Potassium, mmol/L				
N	515	437	378	271
Mean (95% CI)	50.2 (47.5–53.0)	38.6 (36.3–41.0)	38.9 (36.3–41.5)	40.5 (37.5–43.5)
Sodium, mmol/L				
N	515	437	378	271
Mean (95% CI)	93.7 (89.6–97.8)	99.1 (94.8–103.4)	100.3 (95.6–105.0)	101.5 (96.1–106.9)
pH				
N	735	630	576	433
Mean (95% CI)	5.92 (5.87–5.97)	5.90 (5.85–5.94)	5.87 (5.82–5.92)	5.83 (5.78–5.88)
Creatinine, µmol/L				
N	515	437	378	271
Mean (95% CI)	8592.2 (8209.8–8974.6)	9648.2 (9156.4–10,139.9)	10,011.4 (9487.4–10,535.5)	10,741.6 (10,117.4–11,365.8)
Albumin, µmol/L				
N	515	437	378	271
Mean (95% CI)	6.2 (5.1–7.3)	8.7 (7.2–10.3)	8.2 (6.6–9.8)	9.7 (7.3–12.1)
Potassium-to-creatinine ratio				
N	515	437	378	270
Mean (95% CI)	0.62 (0.57–0.67)	0.38 (0.37–0.40)	0.37 (0.35–0.39)	0.35 (0.33–0.37)
Sodium-to-creatinine ratio				
N	515	437	378	270
Mean (95% CI)	1.18 (1.12–1.25)	1.11 (1.05–1.18)	1.11 (1.03–1.19)	1.02 (0.94–1.10)

CI, confidence interval; CP, correction phase; MP, maintenance phase.
[a]The safety population comprised all participants who received ≥1 dose of sodium zirconium cyclosilicate during the given study phase and had any postbaseline follow-up for safety.

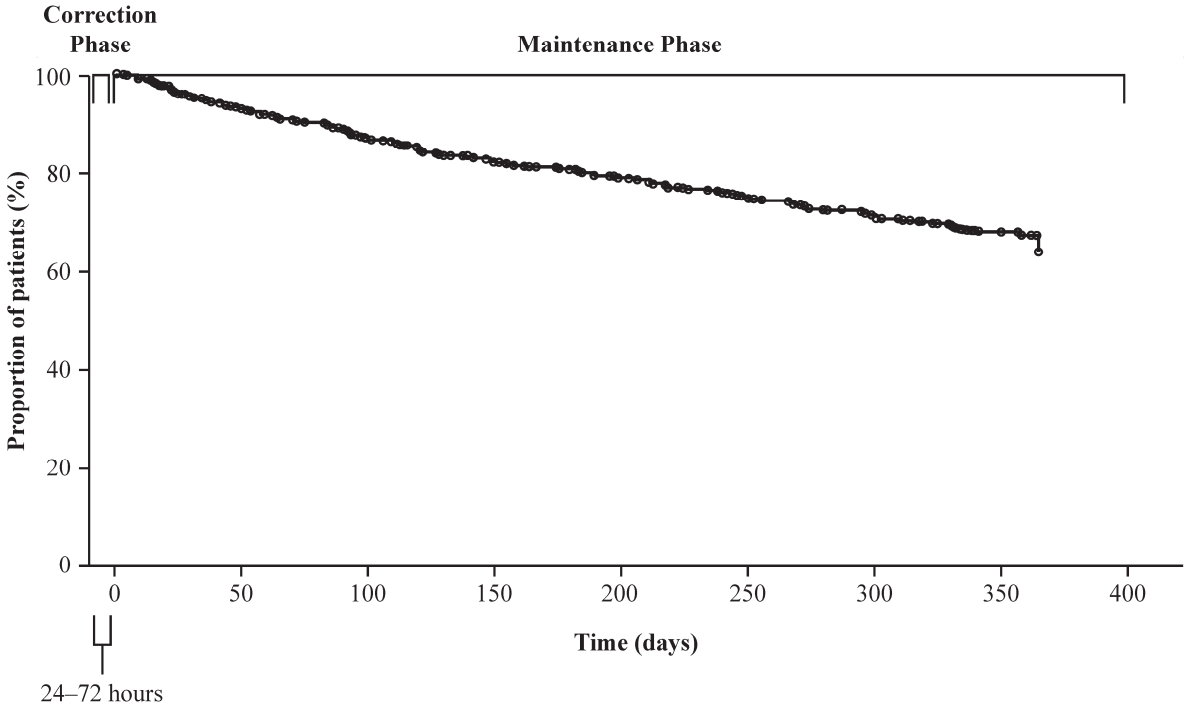
Supplemental Figure 1. Dose titration algorithm.

