

BMJ Open 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

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ABSTRACT

Introduction Patients with kidney failure receiving chronic haemodialysis have elevated risk of arrhythmias potentially increasing the likelihood of sudden cardiac death, stroke and hospitalisation. The DIALIZE study (NCT03303521) demonstrated that sodium zirconium cyclosilicate (SZC) was an efficacious and well-tolerated treatment for predialysis hyperkalaemia in patients undergoing haemodialysis. The DIALIZE-Outcomes study evaluates the effect of SZC on sudden cardiac death and arrhythmia-related cardiovascular outcomes in patients receiving chronic haemodialysis with recurrent hyperkalaemia.

Methods and analysis International, multicentre, randomised, double-blind, placebo-controlled study conducted at 357 study sites across 25 countries. Adults (≥ 18 years) receiving chronic haemodialysis three times per week with recurrent predialysis serum potassium (K^+) ≥ 5.5 mmol/L post long interdialytic interval (LID) are eligible. Patients (~ 2800) will be randomised 1:1 to SZC or placebo, starting at 5 g orally once daily on non-dialysis days and titrated weekly in 5 g increments (maximum 15 g) to target predialysis serum K^+ 4.0–5.0 mmol/L post LID. The primary objective is to evaluate efficacy of SZC versus placebo in reducing occurrence of the primary composite endpoint of sudden cardiac death, stroke or arrhythmia-related hospitalisation, intervention or emergency department visit. Secondary endpoints include efficacy of SZC versus placebo in maintaining normokalaemia (serum K^+ 4.0–5.5 mmol/L post LID) at the 12-month visit, preventing severe hyperkalaemia (serum K^+ ≥ 6.5 mmol/L post LID) at the 12-month visit and reducing the incidence of individual cardiovascular outcomes. Safety of SZC will be evaluated. The study is event driven, with participants remaining in the study until 770 primary endpoint events

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The study is designed to evaluate outcomes that are important to patients and important from the perspective of healthcare resource utilisation in the haemodialysis setting.
- ⇒ The global nature of this trial will allow analyses of country-specific or regional differences in the efficacy of the intervention.
- ⇒ As patients receiving haemodialysis are at increased risk of mortality from COVID-19, a limitation is that the competing risk of death from COVID-19 may decrease the detectable benefit of the trial intervention.

have occurred. Average time in the study is expected to be ~ 25 months.

Ethics and dissemination Approval was obtained from the relevant institutional review board/independent ethics committee from each participating site (approving bodies in supplementary information). The results will be submitted to a peer-reviewed journal.

Trial registration numbers EudraCT 2020-005561-14 and clinicaltrials.gov identifier NCT04847232.

INTRODUCTION

Patients with kidney failure who are receiving haemodialysis have a markedly increased mortality rate compared with the general population. In the USA, mortality rates (per 1000 person-years) were 156.6 for those receiving dialysis and 8.7 for the general population, in 2019.^{1,2} Cardiovascular disease

is highly prevalent within the haemodialysis population, specifically cardiac arrhythmias, cardiac arrest, heart failure, stroke and sudden cardiac death.^{3–8} For example, in studies using implanted loop recorders, atrial fibrillation was detected in 41% of patients.⁹ Compared with the general population,¹⁰ arrhythmias and cardiac arrest are disproportionately more common causes of death in patients receiving haemodialysis,^{11 12} and sudden cardiac death is responsible for almost one-third of mortality.¹³ Furthermore, rates of hospitalisation due to stroke are reported to be 4-fold to 10-fold higher in patients receiving dialysis compared with individuals without kidney failure.¹⁴

