The randomized DIALIZE-Outcomes trial evaluated sodium zirconium cyclosilicate in hemodialysis

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Abstract

Introduction: Patients receiving maintenance hemodialysis frequently experience predialysis hyperkalemia, with associated arrhythmias and cardiovascular events. The DIALIZE-Outcomes trial evaluated the effect of sodium zirconium cyclosilicate (SZC) on arrhythmia-related cardiovascular outcomes.

Methods: Adults receiving thrice-weekly hemodialysis with predialysis hyperkalemia (serum potassium was 5.5 mmol/l or more) were randomized 1:1 to SZC (5 g once daily on nondialysis days, then titrated weekly over 4 weeks between 0 and 15 grams to attain normokalemia [serum potassium 4.0–5.0 mmol/l]) or placebo. The primary outcome was a composite end point of sudden cardiac death, stroke, or arrhythmia-related hospitalization, intervention, or emergency department visit. Secondary end points included individual cardiovascular outcomes from the primary composite end point, and those reflecting serum potassium control. Safety was evaluated throughout.

Results: Overall, 2690 participants were randomized. The trial was terminated early due to low event rates (~33% of planned) and high study medication discontinuation rates, limiting generalizability of the results. No treatment effect was observed on the primary composite end point (SZC, 8.8% [119 patients] vs. placebo, 8.9% [119 patients]; hazard ratio 0.98; 95% confidence interval 0.76–1.26) or individual cardiovascular outcomes. Maintenance of normokalemia at 12 months was significantly better with SZC than placebo (74.0% [495 patients] vs. 47.0% [293 patients]; odds ratio 3.36; 95% confidence interval 2.64–4.26). Serious adverse events occurred in 38.6% (SZC) and 37.6% (placebo) of participants; hypokalemia occurred in 3.0% (SZC) and 1.4% (placebo).

Conclusions: SZC did not demonstrate a treatment effect on arrhythmia-related cardiovascular outcomes despite efficacy on serum potassium control.

Trial Registration: Registered at ClinicalTrials.gov with study number NCT04847232.

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Patients with kidney failure have severely reduced potassium (K^+) excretion. Hemodialysis is the most common treatment for kidney failure, but despite thrice-weekly hemodialysis, patients still commonly experience predialysis hyperkalemia.[1] Additionally, serum potassium (sK^+) levels often decrease rapidly during hemodialysis sessions.[1] These sK^+ shifts are associated with cardiac arrhythmias, sudden cardiac death (SCD), and elevated risks of cardiovascular-related mortality and all-cause mortality,[2,3] particularly after the long interdialytic interval.[2,3] The time between hemodialysis sessions may also play a role as this may affect the degree of K^+ fluctuation. However, studies have observed conflicting reports, with some observing increased cardiac deaths at the end of the long interdialytic interval when compared with noncardiac deaths in patients receiving thrice-weekly hemodialysis,[4] whereas others have observed no difference.[5]

To address these potentially serious outcomes, recent guidelines for the management of chronic kidney disease suggest to consider the use of newer K^+ binders, such as sodium zirconium cyclosilicate (SZC), in patients who develop hyperkalemia while receiving treatment for chronic kidney disease.[6] SZC is indicated for hyperkalemia correction

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Lay Summary

People with kidney failure who undergo regular hemodialysis can experience both high and low blood potassium (K^+) concentrations, which may cause sudden death and heart rhythm disorders. In the DIALIZE-Outcomes (Effect of sodium zirconium cyclosilicate on arrythmia-related cardiovascular outcomes in participants on chronic hemodialysis with recurrent hyperkalemia) trial, adults with kidney failure receiving hemodialysis with predialysis high blood K^+ concentrations were randomly assigned to receive the K^+ binder sodium zirconium cyclosilicate (SZC) or placebo. The primary outcome was the composite end point of sudden cardiac death, stroke, or heart rhythm disorder–related hospitalization, intervention, or emergency department visit with SZC versus placebo. There were 2690 participants in the trial. The trial was terminated early because of low events (approximately one-third of planned) and high treatment discontinuation. An effect of SZC versus placebo on the primary end point was not evident. K^+ control was better with SZC than placebo. Adverse events were similar between treatment groups, most of which were mild or moderate in intensity.

in adults in the United States and the European Union, and effectively restores and maintains normokalemia in nondialysis patients with chronic kidney disease and/or heart failure experiencing hyperkalemia.[7–12] More recently, 2 phase 3b studies ("DIALIZE") of global and Chinese populations demonstrated that SZC could restore and maintain normokalemia in participants with kidney failure receiving chronic hemodialysis who had predialysis hyperkalemia.[13,14]

Here, we report findings from the phase 3b DIALIZE-Outcomes (Effect of sodium zirconium cyclosilicate on arrythmia-related cardiovascular outcomes in participants on chronic hemodialysis with recurrent hyperkalemia, ClinicalTrials.gov identifier: NCT04847232)[15] trial, which evaluated the treatment effect of SZC on arrhythmia-related cardiovascular outcomes in participants with kidney failure receiving chronic hemodialysis who had predialysis hyperkalemia.

