Online Supplementary Materials

Supplementary Methods

Study Design

Protocol-mandated reasons for discontinuation included development of acute heart failure, serious arrhythmia, significant increase in PR interval, or widening of the QRS complex or peaked T-wave or increase in corrected QT interval by >25 ms to >500 ms or, among those with a QT interval >500 ms at baseline, a further increase of >25 ms. Treatment was immediately discontinued without dose titration if potassium (K^+) measured <3.0 mmol/L at any time or >7.0 mmol/L during the extension maintenance phase (Extension-MP).

Clinical Laboratory Evaluations

Additional laboratory assessments included serum chemistry variables (magnesium, calcium, sodium, blood urea nitrogen, bicarbonate, phosphate, and aldosterone [at North American sites only]), urinalysis (urine pH and, at North American sites only, urine albumin, sodium, protein, creatinine, and K^+), vital signs (temperature, pulse rate, weight, and blood pressure), and physical examinations, each assessed at screening and follow-up.

Study End Points

Other efficacy end points included a mixed-model analysis of all available serum K^+ values through days 8–337, descriptive mean serum K^+ values at each scheduled Extension-MP visit, absolute and percent change in serum K^+ from HARMONIZE-CP and Extension-MP baselines to each Extension-MP follow-up time point, mean change in serum K^+ from day 337 to study end, and the proportion of patients with normal serum aldosterone levels

(0.11–0.86 nmol/L) at planned aldosterone assessment visits (North American sites only). Serum bicarbonate levels were also recorded.

Statistical Considerations

A longitudinal mixed model using all available log-transformed serum K^+ values as response and fixed effects of visit and covariates included for the primary end point was used to derive the back-transformed geometric least squares mean serum K^+ value through days 8–337. Random effect was the patient, and an unstructured variance-covariance matrix was specified. Descriptive log-transformed serum K^+ values at each scheduled Extension-MP visit were generated to stabilize variance and calculate confidence intervals and were then back-transformed to the original scale for graphical presentation.

Sample size calculations for the primary end point determined that ≥140 patients would provide ≥90% power at a 5% Type 1 error rate (2-sided) to detect an observed proportion of 65% versus the expected 50% of patients achieving mean serum K^+ ≤5.1 mmol/L. For the secondary end point, the corresponding values were ≥140 patients for ≥80% power at a 5% Type 1 error rate (2-sided) to detect an observed proportion of 72% versus the expected 60% of patients achieving mean serum K^+ ≤5.5 mmol/L.

Supplementary Tables

Supplementary Table S1. Study sites and investigators by country

Investigator name	Affiliation	Location
United States		
Ravindra Agarwal	Agarwal Nephrology and Hypertension	Columbus, GA
Rajesh Ailani	Creekside Medical Research Riverside Clinical Research	Deland, FL Edgewater, FL
Sreedhara Alla	Northwest Louisiana Nephrology	Shreveport, LA
Sady Alpizar	Clinical Research Trials of Florida, Inc.	Tampa, FL
German Alvarez	Clinical Research of Brandon	Brandon, FL
Stella Awua-Larbi	Kidney Care Center	Joilet, IL
Kai Shen Chang	Lakeview Medical Research	Summerfield, FL
Robert Cohen	Southwest Clinical Research Institute	Tempe, AZ
Mohamed El-Shahawy	Academic Medical Research Institute	Los Angeles, CA
Julio Fernandez Bombino	San Marcus Clinical Research Clinic, Inc.	Miami, FL
Claude Galphin	Southeast Renal Research Institute	Chattanooga, TN
Susan Hole	Riverside Clinical Research	Edgewater, FL
Mohammad Ismail	Mohammad Ismail MD, Inc.	Paramount, CA
Mikhail Kosiborod	Saint Luke's Lipid and Diabetes Research Center	Kansas City, MO
Kelli Maw	Meridien Research	Brooksville, FL
Moustafa A. Moustafa	South Carolina Nephrology & Hypertension	Orangeburg, SC
Javier Ricardo	Empire Clinical Research	Miami Lakes, FL
John Robertson	Apex Research of Riverside	Riverside, CA
Luis Serentill	Savin Medical Group, LLC	Miami Lakes, FL
Douglas Shemin	Rhode Island Hospital	Providence, RI
Kenneth Smith	Clinical Research Trials Institute of Michigan, LLC	Chesterfield, MI
Jalal Taslimi	Medical Consulting Center	Miami, FL
Theodossis Zacharis	Creekside Clinical Research	Deland, FL
Australia		
Peter Mount	Austin Health	Heidelberg
David Mudge	Princess Alexandra Hospital	Woolloongabba
David K. Packham	Melbourne Medical Research Group	Reservoir
Simon D. Roger	Renal Research	Gosford
South Africa		
Graham Ellis	Helderberg Clinical Trials Centre	Somerset West
Zelda Punt	Phoenix Pharma (Pty) Ltd	Port Elizabeth
Tasneem Vally	Synexus SA	Meyerspark