Individuals with kidney failure receiving chronic haemodialysis typically undergo dialysis three times per week, with two short interdialytic intervals (SIDs; 1 day each) and one long interdialytic interval (LIDI; 2 days).^{4 15} Serious adverse outcomes, such as death and hospitalisation, occur at a higher rate following the LIDI than at other timepoints.^{4 16} Rates of all-cause mortality have been reported to be 22.1 per 100 person-years after the LIDI, compared with 18.0 per 100 person-years on SIDI days.⁴ The frequencies of cardiac arrest, cardiovascular mortality and hospitalisation for cardiovascular causes are also higher following the LIDI.^{4–6 17} In one retrospective analysis, deaths due to cardiac arrest (1.3 vs 1.0 per 100 person-years) and myocardial infarction (6.3 vs 4.4 per 100 person-years) were significantly higher after the LIDI than at other times in the weekly dialysis schedule.⁴ This is supported by recent studies using continuous heart rhythm monitoring with implantable loop recorders, which have demonstrated the risk of sudden cardiac death and cardiac arrhythmias, including atrial fibrillation, bradyarrhythmias and asystole, to be greatest around the end of the LIDI.^{9 18}

Despite haemodialysis, several patients have persistent predialysis hyperkalaemia and this is two times as common after the LIDI than after the SIDI.^{19 20} Predialysis hyperkalaemia is associated with an increased mortality risk; the unadjusted HR for mortality between different serum potassium (K^+) categories is U-shaped,^{19 21} with the best survival observed in patients with serum K^+ concentrations of 4.6–5.6 mmol/L.¹⁹ For patients receiving haemodialysis, hyperkalaemia or electrolyte shifts are associated with cardiac arrhythmias, sudden cardiac death and increased cardiovascular mortality.^{7 9 11 13 19–25} This high risk of cardiac arrhythmias and cardiovascular death in patients receiving haemodialysis makes an association with hyperkalaemia clinically relevant, either directly or as a contributing factor, especially as significant electrophysiologic alterations may result from intradialytic K^+ shifts.^{7 11 13 19} Therefore, there is an unmet need to determine whether the management of predialysis serum K^+ and avoidance of predialysis hyperkalaemia can minimise susceptibility to cardiovascular events and serious cardiac arrhythmias.²⁶

Sodium zirconium cyclosilicate (SZC) is an oral anti-hyperkalaemia therapy (K^+ binder) indicated for use in

adults, which provides rapid serum K^+ reduction and sustained K^+ control. Previous international, phase III clinical trials have demonstrated the safety and efficacy of SZC for up to 12 months in non-dialysis individuals with hyperkalaemia.^{27 28} The phase IIIb DIALIZE study (clinicaltrials.gov identifier: NCT03303521) demonstrated that SZC is an efficacious and well-tolerated treatment for predialysis hyperkalaemia when administered once daily over 8 weeks on non-dialysis days in patients with kidney failure undergoing chronic haemodialysis, but the study was not powered to evaluate clinical outcomes.²⁹

Given the potential association between cardiovascular events and hyperkalaemia in patients receiving haemodialysis, the DIALIZE-Outcomes study was designed to assess whether SZC effectively reduces the incidence of sudden cardiac death, stroke and arrhythmia-related hospitalisations, interventions and emergency department visits in patients with hyperkalaemia who are receiving chronic haemodialysis. Several key considerations influenced the design of the DIALIZE-Outcomes study; the likelihood of treatment with SZC raising safety concerns is deemed to be low, as no clinically relevant safety findings were observed in the DIALIZE study.²⁹ Furthermore, the risk for hypokalaemia is mitigated by periodic monitoring of serum K^+ and adjustment of the SZC dose as necessary in the titration period. As the first study of its type, it is anticipated the DIALIZE-Outcomes study will facilitate improved understanding of the clinical value of hyperkalaemia therapy in the haemodialysis setting for the management of arrhythmia-related cardiovascular outcomes. Furthermore, the results may provide supportive evidence for the relationship between hyperkalaemia and cardiovascular morbidity and mortality among patients receiving chronic haemodialysis. Here, we describe the design of the DIALIZE-Outcomes study.

