Clinical Study Report Synopsis	
Drug Substance	Sodium Zirconium Cyclosilicate (SZC)
Study Code	D9487C00001
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An International, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Sodium Zirconium Cyclosilicate on Arrhythmia-Related Cardiovascular Outcomes in Participants on Chronic Hemodialysis with Recurrent Hyperkalemia (DIALIZE-Outcomes)

Study dates:
First participant enrolled: 30 April 2021
Last participant last visit: 07 March 2024
The analyses presented in this report are based on a clinical data lock date of 08 July 2024.
Date of early study termination: 30 November 2023. The Sponsor discontinued the study early due to a lower-than-expected event rate and a higher-than-anticipated drop-out rate.

Phase of development:
Therapeutic confirmatory (III)

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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

Study Center(s)

Participants were randomized at 324 study sites in 26 countries.

Publications

The study design has been published: Fishbane S, Jadoul M, Dember L, et al. Evaluation of the effect of sodium zirconium cyclosilicate on arrhythmia-related cardiovascular outcomes in patients receiving chronic haemodialysis with hyperkalaemia: protocol for the multicentre, randomised, controlled DIALIZE-Outcomes study. BMJ Open. 2023;13(5):e071309.

Objectives and Criteria for Evaluation

Objectives and Endpoints

Objectives	Estimand description/endpoints [a]
Primary	
• To evaluate the efficacy of SZC compared with placebo in reducing the incidence of the primary composite endpoint of SCD, all stroke, or hospitalization/intervention/ED visit due to arrhythmias	Endpoint: Time to first occurrence of SCD, stroke, or hospitalization/intervention/ED visit due to arrhythmias (AF [b], bradycardia, asystole, ventricular tachyarrhythmia [such as VF, VT, etc]). Targeted population: All participants receiving chronic hemodialysis with recurrent hyperkalemia and satisfying other inclusion/exclusion criteria. Treatment condition: Study intervention/placebo taken on non-dialysis days and titrated per protocol. Intercurrent events: The main intercurrent events are treatment discontinuation, introduction of rescue therapy or other potassium altering treatment and deaths that are not SCD. The main approach of handling intercurrent events in the study is treatment policy. In the primary analysis, event free participants will be censored at non-SCD if it occurs. [c] Population-level summary: HR for SZC versus placebo.
Secondary	
• To evaluate the efficacy of SZC compared with placebo in maintaining normokalemia at one year	• S-K of 4.0 - 5.5 mmol/L (yes/no) after the LIDI at the 12-month visit
• To evaluate the efficacy of SZC compared with placebo in reducing the incidence of hospitalization/intervention/ED visit due to arrhythmias	• Time to first occurrence of hospitalization/intervention/ED visit due to arrhythmias (AF [b], bradycardia, asystole, ventricular tachyarrhythmia [such as VF, VT, etc])

Objectives	Estimand description/endpoints [a]
• To evaluate the efficacy of SZC compared with placebo in reducing hospitalizations/interventions/ED visits due to arrhythmias	• Number of hospitalizations/interventions/ED visits due to arrhythmias (AF [b], bradycardia, asystole, or ventricular tachyarrhythmia [such as VF, VT, etc])
• To evaluate the efficacy of SZC compared with placebo in reducing the need for rescue therapy for hyperkalemia	• Time to first instance of rescue therapy use for hyperkalemia
• To evaluate the efficacy of SZC compared with placebo in preventing severe hyperkalemia at one year	• S-K > 6.5 mmol/L (yes/no) after the LIDI at the 12-month visit
• To evaluate the efficacy of SZC compared with placebo in reducing the incidence of SCD	• Time to SCD
• To evaluate the efficacy of SZC compared with placebo in reducing the incidence of all stroke	• Time to first occurrence of stroke
• To evaluate the efficacy of SZC compared with placebo in reducing the incidence of CV death	• Time to CV death
• To evaluate the efficacy of SZC compared with placebo in reducing the incidence of all-cause mortality	• Time to death of any cause
Safety	
• To assess the safety and tolerability of SZC compared to placebo in participants on hemodialysis	Safety and tolerability will be evaluated in terms of AEs/SAEs and clinical laboratory variables. Assessments related to AEs will include: • Occurrence/frequency • Relationship to study intervention as assessed by the investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of study intervention Other safety-related events that will be assessed include: • IDWG • Events of pre-dialysis hypokalemia (S-K < 3.0 mmol/L)

[a] See Section 8.1.1 of CSP v3 [Appendix 16.1.1]) for details on adjudication of potential endpoint events: death, stroke and TIA, and hospitalizations, interventions, or ED visits due to arrhythmias (AF, bradycardia, asystole, and ventricular tachyarrhythmia [such as VF, VT, etc]).