METHODS

The protocol for the DIALIZE-Outcomes trial has been reported previously.[16]

Trial design

DIALIZE-Outcomes was an international, multicenter, randomized, double-blind, placebo-controlled, phase 3, event-driven trial conducted at 344 sites across 26 countries between April 30, 2021, and March 7, 2024 (ClinicalTrials.gov identifier: NCT04847232). The trial conduct adhered to the Declaration of Helsinki and the International Council for Harmonisation and Good Clinical Practice. The informed consent form, protocol, and protocol amendments were approved by an independent ethics committee or institutional review board at each site before trial initiation. All participants provided written informed consent.

The trial included a 2- to 6-week screening phase and a treatment phase that was planned to last until the required number of events was accrued. During the treatment phase, participants were randomized 1:1 to receive SZC (5 g) or placebo orally on nondialysis days. During dose titration, the doses of SZC and placebo were titrated weekly over 4 weeks between 0 and 15 g to attain normokalemia, defined as a predialysis sK^+ concentration of 4.0 to 5.0 mmol/l after the long interdialytic interval. This individualized dosing is supported by a recent expert consensus on the use of K^+ binders for the management of hyperkalemia in chronic kidney disease.[17] Additional information regarding assessments is detailed in the Supplementary Appendix.

Study population

Eligible patients were adults (aged ≥18 years) with kidney failure who had been receiving hemodialysis (or hemodiafiltration) 3 times weekly for at least 4 months before enrollment, with recurrent hyperkalemia (at least 2 of 3 predialysis sK^+ concentrations ≥5.5 mmol/l after the long interdialytic interval during screening). Patients with cardiac arrhythmias, conduction defects, or atrial fibrillation requiring immediate treatment, a pacemaker, or implantable cardiac defibrillator, a history of QT prolongation requiring discontinuation of an associated medication, or receiving treatment with a K^+ binder within 7 days before screening were excluded. Patients with pacemakers were excluded, as these can alter or correct the rhythm of the heart, which may hinder detection of arrhythmia events.[18]

Efficacy and safety end points

The primary objective was to evaluate the treatment effect of SZC versus placebo on the composite end point of time to the first occurrence of any of the 3 types of events: SCD, stroke, or arrhythmia-related hospitalization; intervention; or emergency department visit due to arrhythmias (defined as atrial fibrillation, bradycardia, asystole, and ventricular tachyarrhythmia such as, but not limited to, ventricular fibrillation or ventricular tachycardia).

Secondary objectives included the evaluation of treatment effect on the following individual cardiovascular components of the primary end point: time to SCD; time to first occurrence of stroke; and time to first occurrence of hospitalization, intervention, or emergency department visit due to arrhythmias. Additional secondary objectives were the evaluation of treatment effect on the following end points: number of hospitalizations, interventions, or emergency department visits due to arrhythmias; time to cardiovascular-related death; time to death due to any cause; proportion of participants maintaining normokalemia (sK^+ 4.0–5.5 mmol/l) after the long interdialytic interval at the 12-month visit; time to first use of rescue therapy to control severe hyperkalemia (guided by local clinical practice); and proportion of participants with severe hyperkalemia after the long

interdialytic interval at the 12-month visit. In the setting of an adverse event (AE) of severe hyperkalemia, rescue therapy for controlling hyperkalemia was defined as any short-term (24–48 hour) therapeutic intervention during the study, which was considered necessary per the investigator's judgment and in accordance with local practice patterns to reduce sK^+. Safety and tolerability were evaluated on the basis of AEs, laboratory assessments, interdialytic weight gain (IDWG), and events of predialysis hypokalemia. Safety evaluation results are presented as the number/proportion of participants with the respective AE, and only the first event in each participant was counted.

Statistical analysis

Sample size determination. For the primary outcome, assuming a true hazard ratio (HR) for SZC versus placebo of 0.8, it was determined that 730 events would provide ∼85% power to detect statistically significant differences at an overall 2-sided significance level of 5% (which included testing for efficacy at the interim analysis using a 2-sided significance level of 1.64% or at the final analysis using a 2-sided significance level of 4.46%). Assuming the event rate of the primary composite end point was ∼0.11 per person-year in the placebo group, it was expected that ∼2800 participants would need to be randomized. Assuming a screen failure rate of 50%, the targeted enrollment was ∼5600 participants to ensure that ∼2800 participants were randomized.