[a]Participants who achieved normokalemia (K^+ 3.5–5.0 mmol/L) as measured by the point-of-care device i-STAT at any point during the correction phase were immediately eligible to enter the 12-month maintenance phase and received 5 g once daily treatment with SZC. [b]Drug to be discontinued if K^+ <3.0 or >6.5 mmol/L at any time. [c]Based on i-STAT K^+ value at visit. [d]If i-STAT K^+ >5.5 mmol/L. K^+, potassium; QD, once daily; QoD, every other day; SZC, sodium zirconium cyclosilicate.

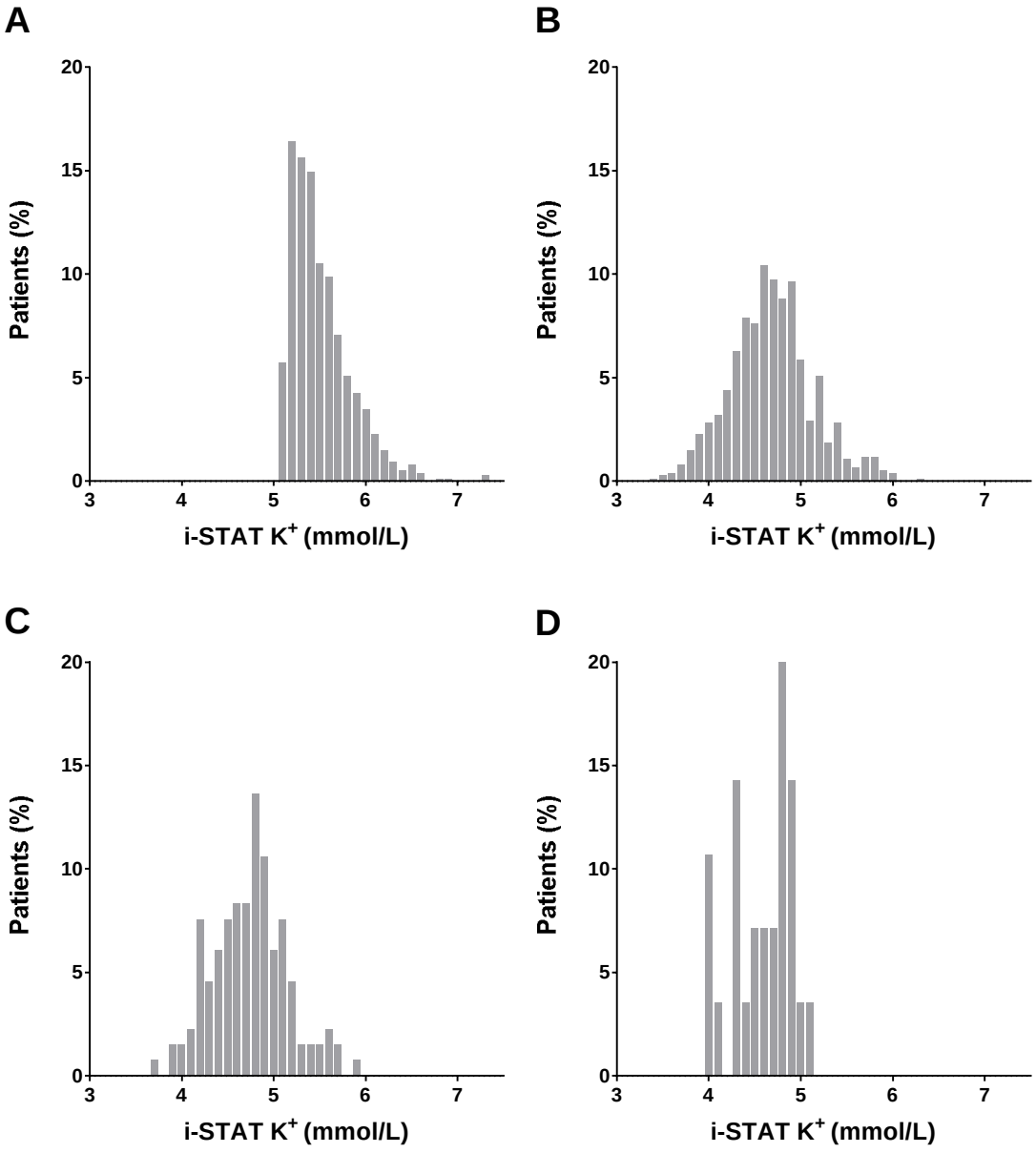
Correction Phase		**Maintenance Phase**				
Participants received SZC 10 g TID until i-STAT K^+ 3.5–5.0 mmol/L was achieved[a,b]		**Observed K^+[c] mmol/L**	**Current SZC Dose**			
			5 g QoD	**5 g QD**	**10 g QD**	**15 QD**
		3.0 to 3.4[b]	Discontinue	Reduce to 5 g QoD	Reduce to 5 g QD	Reduce to 10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