[b] AF includes flutter.

[c] Participants with no observed events are censored at death, provided the cause of death is not a component of the endpoint, 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.

Exploratory objectives and endpoints are not included in the CSR Synopsis but can be found in the main body of the CSR.

AE, adverse event; AF, atrial fibrillation; CSP, clinical study protocol; CSR, clinical study report; CV, cardiovascular; ED, emergency department; HR, Hazard ratio; IDWG, interdialytic weight gain; LIDI, long interdialytic interval; SAE, serious adverse event; SCD, sudden cardiac death; S-K, serum potassium; SZC, sodium zirconium cyclosilicate; TIA, transient ischemic attack; VF, ventricular fibrillation; VT, ventricular tachycardia.

Study Design

This was an international, multicenter, event-driven, randomized, double-blind, parallel-group, placebo-controlled study, evaluating the utility of sodium zirconium cyclosilicate (SZC; LOKELMA®) versus placebo to reduce the incidence of sudden cardiac death (SCD), stroke, and arrhythmia-related hospitalizations, interventions, and emergency department (ED) visits in participants on chronic hemodialysis with recurrent hyperkalemia.

All participants who fulfilled eligibility criteria were centrally assigned to randomized study intervention using an Interactive Response Technology (IRT)/Randomization and Trial Supply Management (RTSM). The participants, investigators, outcomes assessors, and Sponsor were blinded to the treatment assignment.

The study was designed, directed, and published by an Executive Committee. The following additional committees were selected: a National Lead Investigator Committee, an Adjudication Committee, and an independent Data Monitoring Committee (DMC).

Target Population and Sample Size

The target population for the study was adult participants (≥ 18 years of age) receiving hemodialysis (or hemodiafiltration) 3 times a week for treatment of end-stage renal disease (ESRD) for ≥ 4 months before enrollment and who had at least 2 out of 2 or 2 out of 3 pre-dialysis serum potassium (S-K) values ≥ 5.5 mmol/L after the long interdialytic interval (LIDI) during screening.

Assuming the true hazard ratio (HR) for SZC versus placebo was 0.8, 730 primary endpoint events would result in approximately 85% power to demonstrate a statistically significant difference at either interim efficacy analysis (2-sided significance level of 1.64%) or at final efficacy analysis (2-sided significance level of 4.46%). Based on an assumption that the event rate of the primary composite endpoint was approximately 0.11 per patient-year in the placebo group, approximately 2800 participants would need to be randomized (1400 randomized participants per treatment group).

Investigational Product and Comparator(s): Dosage, Mode of Administration, and Batch Numbers

5 g or 10 g SZC or SZC placebo, powder for oral suspension in a sachet. A single dose contained 5 to 15 g SZC or SZC placebo that was suspended in 45 mL of water by the participant and administered once daily (qd) on non-dialysis days.

Duration of Treatment

This study was event-driven. The study closure procedures were to be initiated when the pre-determined number of primary endpoint events were expected to have occurred (730 events). The anticipated recruitment period was 32 months. The anticipated average treatment period for a participant was approximately 37 months, which in practice would be dependent on the actual event rate observed during the study. The study duration could be changed if the number of participants enrolled, the event rate, or the randomization rate was different than anticipated. Any decision to increase or decrease participant numbers or extend or shorten the study duration was based on blinded event rate data.

On 30 November 2023, AstraZeneca decided to discontinue the study early due to a lower-than-expected event rate and a higher-than-anticipated drop-out rate, which made it prohibitive to deliver study results within a timeframe to meaningfully advance clinical practice. The decision to discontinue the study was not due to safety concerns and was not based on formal futility analysis.

The primary analysis included 238 positively adjudicated events.

Statistical Methods

Efficacy analyses are performed using the Full Analysis Set, defined as all participants who underwent randomization and received a randomization number.