To control the familywise type I error rate, a fixed sequence multiple testing procedure for primary and secondary end points was to be performed. If the null hypothesis concerning the primary efficacy end point was rejected, the hypotheses for the secondary efficacy end points were to be tested in a predefined order with the same α level as the primary end point. Because the trial was terminated early, the planned interim analysis for efficacy was not performed. The primary efficacy end point was tested at the 5% 2-sided significance level. Additional analytical methods are detailed in the Supplementary Appendix.

RESULTS

Disposition and baseline characteristics

In total, 4704 patients were screened, 2014 of whom were excluded (Supplementary Figure S1). Overall, 1349 participants were randomized to receive SZC and 1341 to receive placebo. All randomized participants except 1 in the SZC group and 3 in the placebo group received ≥1 dose of trial medication (≥99.8%). Because of the early termination of the trial by the sponsor, none of the participants completed the full trial follow-up. Mean durations of exposure were 12.4 and 11.3 months for the SZC group and the placebo group, respectively.

Baseline characteristics were generally balanced between the groups (Table 1). Overall, mean (SD) age was 56.1 (13.4) years, mean (SD) predialysis weight was 75.3 (19.8) kg, 62.3% of participants were male, and most were White (50.6%) or Asian (29.0%). Predialysis sK^+ levels at baseline were comparable between groups, and the overall mean (SD) was 6.0 (0.7) mmol/l. Other dialysis parameters were also comparable between the groups; mean (SD) dialysis adequacy was 1.5 (0.4) spKt/V and IDWG was 2.5 (2.1) kg. Nearly all participants had hypertension, approximately one-third had dyslipidemia, and approximately one-third had type 2 diabetes. During treatment, median (quartile 1–quartile 3) adherence in the SZC group was high (100.0% [95.3%–103.8%]), with most participants (77.0%) having 80%–>100% compliance.

The decision was made to terminate the study (November 30, 2023) because of low event rates and high treatment discontinuation rates. At that time, approximately one-third of planned primary events had been accrued. The main reasons for discontinuing study treatment before the study termination in the SZC and placebo groups were participant decision (8.7% vs. 14.5%), development of specific discontinuation criteria of renal transplant (4.3% vs. 4.6%), and AEs (4.2% vs. 6.5%; Supplementary Figure S1).

Primary efficacy end point

Kaplan-Meier analysis of the time to first occurrence of an event in the primary composite end point showed no clear separation between the curves for SZC and placebo (Figure 1), and the event rate for the primary composite end point was similar between the SZC and placebo groups (8.8% [n = 119 events] vs. 8.9% [n = 119 events]; HR, 0.98; 95% confidence interval [CI], 0.76–1.26; $P = 0.867$).

Sensitivity analysis for primary composite outcome

As of November 30, 2023, ∼30.4% and ∼38.6% of SZC and placebo participants, respectively, had discontinued treatment. Given that a large proportion of randomized participants discontinued treatment during the study, a sensitivity analysis of while-on-treatment data was conducted to assess the impact of treatment discontinuations on the primary end point results. In the sensitivity analysis, primary composite events that occurred after treatment discontinuation were excluded. Numerically, the event rate was higher in the SZC group versus the placebo group (7.8% [n = 105] vs. 6.3% [n = 85]; HR, 1.12; 95% CI, 0.84–1.49; $P = 0.429$), although the difference was not statistically significant. The overall conclusions were consistent with those of the primary analysis.

Secondary efficacy end points

Analysis of the time to SCD and time to first occurrence of stroke showed no significant differences between SZC and placebo. Similar percentage of participants in the SZC group compared with the placebo group had an event of SCD (2.5% [n = 34 participants] vs. 2.6% [n = 35 participants]; HR, 0.95; 95% CI, 0.59–1.53; $P = 0.837$) or a first occurrence of all stroke (2.0% [n = 27 participants] vs. 2.1% [n = 28 participants]; HR, 0.95; 95% CI, 0.56–1.61; $P = 0.839$).