METHODS AND ANALYSIS

Study design

DIALIZE-Outcomes is an ongoing, international, multi-centre, randomised, double-blind, parallel-group, placebo-controlled study designed to evaluate the ability of SZC versus placebo to reduce the incidence of arrhythmia-related cardiovascular outcomes in patients receiving chronic haemodialysis with hyperkalaemia (EudraCT number: 2020-005561-14). The study is being conducted at 357 study sites across 25 countries, and ~2800 patients will be randomised to treatment. Data will be collected from the following countries: Argentina, Austria, Brazil, Bulgaria, Canada, China, Czechia, Germany, Hungary, Italy, Japan, Malaysia, Mexico, Peru, Poland, Russian Federation, Slovakia, Spain, Taiwan, Thailand, Turkey, Ukraine, the UK, the USA and Vietnam, with study sites provided at clinicaltrials.gov (NCT04847232). The first participants were enrolled on 30 April 2021 in Taiwan, and the expected study completion date is 13 March 2026.

The study consists of two phases (figure 1): a screening phase of 2–6 weeks and a randomised treatment phase

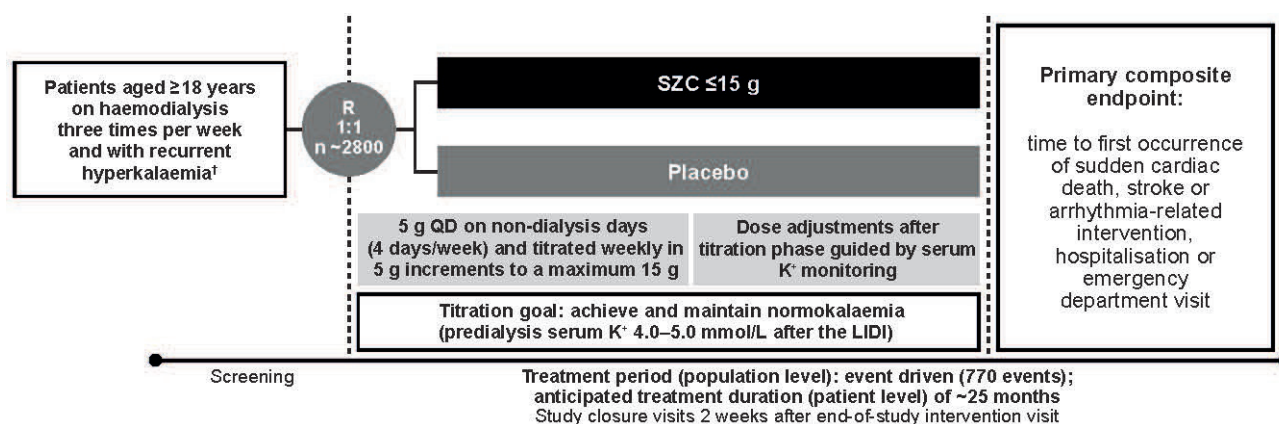


Figure 1 Study design. †At least two from three predialysis serum K^+ concentrations ≥ 5.5 mmol/L after the LIDI during screening. SZC was administered 5 g orally once daily and titrated weekly in 5 g increments (maximum 15 g). K^+ , potassium; LIDI, long interdialytic interval; QD, once daily; R, randomisation; SZC, sodium zirconium cyclosilicate.

that will continue until the required number of events accrue. The treatment phase will begin with a titration period, during which the study intervention will be titrated to target normokalaemia. The recruitment period is planned to be 21 months, extended from 15 months principally due to the COVID-19 pandemic. The mean treatment period is expected to be ~25 months, although this may change if the number of participants enrolled, the event rate (based on blinded data) or the randomisation rate is different from anticipated.

The study was designed and is being directed by an executive committee, which will also be responsible for reporting the results of the study as a peer-reviewed publication. An independent data monitoring committee (DMC) is responsible for monitoring the progress of the study with respect to randomisation, compliance and follow-up, as well as for reviewing the unblinded data for evidence of benefit or harm. The DMC can make recommendations to the sponsor and the executive committee to alter or terminate the trial. The DMC comprises five members, as follows: one internist/cardiologist, two nephrologists, one clinical cardiac electrophysiologist and one statistician.