The analysis of the primary composite endpoint, time to first occurrence of SCD, stroke, or hospitalization/intervention/ED visit due to arrhythmias, was based on a Cox regression model that included factors/covariates of treatment group and geographic region. The estimate of the HR corresponding to the difference between treatment arms, the corresponding 95% 2-sided confidence interval (CI) as well as the 2-sided p-value for the null hypothesis of no difference were reported.

The contribution of each component of the primary composite endpoint to the overall treatment effect was assessed descriptively. Each component in the composite endpoint was analyzed similarly to the primary composite endpoint. Kaplan-Meier estimates of time to the first occurrence of any event in the composite endpoint were calculated and plotted. In the analysis of the components, all first events of the given type were included, irrespective of any preceding non-fatal component of a different type.

In addition to the main analysis of the primary composite endpoint, and its components, the difference between the 2 treatment arms in the secondary endpoints, time to first instance of rescue therapy use for hyperkalemia, time to cardiovascular (CV) death, and time to death of any cause, were analyzed similarly to the primary composite endpoint.

A logistic model with the binary variable (yes/no) as response and treatment group and geographic region as covariates was used to evaluate the efficacy of SZC as compared with placebo in the secondary endpoints measuring S-K of 4.0 to 5.5 mmol/L (yes/no) and > 6.5 mmol/L (yes/no) after the LIDI at 12 months. The estimated odds ratio, corresponding 95% CI, and 2-sided p-value were presented. The proportion of participants fulfilling each endpoint criteria was also presented by treatment arm, with the number of participants with available S-K data in the respective treatment arms used as the denominator.

A negative binomial regression model with number of events as response and study intervention arm and geographic region as covariates (other covariates included as appropriate) was used to evaluate the efficacy of SZC as compared with placebo for the secondary endpoint, number of hospitalizations/interventions/ED visits due to arrhythmias. The logarithm of the participant's corresponding follow-up time was used as an offset variable in the model to adjust for participants having different exposure times during which the events occurred. Number of events were presented by study intervention arm. The estimated rate ratio, corresponding 95% CI, and 2-sided p-value were presented.

A non-binding futility interim analysis and an efficacy interim analysis were planned as described in the protocol. However, the interim analyses were not performed as the study was stopped early due to lower-than-expected event rate and a higher-than-anticipated drop-out rate.

To control the familywise Type I error rate, a fixed sequence multiple testing procedure for primary and secondary endpoints was to be performed. For the primary composite endpoint, the null hypothesis of no difference between study intervention arms was to be tested at the 4.46% 2-sided level (assuming one interim analysis for efficacy). Since the trial was terminated early for reasons unrelated to efficacy and safety and since the interim analysis for efficacy was not performed, the primary composite endpoint was to be tested at the 5% 2-sided significance level. Once the null hypothesis concerning the primary efficacy composite endpoint was rejected, the hypotheses for the secondary efficacy endpoints was to be tested sequentially in the order listed in the table above with the same alpha level as the primary endpoint. The testing procedure would continue down the hierarchy if the current endpoint was rejected at a 2-sided 5% level and stop if the current endpoint was not rejected at a 2-sided 5% level.

Safety analyses were performed using the Safety Set, defined as all randomized participants who received at least one dose of study intervention. Safety data were presented using descriptive statistics unless otherwise specified.

Study Population

This study was conducted at 344 sites across 26 countries, and participants were randomized at 324 sites. The first participant was screened (consented) on 30 April 2021. On 30 November 2023, AstraZeneca decided to discontinue the study early due to a lower-than-expected event rate and a higher-than-anticipated drop-out rate. Study closure visits started after 30 November 2023, and adjudicated events were collected until the end of each participant's last visit. The last participant last visit was 07 March 2024, and the clinical database was locked on 08 July 2024.

A total of 4704 participants were screened (consented) in the study, of whom 2690 were randomized to study treatment (SZC: 1349 participants; placebo: 1341 participants). Of the 2690 participants randomized, 2686 received at least one dose of study intervention. One participant in the placebo group was randomized but did not receive study treatment as their investigational product (IP) was interrupted due to an event leading to hospitalization and eventual death. Three participants were incorrectly identified as randomized but not dosed; however, they received at least one dose of study treatment.