Supplementary Table S2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Provision of written informed consent • Age ≥18 years • Completed the HARMONIZE maintenance phase study day-29 visit and had an i-STAT K^+ 3.5–6.2 mmol/L or discontinued the study during the maintenance phase because of hypo- or hyperkalemia and had a mean i-STAT K^+ of 3.5–6.2 mmol/L from 2 consecutive measurements at 0 and 60 minutes on correction phase study day 1/maintenance phase study day 1 • Able to start dosing in the extension study within 2 days after the last dose of study drug in HARMONIZE	• Pseudohyperkalemia signs and symptoms, such as hemolyzed blood specimen due to excessive fist clenching to make veins prominent, difficult or traumatic venipuncture, or history of severe leukocytosis or thrombocytosis • Alternative treatment for hyperkalemia while participating in HARMONIZE • Life expectancy of <3 months • Severely physically or mentally incapacitated and, in the opinion of 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 that, in the opinion of the investigator, placed the patient at undue risk or potentially jeopardized the quality of data to be generated • Known hypersensitivity or previous anaphylaxis to SZC or to components thereof • 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 • Receiving dialysis

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

Supplementary Table S3. Adverse events and deaths in the Extension-MP safety population[a]

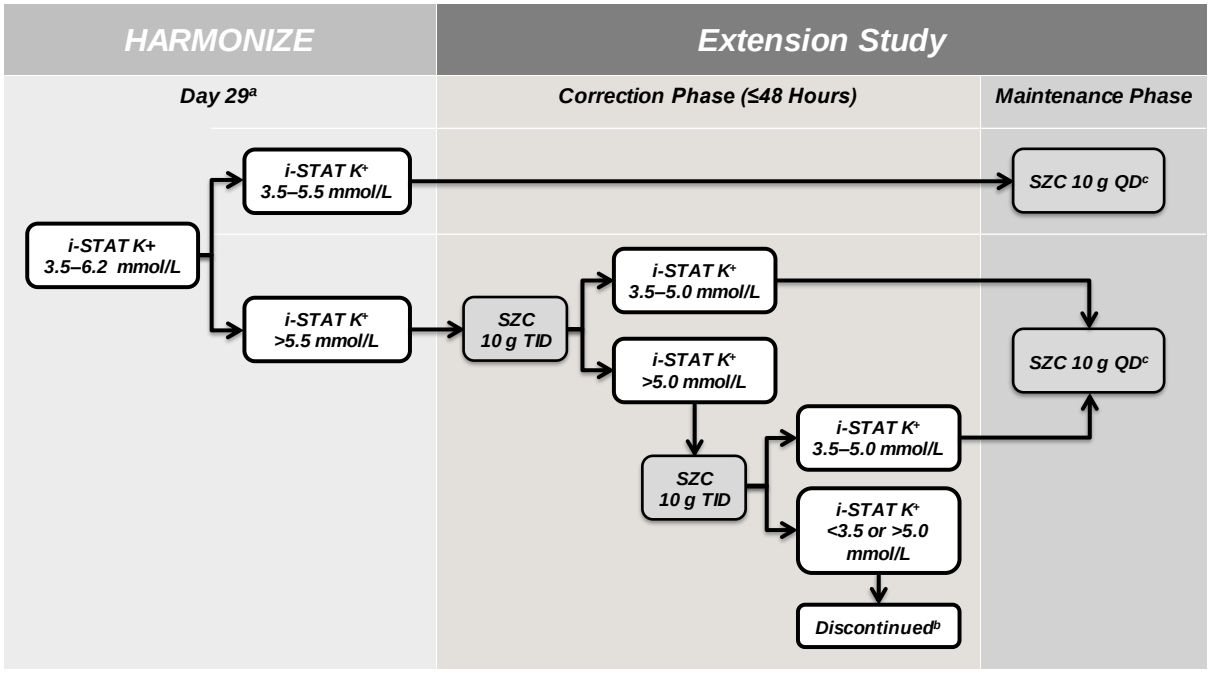
MedDRA preferred term	Extension-MP (*N* = 123)
AEs (≥5% of patients)	82 (66.7)
Constipation	7 (5.7)
Hypertension[b]	15 (12.2)
Peripheral edema	10 (8.1)
Urinary tract infection	11 (8.9)
Serious AEs	24 (19.5)
Abdominal pain	1 (0.8)
Acute myocardial infarction	1 (0.8)
Adenocarcinoma of colon	1 (0.8)
Anemia	1 (0.8)
Cardiac failure	1 (0.8)
Cerebrovascular accident	1 (0.8)
Chest pain	1 (0.8)
Chronic obstructive pulmonary disease	2 (1.6)
Congestive cardiac failure	2 (1.6)
Convulsion	1 (0.8)
Diabetic foot infection	1 (0.8)
Dry gangrene	1 (0.8)
Gangrene	1 (0.8)
Gastritis hemorrhagic	1 (0.8)
Hyperkalemia	1 (0.8)[c]
Lobar pneumonia	1 (0.8)
Localized infection	1 (0.8)
Morganella infection	1 (0.8)
Myocardial infarction	1 (0.8)
Patella fracture	1 (0.8)
Pneumonia	2 (1.6)
Pulmonary edema	1 (0.8)
Retinal artery occlusion	1 (0.8)
Sepsis	1 (0.8)
Tooth abscess	1 (0.8)
Urinary tract infection	2 (1.6)
AEs leading to discontinuation	11 (8.9)
Acute myocardial infarction	1 (0.8)
Blindness unilateral	1 (0.8)

