Abbreviated Clinical Study Report Synopsis	
Drug Substance	Sodium Zirconium Cyclosilicate (SZC)
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A Double-blind Randomized Placebo-controlled Parallel Design Multicenter Phase IIIb Study of the Effect of Sodium Zirconium Cyclosilicate (SZC) on Serum Potassium and Serum Bicarbonate in Patients with Hyperkalemia and Metabolic Acidosis Associated with Chronic Kidney Disease (NEUTRALIZE)

Study Dates:
First subject enrolled: 22 March 2021
Last subject last visit: 16 September 2022
Date of early termination decision: 14 September 2022, due to recruitment issues
The analyses presented in this report are based on a clinical data lock date of 13 December 2022.

Phase of Development:
Therapeutic confirmatory (III b)

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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centres

30 sites in the USA.

Publications

Ash SR, Batlle D, Kendrick J, Oluwatosin Y, Pottorf W, Brahmbhatt Y, Guerrieri E, Fried L (2022). Effect of Sodium Zirconium Cyclosilicate on Serum Potassium and Bicarbonate in Patients with Hyperkalemia and Metabolic Acidosis Associated with Chronic Kidney Disease: Rationale and Design of the NEUTRALIZE Study Nephron 2022. doi: 10.1159/000523911.

Objectives and criteria for evaluation

Objectives	Endpoints	Hypotheses
Primary		
• To evaluate the efficacy of SZC as compared to placebo in maintaining normal sK+ in patients with HK and metabolic acidosis associated with CKD	• Occurrence (yes/no) of patients having normal sK+ between 3.5 and 5.0 mmol/L inclusive at EOT without need for rescue treatment for HK at any point during the randomized phase	• Null: No difference in the occurrence of patients having a normal sK+ on Day 29 without need for rescue treatment for HK at any point during the randomized phase between SZC and placebo
Secondary		
• To evaluate the efficacy of SZC as compared to placebo in increasing serum bicarbonate in patients with HK and metabolic acidosis associated with CKD	• Mean change in serum bicarbonate at Day 29 compared to baseline (Day 1) • Occurrence (yes/no) of patients having an increase in serum bicarbonate of ≥3 mmol/L from baseline (Day 1) to EOT (Day 29) without need for rescue treatment for metabolic acidosis (low bicarbonate) • Occurrence (yes/no) of patients having serum bicarbonate ≥22 mmol/L • Occurrence (yes/no) of patients having an increase in serum bicarbonate of ≥2 mmol/L from baseline (Day 1) to EOT without need for rescue treatment for metabolic acidosis (low bicarbonate)	• Null: No difference in mean change in serum bicarbonate from baseline (Day 1) to Day 29 between SZC and placebo • Null: No difference in the occurrence of patients having an increase in serum bicarbonate of ≥2 mmol/L or ≥3 mmol/L from baseline (Day 1) to Day 29 without need for rescue treatment for metabolic acidosis (low bicarbonate) between SZC and placebo
• To evaluate the efficacy of SZC as compared to placebo in normalizing sK+ and increasing serum bicarbonate in patients with HK and metabolic acidosis associated with CKD	• Occurrence (yes/no) of patients having normal sK+ between 3.5 and 5.0 mmol/L inclusive at EOT and an increase in serum bicarbonate of ≥3 mmol/L from baseline (Day 1) without need for rescue treatment for metabolic acidosis (low bicarbonate) or HK	• Null: No difference in the occurrence of patients having NK and an increase in serum bicarbonate of ≥3 mmol/L from baseline (Day 1) to Day 29 or mean serum bicarbonate ≥22 mmol/L at Day 29 without need for rescue treatment for HK or metabolic acidosis (low

Objectives	Endpoints	Hypotheses
	• Occurrence (yes/no) of patients having a normal sK+ between 3.5 and 5.0 mmol/L inclusive and bicarbonate ≥22 mmol/L at Day 29 without need for rescue treatment for HK or metabolic acidosis (low bicarbonate)	bicarbonate) between SZC and placebo
• To describe the need for rescue treatment with sodium bicarbonate for metabolic acidosis (low bicarbonate) in SZC and placebo arms	• Occurrence (yes/no) of patients needing rescue treatment for low sodium bicarbonate any time during the randomized phase	• Null: No difference in the occurrence of patients needing rescue treatment for metabolic acidosis (low bicarbonate) between SZC and placebo
Safety		
• To evaluate the safety and tolerability of SZC as compared to placebo in patients with HK and metabolic acidosis associated with CKD	• Safety and tolerability were evaluated in terms of AEs, vital signs, clinical laboratory assessments, and ECG. Assessments related to AEs cover: – Occurrence/frequency – Relationship to SZC/placebo as assessed by investigator – Intensity – Seriousness – Death – AEs leading to discontinuation of SZC/ placebo	• Not applicable

Exploratory objectives are not reported in this synopsis but can be found in Clinical Study Report body.