No participants completed study treatment or completed the study as the study was terminated early. Of the 2690 randomized participants, 410 (30.4%) participants in the SZC group and 517 (38.6%) participants in the placebo group discontinued study treatment prior to the Sponsor's decision to terminate the study. The main reasons for discontinuing study treatment prior to the Sponsor's decision to terminate the study were participant decision (SZC: 117 [8.7%] participants; placebo: 195 [14.5%] participants), development of study-specific discontinuation criteria of renal transplant (SZC: 58 [4.3%] participants; placebo: 62 [4.6%] participants), and adverse event (AE) (SZC: 56 [4.2%] participants; placebo: 87 [6.5%] participants).

Participant demographic and baseline characteristics were well balanced between the treatment groups:

- Overall, 62.3% of participants were male and the age (median [first quartile [Q1], third quartile [Q3]]) was 57 (47, 66) years. Overall, 50.6% of participants were White, 29.0% were Asian, and 9.3% were Black or African-American.
- Overall, pre-dialysis weight (median [Q1, Q3]) was 72.40 (61.70, 85.30) kg, and interdialytic weight gain (IDWG) (median [Q1, Q3]) was 2.80 (2.00, 3.70) kg. Overall, dialysis adequacy (median [Q1, Q3]) was 1.45 (1.28, 1.69) spKt/V.

Participant disease background characteristics and electrocardiogram variables were well balanced between treatment groups and were consistent with the expected profile of participants with ESRD receiving dialysis. Overall, pre-dialysis S-K (median [Q1, Q3]) was 5.90 (5.50, 6.40) mmol/L and the time since first dialysis was 4.45 (2.10, 7.91) years.

Summary of Efficacy Results

Primary Composite Endpoint: Time to First Occurrence of SCD, Stroke, or Hospitalization/Intervention/ED Visit Due to Arrhythmias

No treatment effect was observed on the primary composite endpoint (HR 0.98; 95% CI [0.76, 1.26]; p-value = 0.867). The Kaplan-Meier curves for the primary composite endpoint did not show any clear separation between SZC and placebo groups across all time intervals.

No treatment effect was observed on any of the individual components of the primary composite endpoint. The Kaplan-Meier curves for the individual components of SCD and stroke also showed no clear separation between SZC and placebo groups across all time intervals. For the individual component of hospitalizations/interventions/ED visits due to arrhythmias, an apparent separation in the Kaplan-Meier curve at approximately 15 months was observed but is likely due to chance, considering that the variability of the Kaplan-Meier estimate increases as the number of participants decreases, and the magnitude of the difference is small.

Secondary Endpoints

The proportion of participants with normokalemia (S-K 4.0 to 5.5 mmol/L) at the 12-month visit was higher in the SZC group (74.0%) compared to the placebo group (47.0%). The difference was statistically significant (odds ratio 3.36; 95% CI [2.64, 4.26]; p-value < 0.0001).

Consistent with endpoints related to S-K control, a treatment effect in favor of SZC was observed for time to first instance of rescue therapy use for hyperkalemia (HR 0.39; 95% CI [0.31, 0.48]; p-value < 0.001).

The proportion of participants with hyperkalemia (S-K > 6.5 mmol/L) at the 12-month visit was higher in the placebo group (10.4%) compared to the SZC group (4.0%). The difference was statistically significant (odds ratio 0.35; 95% CI [0.22, 0.56]; p-value < 0.0001).

No statistically significant treatment effect was observed for the endpoint of time to first occurrence of hospitalization/intervention/ED visit due to arrhythmias (a component of the primary composite endpoint).

No treatment effect was observed for the following secondary endpoints:

- The rate of hospitalizations/interventions/ED visits due to arrhythmias.
- Time to first occurrence of SCD (a component of the primary composite endpoint).
- Time to first occurrence of stroke (a component of the primary composite endpoint).
- Time to CV death.
- Time to death of any cause.

Exploratory Endpoints

Results for exploratory endpoints are not included in the clinical study report (CSR) Synopsis but can be found in the main body of the CSR.

Summary of Safety Results

Exposure: The duration of exposure in the study ranged from 0 to 29.0 months in the SZC group and 0 to 29.2 months in the placebo group. In total there were 1393.4 patient-years of exposure to SZC during the study. Duration of exposure was slightly different between the SZC and placebo groups. Median exposure was approximately 2 months higher in the SZC group (SZC: 12.17 months; placebo: 10.23 months).

Adverse Events: Overall, AEs and serious AEs (SAEs) were generally balanced between the treatment groups during the study. The AEs of hypokalemia were more frequent in the SZC group, whereas AEs of hyperkalemia requiring rescue therapy were more frequent in the placebo group. Similar results were observed on treatment.