Bundle branch block right	1 (0.8)
Cardiac failure	1 (0.8)
Chronic obstructive pulmonary disease	1 (0.8)
Diabetic foot infection	1 (0.8)
Drug hypersensitivity	1 (0.8)
Electrocardiogram QT interval prolonged	2 (1.6)
Hyperkalemia	1 (0.8)[c]
Localized infection	1 (0.8)

Values are presented as *n* (%).
[a] Extension-MP safety population included all patients who received at least 1 dose of SZC during the Extension-MP and had any post–Extension-CP baseline safety data.
[b] As reported by site with no specific threshold.
[c] Actual serum K^+ value at discontinuation was 7.0 mmol/L.
AE, adverse event; Extension-CP, extension correction phase; Extension-MP, extension maintenance phase; K^+, potassium; MedDRA, Medical Dictionary for Regulatory Activities; SZC, sodium zirconium cyclosilicate.

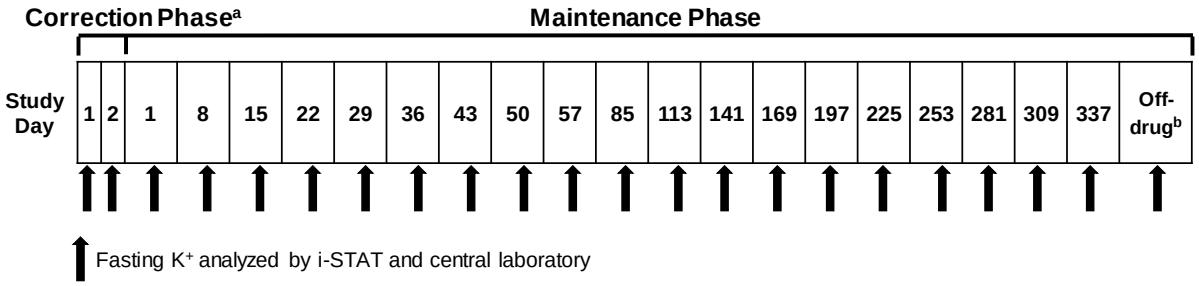
Supplementary Figures

Supplementary Fig. S1. Study design overview. [a]Eligible patients included those who completed the HARMONIZE maintenance phase study day-29 visit and had i-STAT K^+ 3.5–6.2 mmol/L and those who had discontinued HARMONIZE because of hypo- or hyperkalemia and had mean i-STAT K^+ 3.5–6.2 mmol/L from 2 consecutive measurements at 0 and 60 minutes on day 1 of the extension study. [b]Patients who discontinued during the correction phase received standard-of-care treatment at the discretion of their physician and returned to the clinic for the end-of-study visit 7 ± 1 days later. [c]SZC dosing could be increased to 15 g QD in patients whose serum K^+ was not adequately controlled at 10 g QD or decreased to 5 g QD if hypokalemia developed at the 10-g QD dose. K^+, potassium; QD, once daily; SZC, sodium zirconium cyclosilicate; TID, 3 times daily.