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

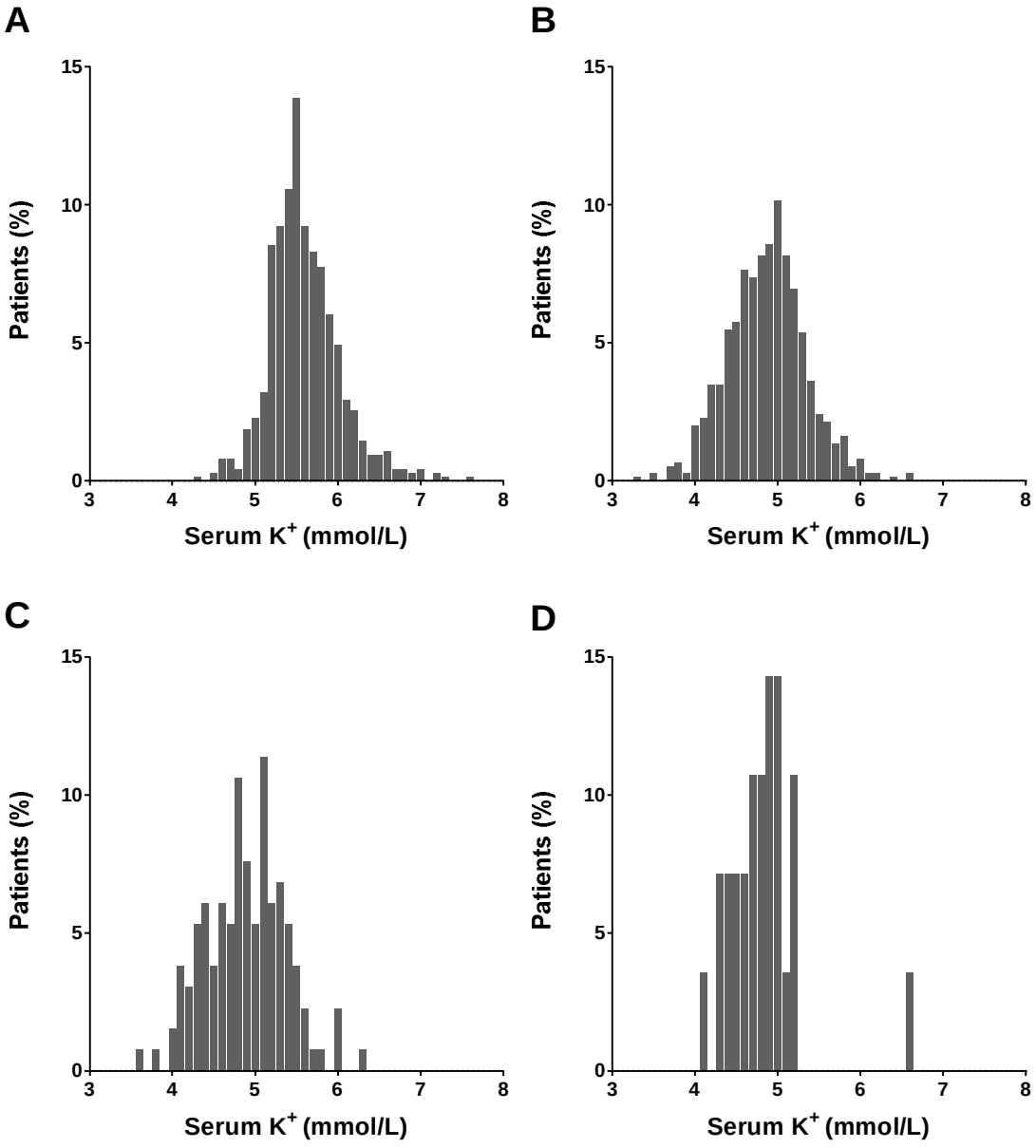
[a]The safety population comprised all participants who received ≥1 dose of sodium zirconium cyclosilicate during the given study phase and had any post-baseline follow-up for safety.



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.