Numerical differences between the treatment groups were observed for the most common AEs. The proportions of participants with AEs of COVID-19, pneumonia, constipation, and anemia were higher in the SZC group; the proportion of participants with AEs of hyperkalemia was higher in the placebo group. In addition, a higher proportion of participants in the SZC group had PTs of sepsis and acute myocardial infarction.

The majority of AEs were mild or moderate in intensity and generally balanced between treatment groups during the study. The proportion of participants with severe AEs was similar between the treatment groups (SZC: 339 [25.1%] participants; placebo: 328 [24.5%] participants).

A numerically higher proportion of participants in the SZC group had at least one AE possibly related to the study treatment during the study (SZC: 159 [11.8%] participants; placebo: 121 [9.0%] participants). The numerical imbalance is primarily due to higher incidence of hypokalemia and constipation. Although a numerically higher proportion of participants in SZC group had at least one AE in system organ class (SOC) Cardiac disorders (SZC: 14 [1.0%] participants; placebo: 5 [0.4%] participants), no clear imbalances in preferred terms (PTs) were observed.

Deaths: The number of deaths was similar between treatment groups during the study (SZC: 120 [8.9%] participants; placebo: 113 [8.4%] participants) and slightly higher in the SZC group on treatment (SZC: 69 [5.1%] participants; placebo: 55 [4.1%] participants). The most common SAEs with outcome of death by PT in the SZC group during the study were death,

cardiac arrest, SCD, and sepsis. No clear difference in SOCs and PTs was observed between treatment groups for deaths during the study.

Serious Adverse Events: The proportion of participants with any SAE was similar between treatment groups during the study (SZC: 521 [38.6%] participants; placebo 503 [37.6%] participants) and slightly higher in the SZC group on treatment (SZC: 460 [34.1%] participants; placebo: 417 [31.2%] participants). The most common SAEs by PT in the SZC group during the study were pneumonia and sepsis.

Adverse Events Leading to Discontinuation: A higher proportion of participants in the placebo group had discontinuation of IP due to an AE (DAEs) (SZC: 59 [4.4%] participants; placebo: 95 [7.1%] participants), primarily due to more DAEs of hyperkalemia in the placebo group. A slightly higher proportion of participants in the SZC group had DAEs of constipation. No other clear differences between the treatment groups were observed.

Clinical Chemistry: A small increase in bicarbonate (a known effect of SZC) and sodium was observed for SZC (bicarbonate mean change from baseline of 0.81 and 0.07 mmol/L in SZC and placebo groups, respectively; sodium mean change from baseline of 0.8 and 0 mmol/L in SZC and placebo groups, respectively). No clinically meaningful differences between the SZC and placebo groups in change from baseline or in shifts from baseline to Month 12 in clinical chemistry variables were noted.

Vital Signs, Pre-dialysis Weight, and Interdialytic Weight Gain: No clinically meaningful differences between the SZC and placebo groups in change from baseline or in shifts from baseline to the end of study intervention visit/premature study intervention discontinuation visit in vital sign variables over time, or in pre-dialysis weight or IDWG and changes from baseline over time were noted.

Conclusion(s)

DIALIZE-Outcomes enrolled 2690 participants on hemodialysis who had recurrent pre-dialysis hyperkalemia (S-K > 5.5 mmol/L). The study was terminated early due to low event rates and high drop-out rate.

- Efficacy: No benefit on clinical outcomes was demonstrated.
  - At the point of study termination, and with about 33% of events, there was no statistically significant difference between SZC and placebo on the primary efficacy composite endpoint (SCD, stroke, hospitalization/intervention/ED visit due to arrhythmias) (HR: 0.98; 95% CI [0.76, 1.26]; p = 0.867) despite clear efficacy on hyperkalemia.

- Safety:
  - There was a higher incidence of hypokalemia on SZC versus placebo (3.03 per 100 patient-years versus 1.32 per 100 patient-years).
  - There was a higher incidence rate of constipation on SZC versus placebo (5.99 per 100 patient years versus 4.66 per 100 patient-years).
  - There were small imbalances in the frequency of AEs related to infections and anemia (higher on SZC versus placebo) and more participants on SZC with arrhythmias.
  - Otherwise, the safety profile of SZC in the study was consistent with pre-trial data.