Supplementary Fig. S2. (**A**) Clinic visit schedule and (**B**) dose titration algorithm for patients included in the HARMONIZE open-label extension study. [a]Patients 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 11-month maintenance phase and received once-daily treatment with SZC. [b]Off-drug values collected 7 ± 1 days after the last dose of SZC. [c]Product provided as a powder suspension in 180 mL water with 2 × 30-mL rinses. [d]Based on i-STAT K^+ at visit. K^+, potassium; QD, once daily; QoD, once every other day; SZC, sodium zirconium cyclosilicate; TID, 3 times daily.

A

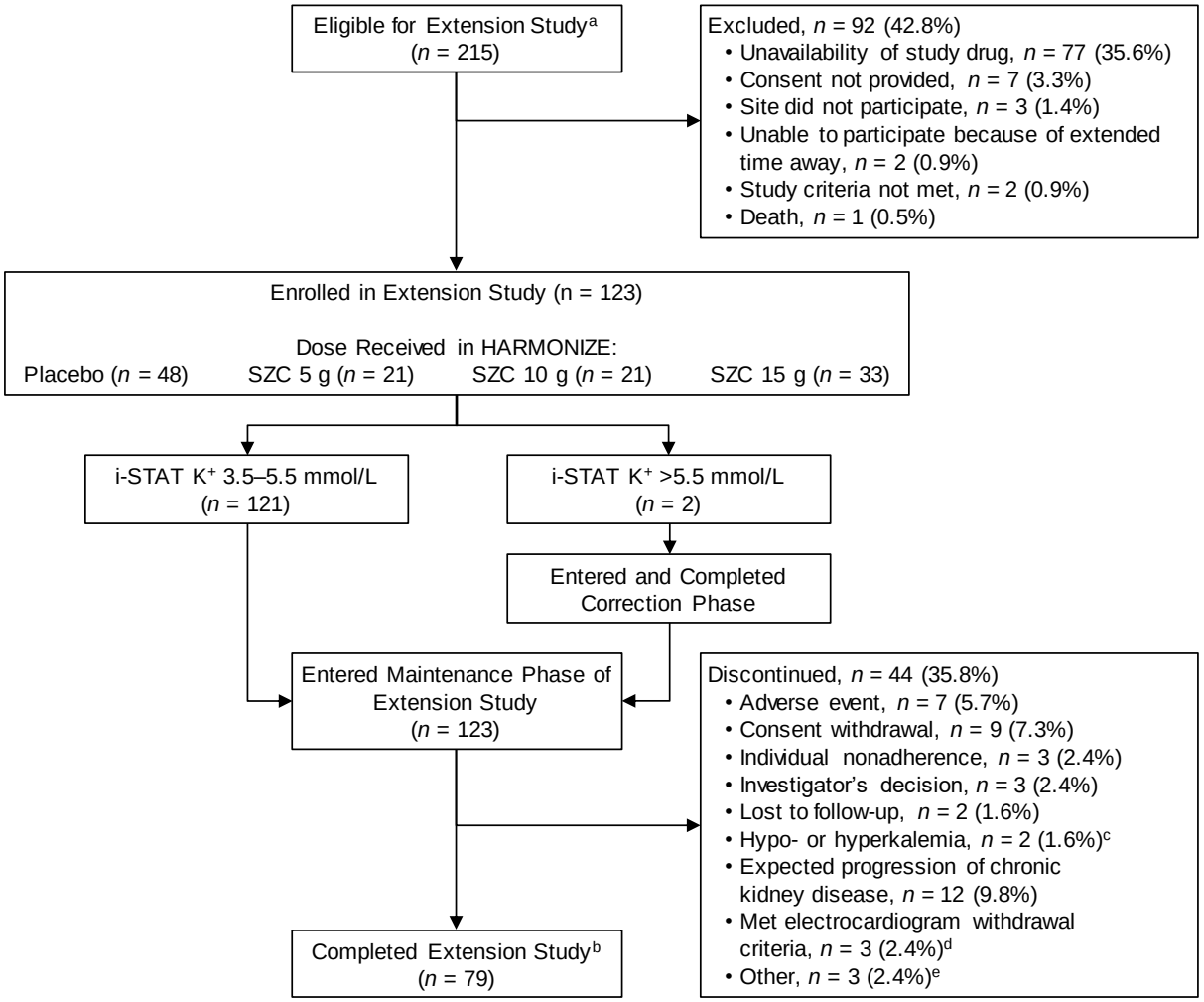


B

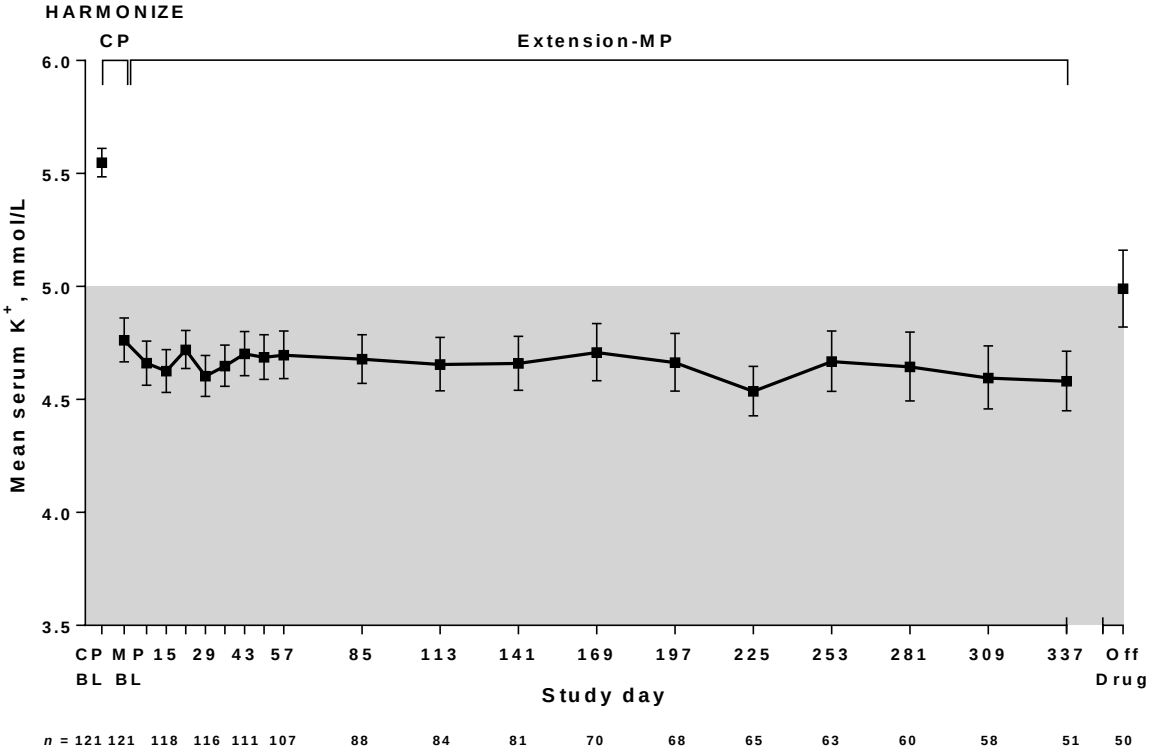
Correction Phase	Maintenance Phase	
	Observed i-STAT K^+, mmol/L[d]	**Dose Modification**
Patients received SZC[c] 10 g TID until i-STAT K^+ 3.5–5.0 mmol/L was achieved[a]	>5.5	Increase in 5-g QD increments up to maximum 15 g QD
	3.5 to 5.5	No change
	3.0 to 3.4	Decrease in 5-g QD decrements to a minimum of 5 g QoD

Treatment was discontinued if patient had K^+ <3.0 at any time during the study, K^+ >7.0 mmol/L during the maintenance phase, or a clinically significant cardiac arrhythmia.