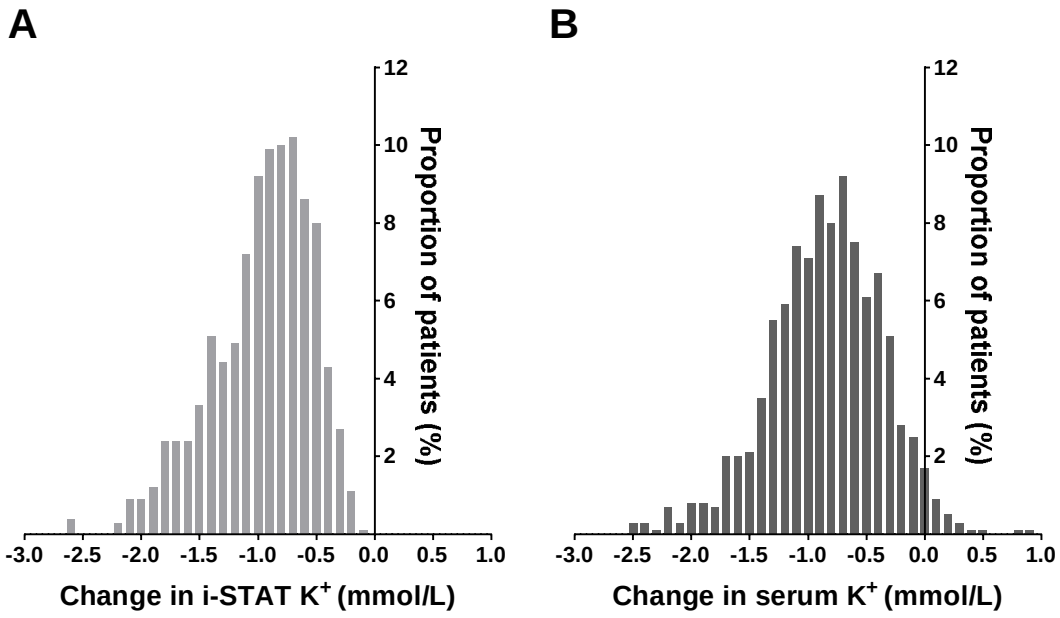


Supplemental Figure 4. Proportion of participants with a serum K^+ measurement at (A) baseline (n=749) and at (B) 24 (n=748), (C) 48 (n=132), and (D) 72 hours (n=28) during the correction phase.

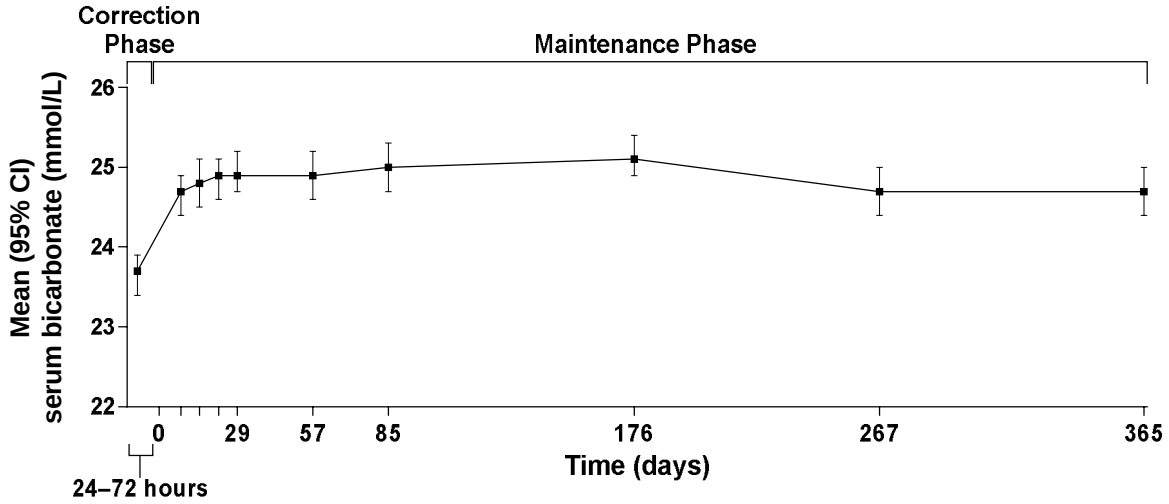


Supplemental Figure 5. Proportion of participants (N=751) who achieved a mean change in (A) i-STAT K^+ and (B) serum K^+.

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.