Analysis of time to first hospitalization, intervention, or emergency department visit due to arrhythmias showed a numerical difference in favor of placebo. This was not statistically significant (SZC group 5.5% [n = 74 participants

Table 1 | Baseline demographics and clinical characteristics

Characteristic	SZC (n = 1349)	Placebo (n = 1341)	Overall (n = 2690)
Age, yr, mean (SD)	55.8 (13.3)	56.3 (13.6)	56.1 (13.4)
18–50	442 (32.8)	441 (32.9)	883 (32.8)
51–64	526 (39.0)	509 (38.0)	1035 (38.5)
65–84	373 (27.7)	378 (28.2)	751 (27.9)
≥85	8 (0.6)	13 (1.0)	21 (0.8)
Sex, n (%)			
Male	851 (63.1)	824 (61.4)	1675 (62.3)
Race, n (%)			
White	688 (51.0)	672 (50.1)	1360 (50.6)
Asian	392 (29.1)	389 (29.0)	781 (29.0)
Black or African American	121 (9.0)	130 (9.7)	251 (9.3)
Hispanic or Latino, n (%)			
Yes	357 (26.5)	354 (26.4)	711 (26.4)
Height, cm, mean (SD)	166.9 (10.3)	167.0 (10.1)	166.9 (10.2)
Weight, kg, mean (SD)			
Predialysis	75.4 (19.7)	75.1 (19.8)	75.3 (19.8)
Postdialysis	72.7 (19.2)	72.5 (19.6)	72.6 (19.4)
IDWG, kg, mean (SD)	2.6 (2.1)	2.5 (2.0)	2.5 (2.1)
BMI, kg/m^2, mean (SD)			
Predialysis	27.1 (9.0)	26.8 (6.1)	26.9 (7.7)
Postdialysis	26.1 (8.7)	25.9 (6.1)	26.0 (7.5)
Dialysis adequacy, spKt/V, mean (SD)	1.5 (0.4)	1.5 (0.5)	1.5 (0.4)
Dialysis vintage, yr, mean (SD)	6.0 (5.4)	5.8 (5.2)	5.9 (5.3)
Predialysis SBP, mm Hg, mean (SD)	145.7 (22.2)	145.7 (21.8)	145.7 (22.0)
Predialysis DBP, mm Hg, mean (SD)	80.5 (12.9)	80.1 (13.5)	80.3 (13.2)
Predialysis sK^+, mmol/l, mean (SD)	6.0 (0.7)	6.0 (0.7)	6.0 (0.7)
Hemodialysis access type, n (%)			
Arteriovenous fistula	1046 (77.5)	1015 (75.7)	2061 (76.6)
Arteriovenous fistula/arteriovenous graft	1 (0.1)	1 (0.1)	2 (0.1)
Arteriovenous fistula/tunneled catheter	0	1 (0.1)	1 (<0.1)
Arteriovenous graft	49 (3.6)	59 (4.4)	108 (4.0)
Tunneled catheter	243 (18.0)	252 (18.8)	495 (18.4)
Other	10 (0.7)	12 (0.9)	22 (0.8)
Medical history, %			
Hypertension	93.4	94.3	93.9
Hyperkalemia	75.6	74.2	74.9
Dyslipidemia	36.2	37.1	36.7
Type 2 diabetes	34.0	34.8	34.4
Coronary artery disease	16.1	15.5	15.8
Cardiac failure	14.8	15.7	15.2
Peripheral neuropathy	11.3	12.5	11.9

BMI, body mass index; DBP, diastolic blood pressure; IDWG, interdialytic weight gain; SBP, systolic blood pressure; sK^+, serum potassium; SZC, sodium zirconium cyclosilicate.

with events] vs. placebo group 4.8% [n = 65 participants with events]; HR, 1.12; 95% CI, 0.80–1.56; $P = 0.510$).

The rate of hospitalizations, interventions, or emergency department visits due to arrhythmias was similar in the SZC group compared with the placebo group (0.07 vs. 0.07 per person-year; rate ratio, 0.96; 95% CI, 0.64–1.45; $P = 0.858$). Kaplan-Meier analyses of the time to cardiovascular-related death (Figure 2a) and time to death due to any cause (Figure 2b) showed no clear separation between the curves for SZC and placebo. The proportion of participants with an event was similar in the SZC group compared with the placebo group for the end points of time to cardiovascular death (4.5% [n = 61 participants] vs. 4.5% [n = 60 participants]; HR, 1.00; 95% CI, 0.70–1.42; $P = 0.986$) and time to death due to any cause (8.8% [n = 119 participants] vs. 8.2% [n = 110 participants]; HR, 1.06; 95% CI, 0.82–1.38; $P = 0.647$).