Abbreviations: AE = adverse event; CKD = chronic kidney disease; ECG = electrocardiogram; EOT = end of treatment; HK = hyperkalemia; NK = normokalemia; sK+ = serum potassium; SZC = sodium zirconium cyclosilicate.

Study design

NEUTRALIZE was a prospective, randomized, double-blind, placebo-controlled, parallel, multicenter, Phase IIIb study to investigate the safety and efficacy of sodium zirconium cyclosilicate (SZC) in patients with hyperkalemia (HK) and low serum bicarbonate (or metabolic acidosis) associated with chronic kidney disease (CKD).

The study was conducted in the United States (US) at 30 investigative sites.

This study consisted of a short screening visit (Day 1), an open-label correction period (up to 48 hours), 4-week maintenance phase with randomized treatment, and a follow-up period (7 days after the last administration of study medication). The total study treatment duration, consisting of open-label and randomized periods, was 29 days.

Screening was performed using serum potassium (sK+) and bicarbonate values from a study-approved point of care test (POCT) to determine eligibility of consenting patients to enter the open-label correction phase. Patients who met the POCT eligibility criteria of sK+ between 5.1 and 5.9 mmol/L inclusive, and serum bicarbonate between 16 and 20 mmol/L inclusive, were enrolled into the open-label correction phase. All baseline parameters were measured/collected prior to administration of the first dose of investigative product (IP) in the open-label correction phase.

In the open-label correction phase, patients received open-label SZC orally at a dose of 10 g three times daily (TID) for up to 48 hours, depending on normalization of sK+ based on the POCT value.

Patients who achieved normokalemia (NK; potassium [K+] between 3.5 and 5.0 mmol/L inclusive) within 24-48 hours were randomized 1:1 into the 4-week maintenance phase with randomized treatment to receive 10 g SZC or placebo once daily (QD) starting dose for the following 28 (or 27) days. Patients who achieved NK after 24 hours were randomized and did not need to continue on 10 g SZC TID for another 24 hours.

Study treatment ended with the Day 29 visit, which was followed by the follow-up visit (end of study [EOS]), 7 days after the last administration of IP.

Target subject population and sample size

Patients had to be aged ≥18 years with stage 3 to 5 CKD and not on dialysis, with an estimated glomerular filtration rate (eGFR) ≤59 mL/min/m^2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. They had to have POCT K+ level >5 mmol/L to ≤5.9 mmol/L and POCT bicarbonate levels between 16 and 20 mmol/L inclusive prior to the first SZC dose on study Day 1. Patients were excluded if they had cardiac arrhythmias requiring immediate treatment, active or suspected diabetic ketoacidosis, or were on dialysis therapy.

It was planned to screen approximately 477 patients to enrol approximately 148 patients to the open-label phase to achieve 136 randomized.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

SZC:

Open-label correction phase: SZC 10 g TID, orally.

Randomized placebo-controlled maintenance phase: SZC 10 g QD, orally. Dose could be titrated during the first 2 weeks of the randomized phase based on POCT K+.

Manufacturer: CCI [redacted]

SZC matching placebo:

Randomized placebo-controlled maintenance phase: Placebo 10 g QD, orally. Dose could be titrated during the first 2 weeks of the randomized phase based on POCT K+.

Manufacturer: CCI [redacted]

Duration of treatment

Open-label correction phase: up to 48 hours.

Randomized placebo-controlled maintenance phase: approximately 4 weeks.

Statistical methods

The analysis of the primary endpoint was conducted according to the intention-to-treat principle using the full analysis set (FAS). All randomized patients were included in the analyses.

The primary endpoint was a classification of each randomized patient into a responder or a non-responder category (ie, a 0 to 1 type of response), with a patient being a responder if he/she:

1 Was NK (central laboratory sK+ between 3.5 and 5.0 mmol/L inclusive) at the end of treatment (EOT) visit (Day 29)

2 Did not receive any rescue therapy for HK during the randomized maintenance phase.

The occurrence was compared between treatment groups in the FAS using a logistic regression model (excluding non-evaluable responses), including response as the dependent variable and randomized treatment as an independent factor; it was tested using a 2-sided alpha = 0.05. The common odds ratio was derived together with the 2-sided 95% confidence interval (CI).