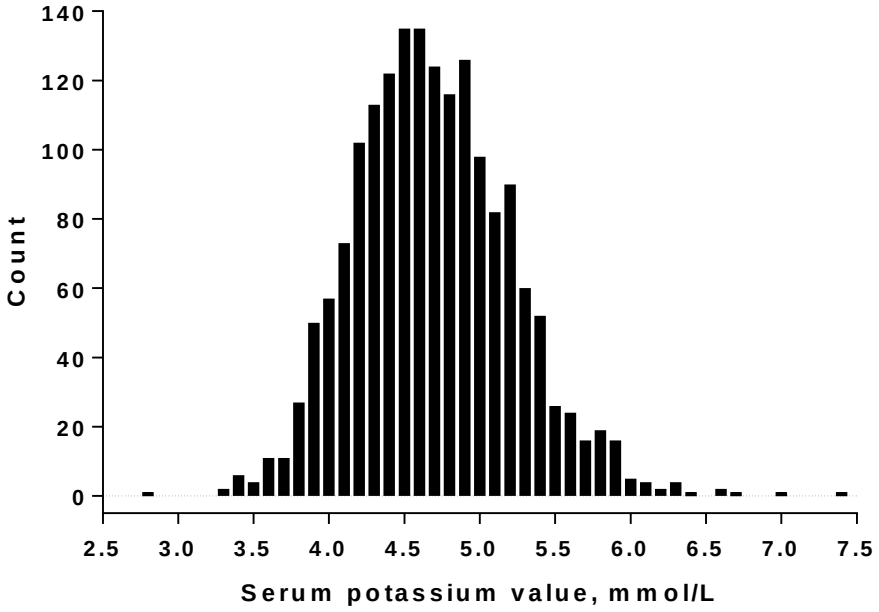
Supplementary Fig. S3. Patient disposition. [a]Eligibility limited to patients who completed HARMONIZE or patients who withdrew from HARMONIZE because of hypo- or hyperkalemia. [b]Duration of the study extended following several protocol amendments; as such, the study includes 15 patients who completed 56 days of dosing under the original protocol, 7 patients who completed 140 days of dosing under a protocol amendment, and 57 patients who completed 336 days of dosing under a subsequent protocol amendment. [c]One patient prematurely discontinued because of hypokalemia (actual value 2.8 mmol/L) and one patient prematurely discontinued because of hyperkalemia (actual value 7.0 mmol/L). [d]Adverse events of prolonged QT interval (*n* = 2) and right bundle branch block (*n* = 1) were recorded. [e]Patients withdrawn because of worsening of edema, use of a K^+ supplement, or investigator error (*n* = 1 each). K^+, potassium; SZC, sodium zirconium cyclosilicate.



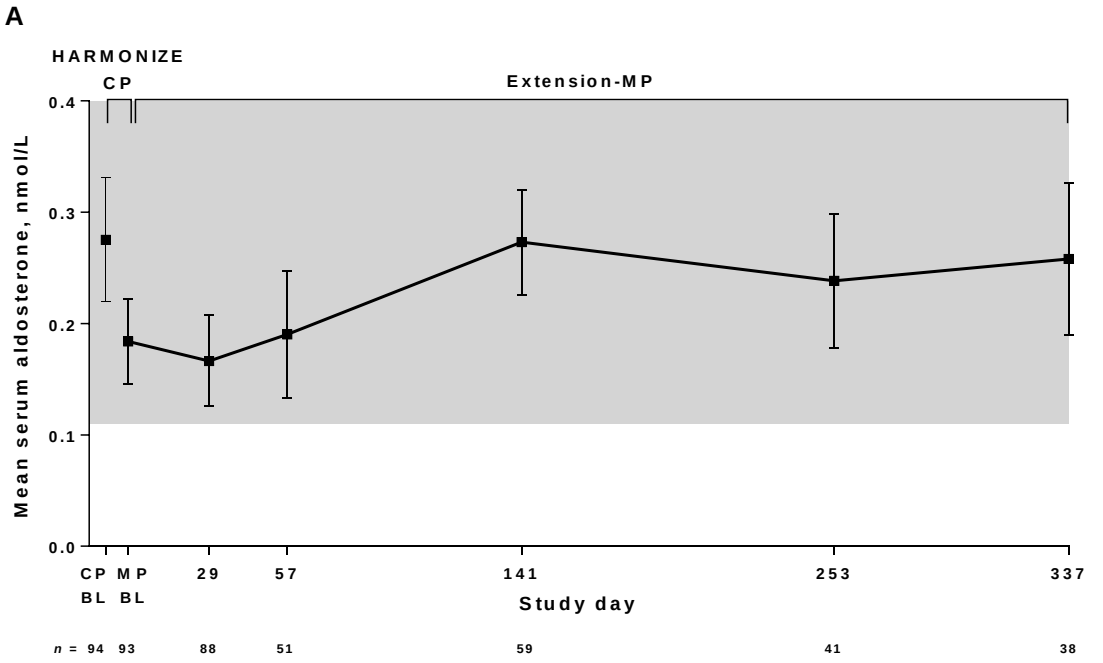
Supplementary Fig. S4. Mean serum K^+ levels with SZC over time in the MP ITT population. Data from all SZC doses were pooled. Off-drug values were recorded at 7 ± 1 days following the last dose of SZC. Error bars represent 95% confidence intervals. Grey shading indicates normokalemic range (3.5–5.0 mmol/L). BL, baseline; CP, correction phase; ITT, intent to treat; K^+, potassium; MP, maintenance phase; SZC, sodium zirconium cyclosilicate.