Compared with the placebo group, a significantly higher proportion of participants in the SZC group had maintained normokalemia (74.0% [n = 495 participants] vs. 47.0% [n = 293 participants]; odds ratio, 3.36; 95% CI, 2.64–4.26; $P < 0.0001$) and a significantly lower proportion had an event of

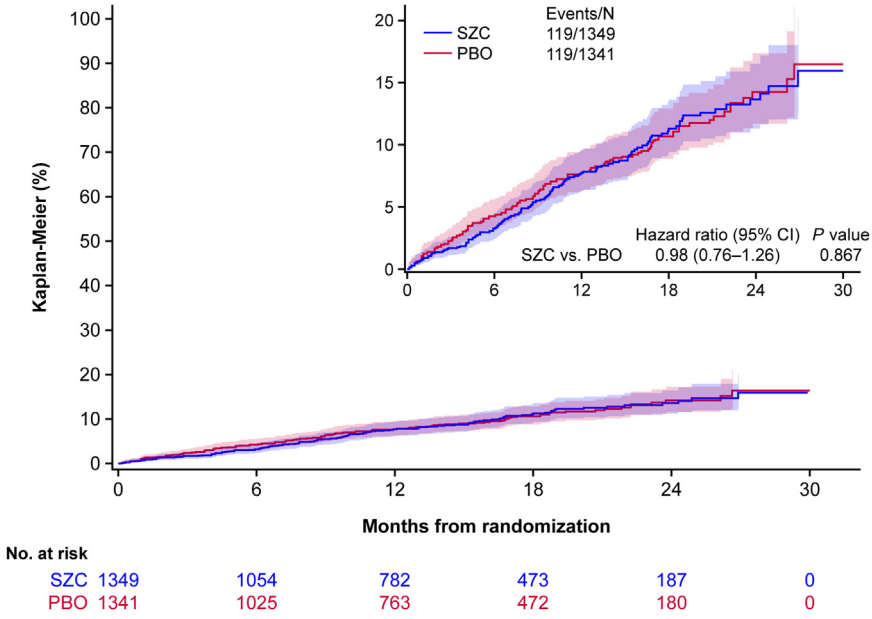

Figure 1 | Kaplan-Meier analysis of the primary composite end point. Participants with no observed events were censored at death, provided the cause of death is not a component of the end point in question, or alternatively if death does not occur, at the earliest of either final clinical assessment date or disposition event. A disposition event corresponds to withdrawal of consent, lost to follow-up, or other unspecified disposition event. The analysis was performed using a Cox regression model with treatment and region as covariates. A hazard ratio of <1 favors sodium zirconium cyclosilicate (SZC). CI, confidence interval; PBO, placebo.

severe hyperkalemia (4.0% [n = 27 participants] vs. 10.4% [n = 65 participants]; odds ratio, 0.35; 95% CI, 0.22–0.56; $P < 0.0001$), after the long interdialytic interval at the 12-month visit. Kaplan-Meier analysis of the time to first use of rescue therapy for hyperkalemia showed early and prolonged separation of the curves for SZC and placebo (Figure 3), and a significantly lower proportion of participants in the SZC group compared with the placebo group required use of rescue therapy for hyperkalemia (guided by local clinical practice patterns) (8.7% [n = 117 participants] vs. 20.4% [n = 273 participants]; HR, 0.39; 95% CI, 0.31–0.48; $P < 0.001$).

Safety

AEs are summarized in Table 2. Overall, 951 (70.5%) participants in the SZC group and 943 (70.5%) in the placebo group experienced an AE, most of which were mild or moderate in intensity. In the SZC group, the mean duration of exposure (excluding interruptions) on 5-, 10-, and 15-g doses was 2.9, 4.6, and 8.4 months, respectively. The most common AEs were coronavirus disease 2019 (COVID-19) (12.0% in the SZC group and 10.2% in the placebo group) and hyperkalemia (10.3% in the SZC group and 22.6% in the placebo group). Severe hyperkalemia requiring rescue therapy (defined as short-term [24–28 hour] therapy to treat an AE of severe hyperkalemia) occurred in 122 (9.1%) participants in the SZC group and 279 (20.9%) in the placebo group. Edema-related AEs occurred in 64 (4.7%) participants in the SZC group and 61 (4.6%) in the placebo group, the most common of which in both groups was hypervolemia. Serious AEs occurred in 521 (38.6%) participants in the SZC group and 503 (37.6%) in the placebo group. The most common serious AEs were pneumonia in the SZC group (4.5%) and in the placebo group (4.5%). Fifteen (1.1%) serious AEs in the SZC group and 8 (0.6%) in the placebo group were considered by the investigator to be related to trial intervention. Serious AEs leading to death occurred in 120 (8.9%) participants in the SZC group and 113 (8.4%) in the placebo group. AEs leading to treatment discontinuation occurred in 59 (4.4%) participants in the SZC group and 95 (7.1%) in the placebo group. Forty (3.0%) participants in the SZC group and 19 (1.4%) in the placebo group experienced hypokalemia; 1 event of hypokalemia in the placebo group was severe.