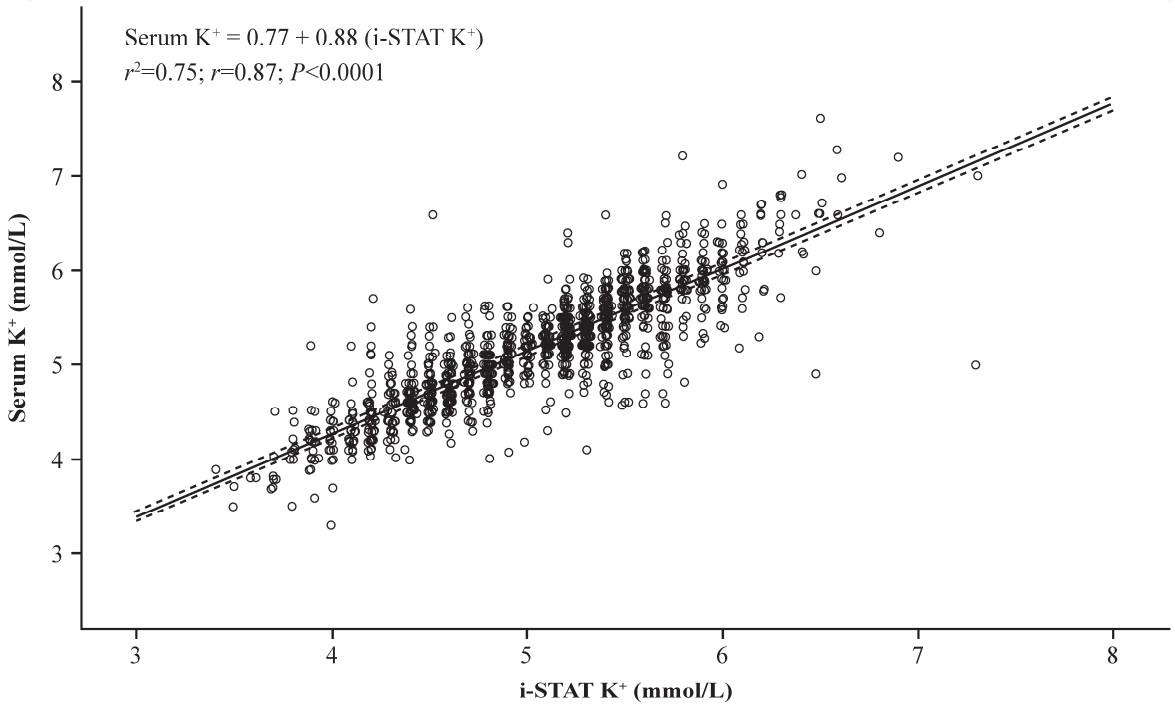


	Day								
	8	**15**	**22**	**29**	**57**	**85**	**176**	**267**	**365**
n	682	672	659	654	628	605	551	492	419
Nominal Δ, mmol/L	1.0	1.1	1.1	1.2	1.1	1.2	1.2	0.8	0.8

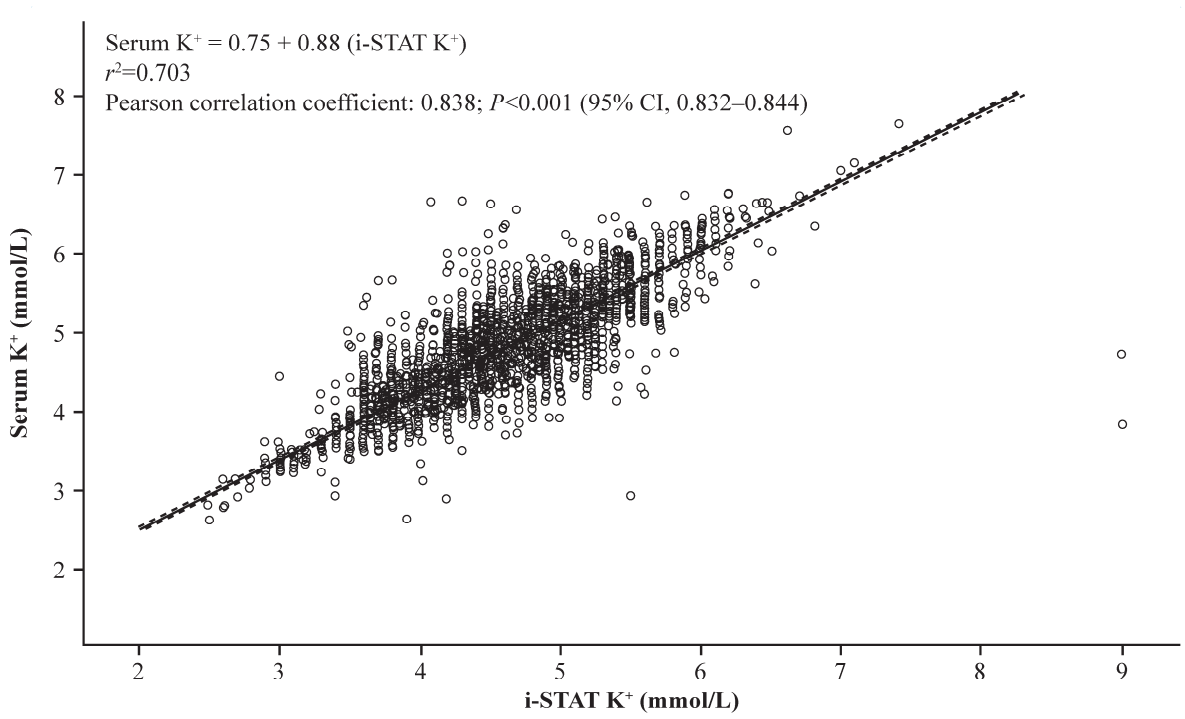
Supplemental Figure 7. Correlation between i-STAT and serum K^+ measurements in the (A) correction phase and (B) maintenance phases (ITT population[a]).

[a]The ITT population included all participants who received sodium zirconium cyclosilicate and had a post-baseline K^+ measure during the study phase. The plot for the maintenance phase is representative of 9780 observations. CI, confidence interval; ITT, intention-to-treat; K^+, potassium.