Patients

The key study inclusion and exclusion criteria are summarised in table 1. The study is enrolling adults (aged ≥ 18 years) who have been receiving haemodialysis (or haemodiafiltration) three times a week for the treatment of kidney failure for ≥ 4 months before enrolment, who have recurrent hyperkalaemia (defined as ≥ 2 out of 3 predialysis serum K^+ concentrations ≥ 5.5 mmol/L after the LIDI 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 treatment with a K^+ binder within 7 days before screening are excluded.

Interventions

Patients are randomised 1:1 to a study intervention of SZC or placebo on study day 1. The randomisation will be performed using an interactive response technology/randomisation and trial supply management (IRT/RTSM), with the randomisation codes generated computationally in blocks using the AstraZeneca Global Randomization System to ensure the 1:1 balance between both intervention arms. This randomisation will also be stratified by country. All participants and investigators will remain blinded to randomised treatment allocation, with blinding upheld at all points except in medical emergencies, and with blind-breaking abilities programmed into the IRT/RTSM. Except for blinded serum K^+ measures at screening and at 12 months, data elements with potential to unblind study team members, and therefore requiring special handling, are serum K^+ measures recorded by local laboratories and any study drug dose adjustment information. Data handling recommendations for the former are included in the monitoring plan, and information in both cases will not be shared with the global study team. A DMC and associated charter will be implemented to ensure maintenance of the blinding and integrity of the study.

The dose of study intervention is titrated weekly for 4 weeks in 5 g increments, starting at 5 g once daily on non-dialysis days (4 days per week), based on local laboratory predialysis serum K^+ values at the LIDI visit, to target a predialysis serum K^+ concentration of 4.0–5.0 mmol/L at the LIDI visit. The maximum dose of study intervention is 15 g once daily on non-dialysis days. Both SZC and placebo will be administered orally as a powder suspended in 45 mL of water.

After the initial titration, predialysis serum K^+ measurements are performed monthly by the local laboratory at the LIDI visit, or more frequently based on clinical judgement, to guide further dose adjustment. The dose adjustments may take place at any time during the study to target a predialysis serum K^+ concentration of 4.0–5.0



Table 1 Inclusion and exclusion criteria

Inclusion criteria

Male or female, aged ≥ 18 years; if < 20 years and enrolled in Japan, a written informed consent form (ICF) will be required from the participant and appropriate legally acceptable representative

Capable and willing to give signed informed consent; including compliance with requirements and restrictions listed in the ICF and the study protocol

Provision of signed and dated, written ICF prior to any mandatory study-specific procedures, sampling or analyses

Receiving haemodialysis (or haemodiafiltration) three times a week for the treatment of kidney failure for ≥ 4 months before enrolment

Haemodialysis access consisting of an arteriovenous fistula, arteriovenous graft or tunnelled (permanent) catheter that is expected to remain in place for the entire duration of the study*

At least two out of three predialysis serum K^+ concentrations ≥ 5.5 mmol/L after the LIDI during screening

Negative pregnancy test for female participants of childbearing potential

Female participants are 1-year postmenopausal, surgically sterile or using one highly effective form of birth control (failure rate $< 1\%$ per year when used consistently and correctly).[†] Stable on birth control for ≥ 3 months before the study and willing to continue until 12 weeks after the last dose

Exclusion criteria

Pseudohyperkalaemia secondary to haemolysed blood specimen (this situation is not considered a screening failure. Sampling or full screening can be postponed to a later time as applicable)

Presence of cardiac arrhythmias or conduction defects that require immediate treatment

Participants who have a pacemaker or implantable cardiac defibrillator

Any medical condition, including active, clinically significant infection or liver disease that, in the opinion of the investigator or sponsor, may pose a safety risk to a participant in this study or interfere with study participation, or any other restrictions or contraindications in the local prescribing information for SZC

History of QT prolongation associated with other medications that required discontinuation of that medication

Congenital long QT syndrome

QTcF > 550 ms³⁴

Atrial fibrillation requiring immediate/urgent intervention at screening or randomisation