There were few notable differences in treatment-emergent changes in laboratory values. Mean sK^+ in both treatment groups at baseline and visit 8 are shown in Supplementary Table S1. There was a small increase observed in mean bicarbonate in the SZC group from baseline to visit 8 of 17.9 to 18.8 mmol/l compared with no change in the placebo group (overall duration of study mean change from baseline of 0.8 mmol/l vs. 0.1 mmol/l in the placebo group); this is a known effect of SZC, and no clinically meaningful differences in this parameter were observed over time. Similarly, no clinically meaningful differences between the groups were observed over time with respect to IDWG (Supplementary Table S2).

DISCUSSION

SZC is a K^+ binder that demonstrated efficacy for the restoration and maintenance of normokalemia in the phase 3b DIALIZE trial of patients with kidney failure receiving chronic hemodialysis who had predialysis hyperkalemia.[13]

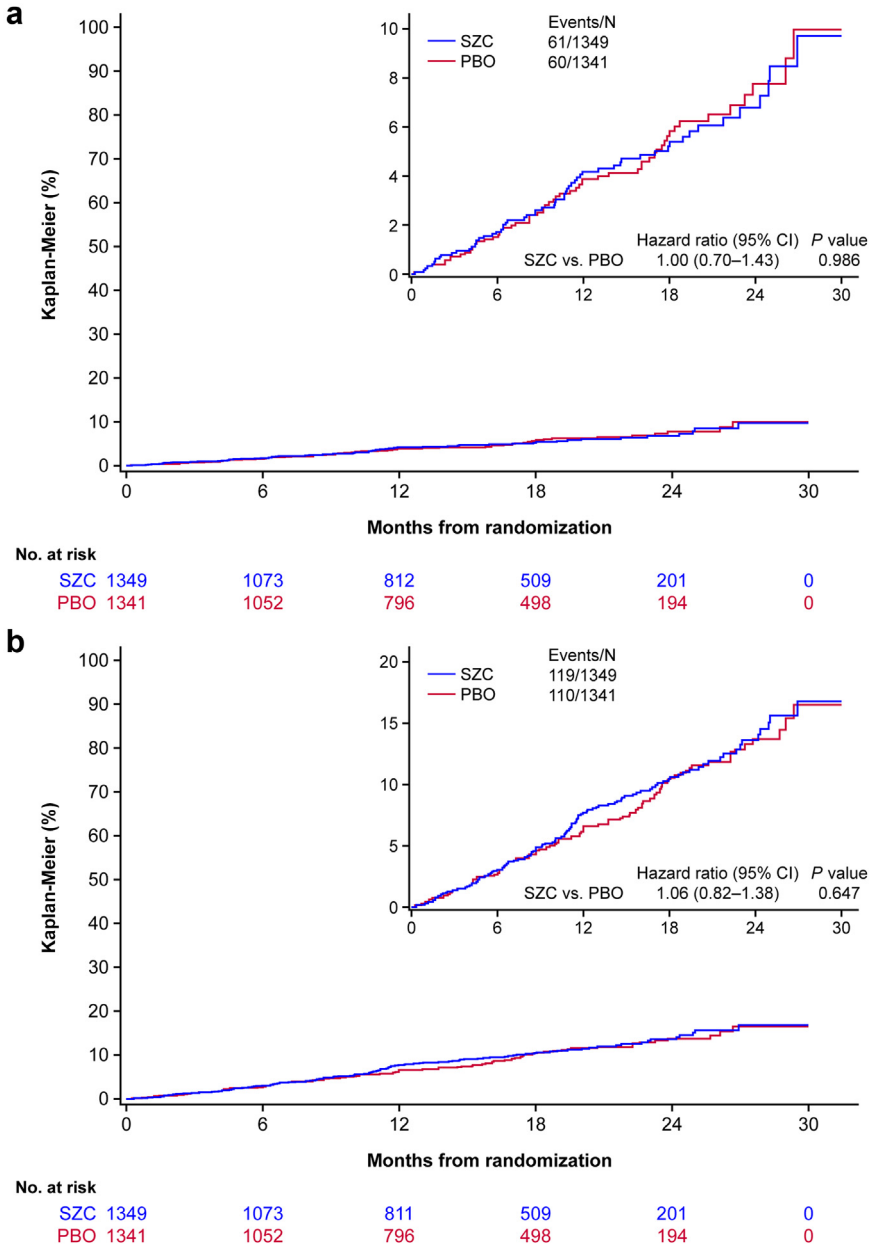

Figure 2 | Kaplan-Meier analysis of (a) time to cardiovascular-related death and (b) time to death due to any cause. CI, confidence interval; PBO, placebo; SZC, sodium zirconium cyclosilicate.

However, that trial was not powered to evaluate clinical outcomes. Given the increasing evidence base for an association between hyperkalemia and cardiovascular events among patients receiving hemodialysis, the DIALIZE-Outcomes trial sought to evaluate the treatment effect of SZC on arrhythmia-related cardiovascular outcomes in this population. The strengths of this trial include the 4-week dose titration period, during which the SZC dose could be adjusted weekly on the basis of measured sK^+, and pragmatic study design.