A

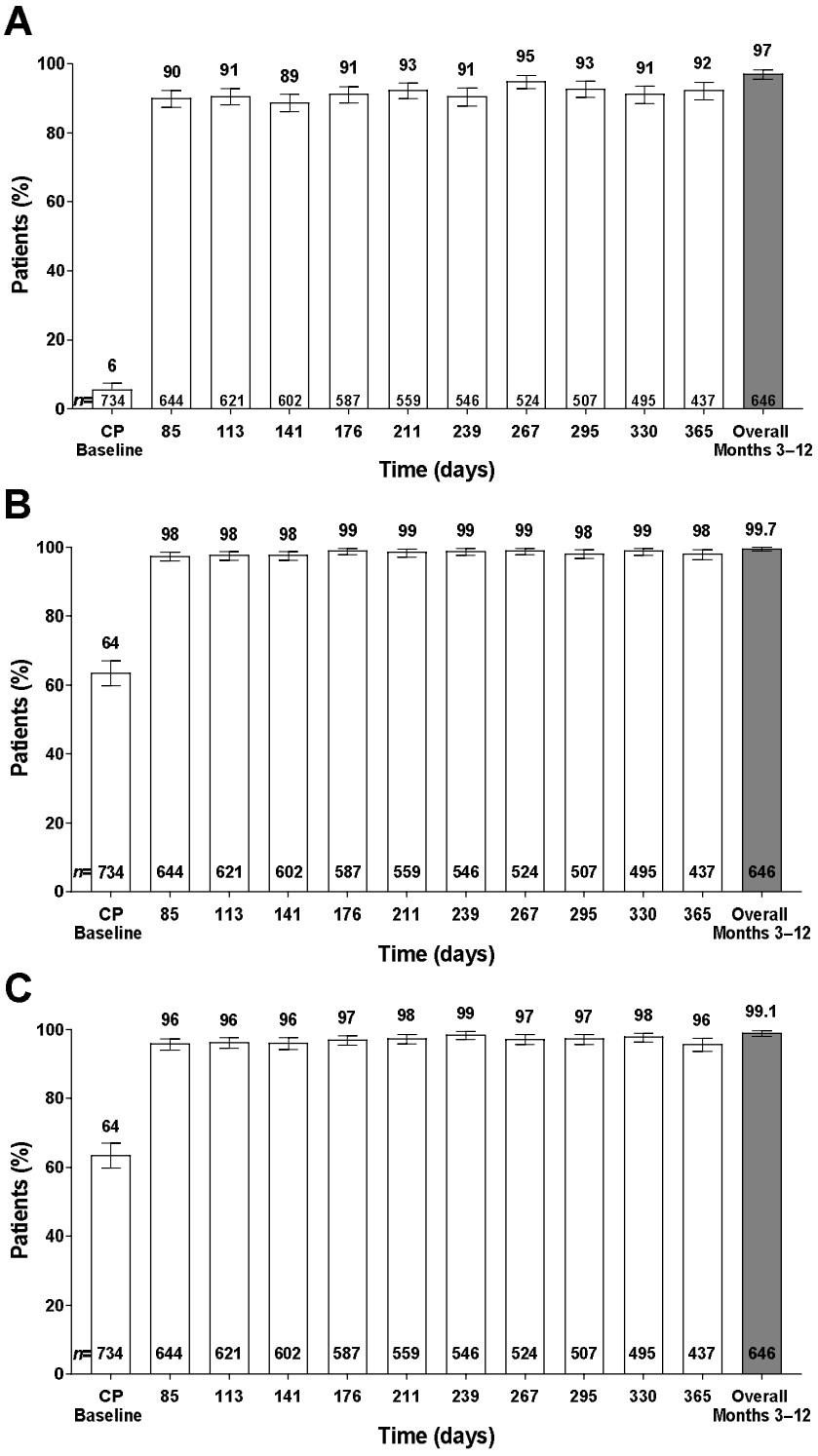


B



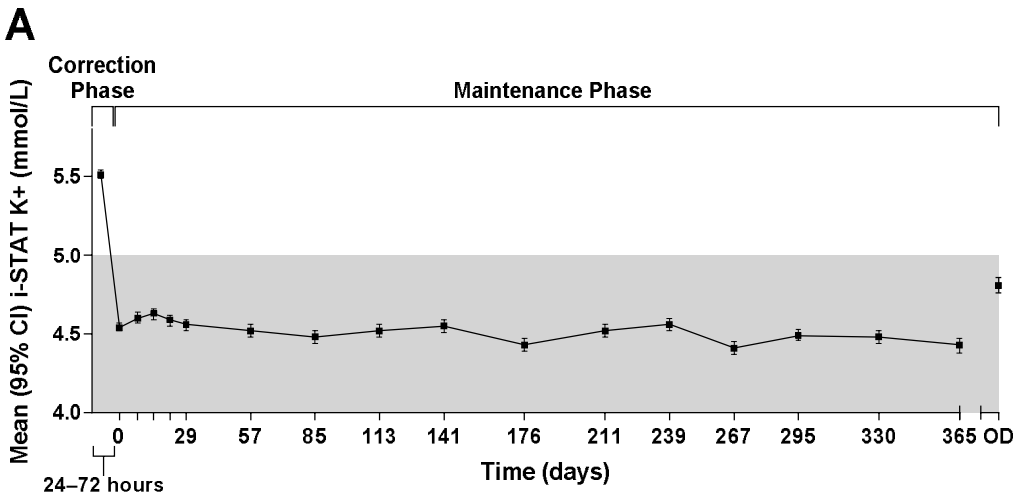
Supplemental Figure 8. Proportion of participants with i-STAT K^+ of (A) ≤5.1 mmol/L, (B) ≤5.5 mmol/L, and (C) 3.5–5.5 mmol/L by visit in the maintenance phase ITT population.[a]