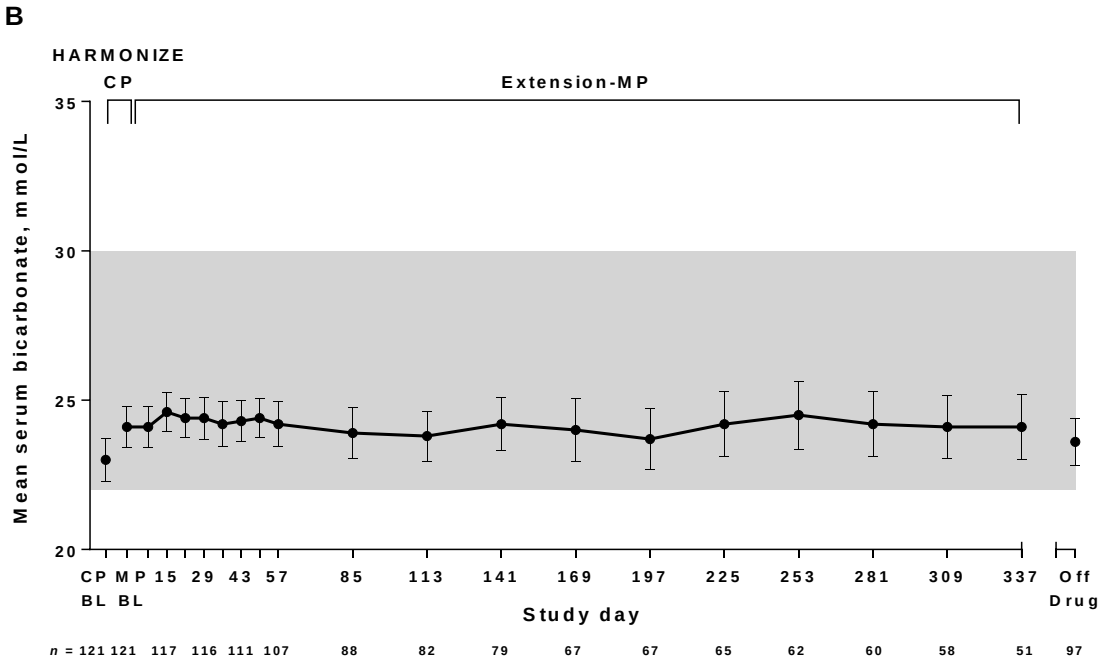


Supplementary Fig. S5. Distribution of serum potassium values from baseline through day 337 in the maintenance phase intent-to-treat population.