Three sensitivity analyses were conducted:

- Primary analysis as described above. In addition to randomized treatment, the logistic regression model included POCT type (i-STAT, Piccolo) as other independent factor.
- Primary analysis as described above but conducted in the per protocol set (PPS).
- The intercurrent event strategy altered to describe the treatment effect in a coronavirus disease 2019 (COVID-19) pandemic-free world.

Study population

A total of 229 patients were screened in 30 study sites across the US. Due to a screening failure rate higher than expected (83.0%) which led to early termination of the study, only 39 (17.0%) patients entered the open-label correction phase and received treatment. At the end

of the open-label phase, 37 patients were randomized and received treatment in the 4-week randomized maintenance phase (17 [44.7%] patients in SZC group and 20 [52.6%] patients in the Placebo group).

Details on disposition are given in the table below:

Table S1 Subject Disposition (Screened Set)

	Number(%) of patients		
	SZC	Placebo	Total
Subjects screened[a]			229
Subjects who did not enter open-label (screening failures)			190 (83.0)
Withdrawn from study due to screen failure			186 (81.2)
Withdrawal by subject			2 (0.9)
Other			2 (0.9)
Subjects entered open-label period			39 (17.0)
Subjects entered open-label period and received treatment			39 (100)
Subjects who entered open-label period and did not receive treatment			0
Subjects randomized	18 (46.2)	20 (51.3)	38 (97.4)
Subjects who did not meet randomization criteria	1 (2.6)	0	1 (2.6)
Subjects randomized who received treatment	17 (44.7)	20 (52.6)	37 (97.4)
Subjects randomized who did not receive treatment	1 (2.6)	0	1 (2.6)
Subjects who completed treatment	16 (42.1)	15 (39.5)	31 (81.6)
Subjects who discontinued treatment	1 (2.6)	5 (13.2)	6 (15.8)
Adverse Event	0	2 (5.3)	2 (5.3)
Severe non-compliance to protocol	0	1 (2.6)	1 (2.6)
Other	1 (2.6)	1 (2.6)	2 (5.3)
Missing	0	1 (2.6)	1 (2.6)
Subjects who completed study	16 (42.1)	15 (39.5)	31 (81.6)
Subjects withdrawn from study	1 (2.6)	5 (13.2)	6 (15.8)
Adverse event	0	1 (2.6)	1 (2.6)
Physician decision	0	1 (2.6)	1 (2.6)
Withdrawal by Subject	1 (2.6)	0	1 (2.6)
Death	0	1 (2.6)	1 (2.6)
Other	0	2 (5.3)	2 (5.3)

[a] Informed consent received

[b] The number of patients discontinuing from treatment due to AE is different in Table S1 and S2, the reason being that data displayed in Table S1 were taken from the eCRF disposition pages, eg discontinuation of investigational product, whereas Table S2 displayed data from AE page. Disposition information reported 2 patients discontinuing treatment due to AEs. Whereas AE pages also had a third patient who was listed as 'other - PI discretion and patient safety' in the disposition information.

[c] The number of patients discontinuing from study due to AEs is different in Table S1 and S2, the reason being that data displayed in Table S1 were taken from the eCRF disposition pages, whereas Table S2 displayed data from AE page. One patient listed as having AEs leading to study discontinuation in Table S2 was reported as 'death' in Table S1.

The denominator used for percentages for subjects who were screened or who did not enter the open-label period (and associated reasons) was calculated using the number of screened subjects. The denominator for subjects who entered the open-label period and received treatment, who entered the open-label period and did not receive treatment (and associated reasons), randomized and not randomized (and associated reasons) was calculated using the number of subjects who entered the open-label period. The remaining subject disposition categories used the number of subjects who were randomized for the denominator.

The demographics were representative of the intended study patient population as defined by protocol eligibility criteria and were generally balanced between the 2 randomized treatment groups. Overall, patients had a mean age (standard deviation [SD]) of 63.3 years (14.09). Sixty-seven point six percent of patients were male and 86.5% were White.

In general, the disease characteristics were well balanced across the treatment groups with no clinically meaningful differences between groups.