The trial was terminated early for reasons unrelated to efficacy or safety. Lower-than-expected event rates and high treatment discontinuation rates contributed to the early termination.

The current trial did not meet its primary efficacy end point of reducing the incidence of SCD, stroke, or arrhythmia-related hospitalization, intervention, or emergency department visits. Differences between the SZC and placebo groups with respect to this composite end point were small and did not reach statistical significance. Because the primary end point was nonsignificant, all secondary end points were also considered nonsignificant based on the multiple testing hierarchy. However, the nominal analysis results show that SZC was effective in controlling sK^+ as expected, and rescue therapy for hyperkalemia was used less frequently in the SZC versus placebo group. It is plausible that the high proportion of patients with limited health

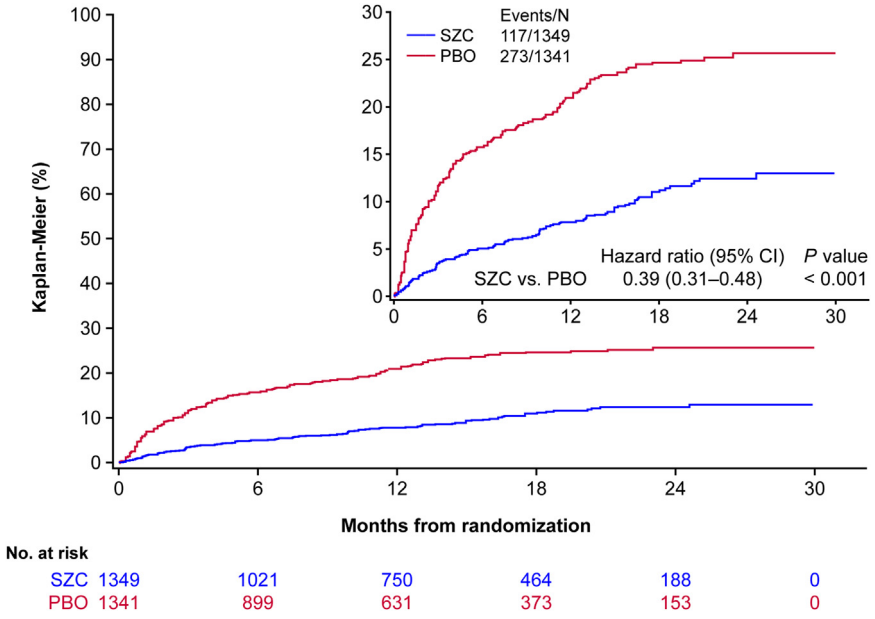

Figure 3 | Kaplan-Meier analysis of time to first use of rescue therapy for hyperkalemia. CI, confidence interval; PBO, placebo; SZC, sodium zirconium cyclosilicate.

complications and a relatively good prognosis may have accounted for the lack of treatment effect of SZC. Furthermore, the recruitment period occurred during the COVID-19 pandemic, which may have impacted the number of patients with dialysis available for the current trial. Only approximately one-third of the targeted number of primary end point events were accrued, and no participants reached the 36-month follow-up visit. Furthermore, the treatment discontinuation rate before study termination was high and slightly imbalanced, with more discontinuations in the placebo versus SZC group. A *post hoc* calculated conditional power of 1.8% (calculated on the basis of observed effect size) indicated a low probability that the trial would have provided significant results if completed according to protocol. The conclusions from several exploratory sensitivity analyses were generally consistent with the conclusions of the primary analysis.

Consistent with the known efficacy profile of SZC, the efficacy of SZC on end points pertaining to sK^+ control was demonstrated in the current trial. Compared with the placebo group, a significantly higher proportion of participants in the SZC group maintained normokalemia (after the long interdialytic interval) up to 12 months after randomization, and significantly fewer required rescue therapy for hyperkalemia. Furthermore, a significantly higher proportion of participants in the SZC group avoided severe hyperkalemia. The secondary end points pertaining to sK^+ control were designed to be evaluated after the long interdialytic interval, a period that has been associated with elevated risks of arrhythmias and cardiovascular events compared with the short interdialytic interval.[2,3] Despite effectively reducing sK^+, and hyperkalemia, there was no improvement in cardiovascular end points.