[a]The ITT population included all participants who received sodium zirconium cyclosilicate and had any postbaseline K^+ values measured during the study phase. Gray bars represent a mean of all visits occurring over months 3–12. CP, correction phase; ITT, intention-to-treat; K^+, potassium.

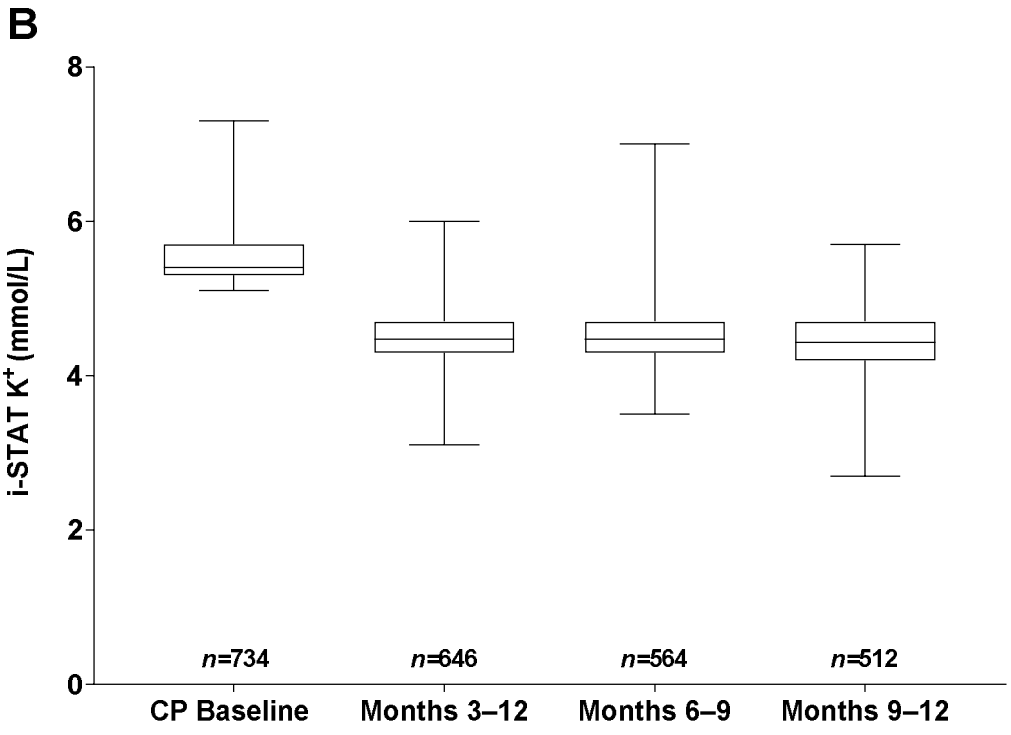


Supplemental Figure 9. i-STAT K^+ (A) over time[a] and (B) at months 3–12, 6–9, and 9–12[b] in the maintenance phase ITT population.[c]

[a]For all bars in Panel A, $P<0.001$ versus CP baseline. Off-drug values were recorded at 7 (± 1) days following the last dose of SZC. [b]The median i-STAT K^+ was 5.4 mmol/L at CP baseline, 4.5 mmol/L from months 3–12 and months 6–9, respectively, and 4.4 mmol/L from months 9–12. [c]The ITT population included all participants who received SZC and had any postbaseline K^+ values measured during the study phase; Δ, change; CI, confidence interval; CP, correction phase; ITT, intention-to-treat; K^+, potassium; OD, off drug; SZC, sodium zirconium cyclosilicate.