In the total population, 10.8% of patients had CKD stage 3, 59.5% CKD stage 4, and 18.9% CKD stage 5 (CKD stage being missing for 10.8% of the patients). At baseline, median sK+ levels were 5.40 mmol/L (range: 4.5, 6.0 mmol/L) in the SZC group and 5.50 mmol/L (range: 4.6, 6.1 mmol/L) in the Placebo group. The median serum bicarbonate levels were 16.20 mmol/L (range: 11.7, 18.5 mmol/L) in the SZC group and 16.05 mmol/L (range: 10.7, 20.3 mmol/L) in the Placebo group.

Summary of efficacy results

Note: Due to the early termination of the study and small sample size, the study was underpowered for the secondary endpoints.

During the open-label correction phase, all patients received SZC 10 g TID at Day 1. Of the 39 patients who entered the open-label correction phase, only 2 (5.1%) patients needed SZC 10 g TID beyond the first 24 hours.

The primary endpoint was met. In the FAS, the odds of having sK+ within 3.5 to 5.0 mmol/L at EOT, with no rescue therapy for HK, were 56.2 times higher for patients treated with SZC than for patients treated with placebo ($p = 0.001$). SZC was significantly superior to placebo in maintaining NK after a 4-week treatment, with 88.2% of patients having NK (mean [SD]

sK+ = 4.55 mmol/L [0.397]) in the SZC group vs 20.0% in the Placebo group (mean [SD] sK+ = 5.29 mmol/L [0.352]) at Day 29.

The results of the sensitivity analysis in the PPS were consistent with those of the primary analysis, with odds ratio (95% CI) of 49.0 (4.8, 495.0), p= 0.001 (vs 56.2 [5.6, 563.6], p = 0.001 in the primary analysis) (see Table 14.2.1.2).

The 2 other sensitivity analyses, expanded logistic regression model in FAS and COVID-19 sensitivity in FAS, were also consistent with the primary analysis.

The treatment difference between the SZC group and the Placebo group in terms of serum bicarbonate increase at EOT was of borderline significance (LSmean difference of 1.64 [0.81] with a 95% CI of [-0.00, 3.29], nominal p-value = 0.050). However, no conclusions could be drawn from this result due to the small sample size.

Although odds ratio consistently favored SZC, no statistically significant differences were found for increase in serum bicarbonate (≥2 mmol/L or ≥3 mmol/L) at EOT, without need for rescue therapy for low bicarbonate.

A trend towards a superiority of SZC over placebo was observed for sK+ within 3.5 to 5.0 mmol/L and increase in serum bicarbonate ≥3 mmol/L at EOT, without need for rescue therapy for HK or low bicarbonate but the observed p-value was nominal (p = 0.039).

Only 2 patients in the SZC group had an increase of serum bicarbonate ≥22 mmol/L, leading to uninterpretable results for 2 endpoints (serum bicarbonate ≥22 mmol/L at EOT, no rescue therapy for low bicarbonate and sK+ within 3.5 to 5.0 mmol/L and serum bicarbonate ≥22 mmol/L at EOT, without need for rescue therapy for HK or low bicarbonate).

It should be noted that during the 4-week maintenance phase with randomized treatment, no patients in any group needed rescue treatment for low serum bicarbonate, and 4 patients in the Placebo group required rescue treatment for HK (none in the SZC group).

Summary of safety results

There were no differences in the duration of exposure between the 2 groups during the randomized maintenance phase. All patients in both groups received IPs at 10 g daily at randomization and starting at Visit 4; more patients in the SZC group remained on a 10-g daily dose of IP compared to patients in the Placebo group (88.2% vs 45.0%, respectively, at Visit 4; 70.6% vs 25.0%, respectively, at Visit 5; and 70.6% vs 25.0%, respectively, at Visit 6).

The median duration of total exposure was 29.0 days for each group and the mean average daily dose of IP was 10.5 g for the SZC group and 12.4 g for the Placebo group.

No new safety concerns were identified during the study. A summary of adverse events (AE) by category is presented below:

Table S2 Number of Subjects with Adverse Events in Any Category (SSR)

AE category	Number (%) of subjects[a]	
	SZC (N=17)	Placebo (N=20)
Any AE	4 (23.5)	9 (45.0)
Any AE assessed by investigator as possibly related to treatment	0	2 (10.0)
Any AE with outcome = death	0	0
Any SAE (including events with outcome = death)	1 (5.9)	2 (10.0)
Any AE leading to treatment discontinuation	0	3[b] (15.0)
Any SAE leading to treatment discontinuation	0	1 (5.0)
Any AE leading to dose interruption	0	1 (5.0)
Any AE leading to dose reduction	0	0
Any AEs leading to study discontinuation	0	2[c] (10.0)

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.