The safety profile of SZC was generally consistent with previous reports of SZC in nondialysis patients and patients receiving chronic hemodialysis.[7–13] The incidences of AEs and serious AEs were similar between the SZC and placebo groups, although AEs of constipation and anemia were slightly more common in the SZC group. Hypokalemia was more common in the SZC group; severe hypokalemia was

Table 2 | Summary of safety outcomes

Safety outcome	SZC (n = 1348)	Placebo (n = 1338)
AEs	951 (70.5)	943 (70.5)
Serious AEs	521 (38.6)	503 (37.6)
AEs leading to treatment discontinuation	59 (4.4)	95 (7.1)
Serious AEs with an outcome of death	120 (8.9)	113 (8.4)
AEs occurring in ≥5% of patients		
Coronavirus disease 2019	162 (12.0)	136 (10.2)
Hyperkalemia	139 (10.3)	302 (22.6)
Pneumonia	106 (7.9)	88 (6.6)
Diarrhea	100 (7.4)	95 (7.1)
Hypertension	89 (6.6)	90 (6.7)
Constipation	79 (5.9)	57 (4.3)
Anemia	74 (5.5)	50 (3.7)
Edema-related AE	64 (4.7)	61 (4.6)
Fluid retention	0	1 (0.1)
Generalized edema	1 (0.1)	1 (0.1)
Hypervolemia	34 (2.5)	31 (2.3)
Edema	2 (0.1)	3 (0.2)
Edema peripheral	16 (1.2)	19 (1.4)
Peripheral swelling	15 (1.1)	8 (0.6)
Hypokalemia	40 (3.0)	19 (1.4)
Severe	0	1 (0.1)
Hyperkalemia requiring rescue therapy	122 (9.1)	279 (20.9)

AE, adverse event; SZC, sodium zirconium cyclosilicate.
Data are provided as n (%).

limited to 1 case in the placebo group. IDWG is predominantly the result of salt and water intake between dialysis sessions.[19] High IDWG can be due to poor adherence to dietary restriction of salt and fluid intake between hemodialysis treatments and consequently raises the risk of cardiovascular events and cardiovascular-related and all-cause mortality.[20,21] In this trial, IDWG was comparable between the groups at all time points, suggesting that there was no difference in fluid retention between SZC and placebo.

There are multiple likely reasons for the low observed event rates in this trial. The absence of implantable loop recorders, which can detect asymptomatic and intermittent arrhythmias over extended periods, may have limited the trial's ability to capture the full spectrum of arrhythmic events.[22] Also, the cutoff for the sK^+ concentration that predisposes patients with heart failure to arrhythmias and poor outcomes may be higher than that assumed in this study (5.5 mmol/l). In patients with heart failure, the optimal K^+ levels that should be maintained are not well established.[23] Additionally, the occurrence of arrhythmia due to severe hyperkalemia may be overestimated. Cardiovascular outcomes have a U-shaped association with K^+ levels.[24] Therefore, it is possible that baseline sK^+ levels were not high enough to induce the planned number of arrhythmia events in the studied population. In a recent study investigating the association of hyperkalemia (severe defined as >6.0 mEq/l) with mode of death in patients with heart failure, it was observed that arrhythmia (6.9%) was the least common cause.[25] Despite this, a meta-analysis showed that hyperkalemia was associated with a 1.4-fold increase in the risk of cardiovascular mortality in dialysis patients, and hypokalemia was more associated with supraventricular arrhythmias (1.6-fold increased risk).[24] Furthermore, patients with other cardiovascular risks, such as structural heart disease, who are predisposed to arrhythmias, were not sufficiently represented in the study population.[26] Notably, the proportion of patients with type 2 diabetes (34.4%) in the current trial was relatively low in comparison with the prevalence of diabetes in the US population who receive hemodialysis.[27] Because diabetes is a well-established risk factor for cardiovascular events, the low proportion of type 2 diabetes may have also contributed to the lower-than-expected event rates in this trial. These reasons highlight the importance of continuous heart rhythm monitoring tools like implantable loop recorders, determining an appropriate sK^+ threshold, and carefully selecting the patient population in trials focusing on K^+-related arrhythmia in patients with kidney failure.

In conclusion, in the phase 3 DIALIZE-Outcomes trial, despite effectively treating hyperkalemia, SZC did not significantly reduce the incidence of arrhythmia-related cardiovascular outcomes. The safety profile of SZC was consistent with previous reports in dialysis and nondialysis populations.

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DATA STATEMENT

Data underlying the findings described in this article may be requested in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

AstraZeneca Group of Companies allows researchers to submit a request to access anonymized patient-level clinical data, aggregate clinical or genomics data (when available), and anonymized clinical trial reports through the Vivli web-based data request platform.

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AUTHOR CONTRIBUTIONS

All authors have contributed to the manuscript per International Committee of Medical Journal Editors guidelines, and all acknowledged individuals have agreed to their inclusion.

Supplementary material is available online at www.kidney-international.org.

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