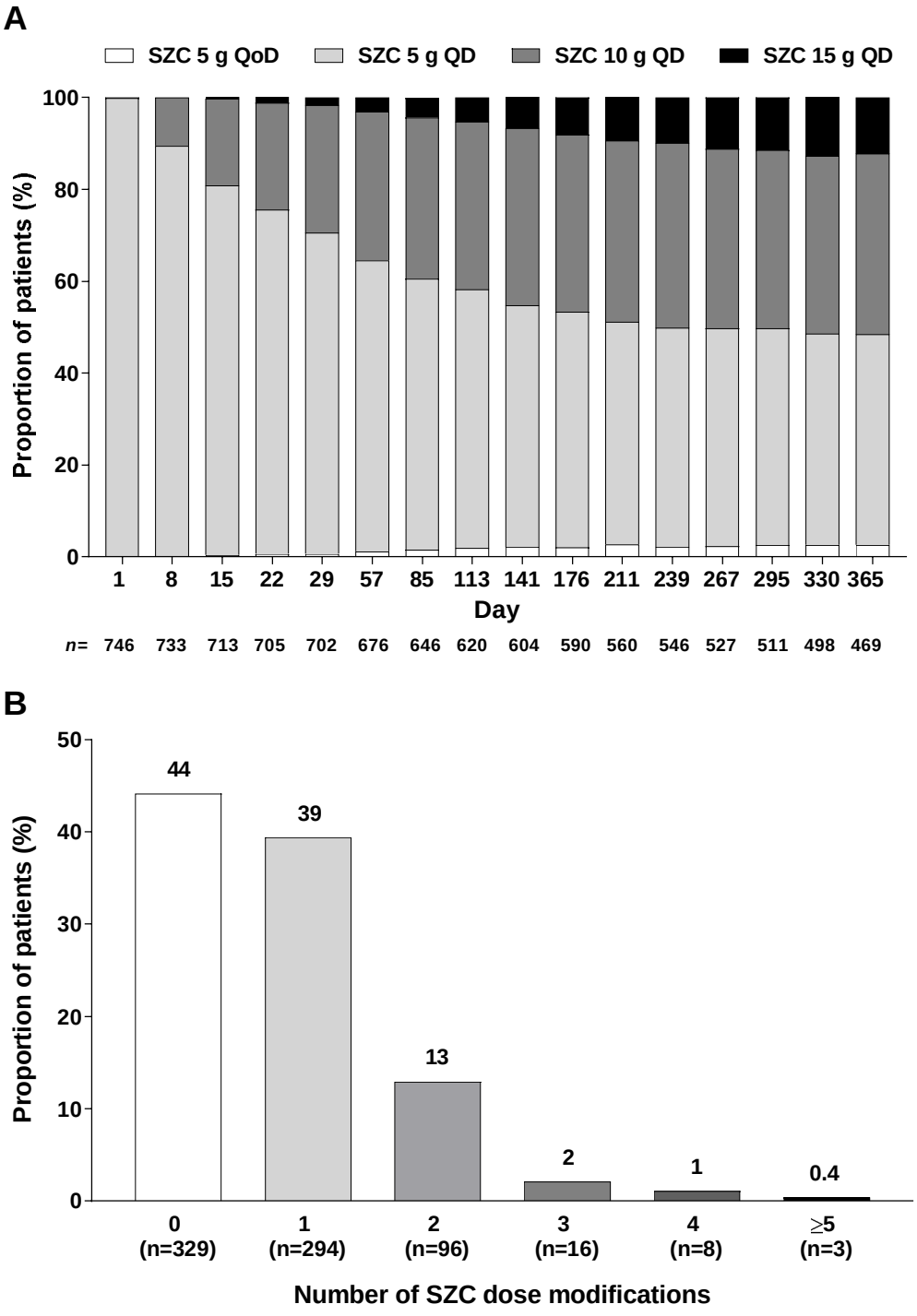


	Day																
	1	8	15	22	29	57	85	113	141	176	211	239	267	295	330	365	OD
n	734	733	712	705	701	674	644	621	602	587	559	546	524	507	495	437	596
Nominal Δ, mmol/L	−0.97	−0.91	−0.89	−0.92	−0.95	−0.99	−1.03	−0.99	−0.96	−1.07	−0.98	−0.95	−1.09	−1.01	−1.03	−1.07	−0.71
Percent Δ, %	−17	−16	−16	−17	−17	−18	−19	−18	−17	−19	−18	−17	−20	−18	−18	−19	−13



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.[a]

[a]The safety population comprised all participants who received ≥1 dose of SZC during the given study phase and had any postbaseline follow-up for safety. QD, once daily; QoD, every other day; SZC, sodium zirconium cyclosilicate.



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.[a]

Study day represents the first occurrence date of an edema SMQ event minus the first dosing date of SZC at MP baseline +1. For participants censored at the end of study, "Study Day" represents the date of study withdrawal/completion minus the first dosing date of SZC at MP baseline +1. [a]The safety population comprised all participants who received ≥1 dose of SZC during the given study phase and had any postbaseline follow-up for safety. MP, maintenance phase; SMQ, standardized Medical Dictionary for Regulatory Activities query; SZC, sodium zirconium cyclosilicate.