[b] The number of patients discontinuing from treatment due to AE is different in Table S1 and S2, the reason being that data displayed in Table S1 were taken from the eCRF disposition pages, eg discontinuation of investigational product, whereas Table S2 displayed data from AE page. Disposition information reported 2 patients discontinuing treatment due to AEs. Whereas AE pages also had a third patient who was listed as 'other - PI discretion and patient safety' in the disposition information.

[c] The number of patients discontinuing from study due to AEs is different in Table S1 and S2, the reason being that data displayed in Table S1 were taken from the eCRF disposition pages, whereas Table S2 displayed data from AE page. One patient listed as having AEs leading to study discontinuation in Table S2 was reported as 'death' in Table S1.

Included adverse events that occurred during the randomized placebo-controlled period and up to 7 days after discontinuation of investigational product. Included treatment emergent adverse events occurring prior to randomized placebo-controlled period which subsequently worsened in severity following dosing in randomized placebo-controlled period.

Percentages were based on the total numbers of subjects in the treatment group.

Abbreviations: AE = adverse event; N = number of subjects in the treatment group; SAE = Serious AE; SZC = sodium zirconium cyclosilicate.

During the randomized maintenance phase, fewer patients in the SZC group had AEs compared to patients in the Placebo group (4 [23.5%] patients with 8 events vs 9 [45.0%] patients with 24 AEs, respectively).

There were 2 (10.0%) patients in the Placebo group with 3 AEs that were judged as possibly related to IP by the investigator.

Only patients from the Placebo group reported AEs leading to treatment discontinuation (3 [15.0%] patients; 4 events), dose interruption (1 [5.0%] patient; one event), or study discontinuation (2 [10.0%] patients; 7 events).

The incidence of edema-related AEs was low for both the SZC and Placebo groups (one patient [5.9%] and 2 patients [10.0%], respectively). The edema-related AEs reported in the general disorders and administration site conditions system organ class (SOC) were all mild in intensity and not assessed as being related to IP by the investigator. One event of moderate hypervolemia in the Placebo group was judged as being related to the IP by the investigator and was a serious AE (SAE).

Serious AEs were reported by one patient (5.9%) in the SZC group (hypertension) and 2 (10.0%) patients in the Placebo group (acute kidney injury and hypervolemia). One patient in the Placebo group had an SAE of hypervolemia that was considered possibly related to IP by the investigator.

No death occurred during the study period, ie, before or at the follow-up visit at Day 36 (±3 days). One investigator reported the death of a patient which happened outside of the predefined observation period.

Low sK+ level (one laboratory measurement of sK+ <3.5 mmol/L) occurred in one patient in the Placebo group, but the investigator did not report an AE of hypokalemia.

Conclusions

- SZC was highly effective at reducing sK+ values in subjects with HK and maintaining NK for up to 4 weeks, consistent with previous findings.
- In this study population (patients with stage 3 to 5 CKD not on dialysis, HK, and metabolic acidosis), the study met its primary endpoint demonstrating reduction in sK+ levels in a greater proportion of patients for SZC compared to placebo (p = 0.001).
- A trend towards increased serum bicarbonate at EOT was observed for SZC compared to placebo but no conclusions could be drawn from these results due to the small sample size of the study:
  - the treatment difference between the SZC group and the Placebo group in terms of serum bicarbonate increase at EOT was of borderline significance.
  - odds ratios consistently favored SZC for increase in serum bicarbonate (≥2 mmol/L or ≥3 mmol/L) at EOT, but no statistically significant differences were found.
  - a trend towards a superiority of SZC over placebo was observed for sK+ within 3.5 to 5.0 mmol/L and increase in serum bicarbonate ≥3 mmol/L at EOT, but the observed p-value was nominal.
- SZC was well tolerated and the incidence of SAEs was low. During the randomized maintenance phase, no SAEs or AEs in the SZC group were considered causally related. There were no AEs or SAE leading to treatment discontinuation in the SZC group. The incidence of edema-related AEs was low for both the SZC and Placebo groups and the only patient having occurrence of abnormally low sK+ levels was in the Placebo group. The safety profile of SZC was consistent with the known safety profile of Lokelma.