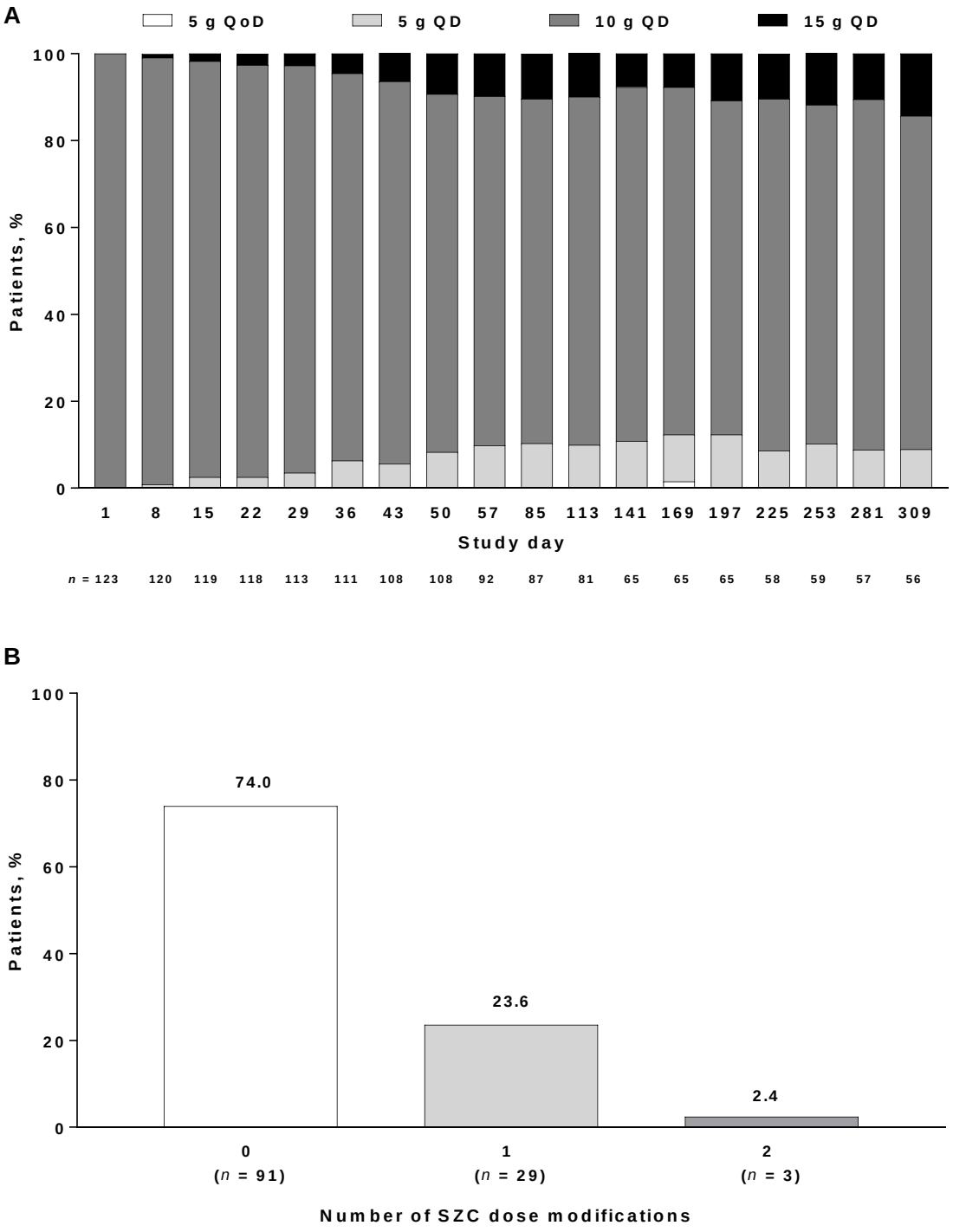


Supplementary Fig. S6. Mean values for (**A**) serum aldosterone and (**B**) serum bicarbonate with SZC over time in the MP ITT population. Data from all SZC doses were pooled. Off-drug values were recorded at 7 ± 1 days following the last dose of SZC. Normal range for serum aldosterone is 0.11–0.86 nmol/L (shown with grey shading). Normal range for serum bicarbonate is 22–30 mmol/L (shown with grey shading). Error bars represent 95% confidence intervals. BL, baseline; CP, correction phase; ITT, intent to treat; MP, maintenance phase; SZC, sodium zirconium cyclosilicate.





Supplementary Fig. S7. (**A**) Distribution of SZC dosing per study visit and (**B**) number of dose modifications (increases or decreases) needed in the Extension-MP safety population. Safety population included all patients who received at least 1 dose of SZC during the maintenance phase and had any post–Extension-CP baseline safety data. At day 337, SZC dosing data were available for only 2 patients; 1 patient was receiving 10 g QD and 1 was receiving 15 g QD. Extension-MP, extension maintenance phase; QD, once daily; QoD, once every other day; SZC, sodium zirconium cyclosilicate.



Supplementary Fig. S8. Mean values for (**A**) weight and (**B**) BP over time with SZC in the safety population. Data from all SZC doses were pooled. Off-drug values were recorded at 7 ± 1 days following the last dose of SZC. Error bars represent 95% confidence intervals. BL, baseline; BP, blood pressure; CP, correction phase; MP, maintenance phase; SZC, sodium zirconium cyclosilicate.