Sustained ventricular tachycardia > 30 s requiring assessment or intervention

Treated with sodium polystyrene sulfonate, calcium polystyrene sulfonate or SZC within 7 days before screening, or anticipated to require chronic use of any of these agents during the study, or requires rescue therapy (K^+ binder or dialysate K^+ change during screening period)

Participation in another clinical study with an investigational product administered within 1 month before screening

Involvement in the planning and/or conduct of the study

Previous randomisation in the present study

Individuals of childbearing potential who are not willing to use defined methods of contraception

Individuals who have a positive pregnancy test at screening or those who are breastfeeding

Known hypersensitivity or previous anaphylaxis to SZC or to components thereof

Scheduled date for living donor kidney transplant

*Included to ensure that patients have permanent vascular access and exclude those dialysed with a temporary vascular access; not intended to prevent patients from switching from one permanent access to another.

[†]Women will be considered postmenopausal if amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. Surgical sterilisation includes: hysterectomy, bilateral oophorectomy or bilateral salpingectomy.

K^+ , potassium; LIDI, long interdialytic interval; QTcF, QT interval corrected by the Fridericia method ($QTcF = QT/RR^{1/3}$); SZC, sodium zirconium cyclosilicate.

mmol/L. Serum K^+ concentration is measured 1 week after all changes in dose. The SZC dosing and titration approaches in this study are consistent with the approved label for the dialysis population. Dialysis clinics will provide patients with dietary advice targeted towards limiting K^+ intake while maintaining adequate nutrition in terms of protein and caloric intake, as performed in

routine clinical care. The use of printed materials to educate participants is encouraged.

Placebo is considered the appropriate comparator for this trial, as no interventions have been demonstrated to reduce the cardiovascular outcomes of interest in the haemodialysis population. However, cases of

Table 2 Study objectives and endpoints

Objective	Endpoint
Primary	Efficacy: time to first occurrence of sudden cardiac death, stroke or arrhythmia-related (AF, bradycardia, asystole or ventricular tachyarrhythmia; for example, VF or VT) hospitalisation, intervention or emergency department visit
Secondary	Serum K ⁺ concentration of 4.0–5.5 mmol/L (yes or no) after the LIDI at the 12-month visit Time to first occurrence of hospitalisation, intervention or emergency department visit due to arrhythmias (AF, bradycardia, asystole or ventricular tachyarrhythmia; eg, VF or VT) Number of hospitalisations, interventions or emergency department visits due to arrhythmias (AF, bradycardia, asystole or ventricular tachyarrhythmia; eg, VF or VT) Time to first instance of rescue therapy use for hyperkalaemia Serum K ⁺ concentration >6.5 mmol/L (yes or no) after the LIDI at the 12-month visit Time to sudden cardiac death Time to first occurrence of stroke Time to cardiovascular-related death Time to death by any cause
Exploratory	Serum K ⁺ concentration of 4.0–5.0 mmol/L (yes or no) after the LIDI at the 12-month visit Time to first occurrence of sudden cardiac death, stroke or arrhythmia-related (AF, bradycardia, asystole or ventricular tachyarrhythmia; eg, VF or VT) hospitalisation, intervention or emergency department visit Number of events of rescue therapy use for hyperkalaemia
Safety	Safety and tolerability in terms of adverse events or serious adverse events, and safety laboratory assessments*, interdialytic weight gain and events of predialysis hypokalaemia (serum K ⁺ concentration <3.0 mmol/L)

*Safety laboratory assessments via central laboratory. Blood: erythrocyte count, haemoglobin, leucocyte count, leucocyte differential count (absolute count and percentage), platelet count. Serum: potassium, calcium (total), sodium, bicarbonate, phosphate, blood urea nitrogen, magnesium, creatinine, bilirubin (total), alkaline phosphatase, aspartate transaminase, alanine transaminase, gamma-glutamyl transferase, albumin, chloride, creatine kinase, glucose, lactate dehydrogenase, total protein, pregnancy test (serum human chorionic gonadotropin). AF, atrial fibrillation; K⁺, potassium; LIDI, long interdialytic interval; VF, ventricular fibrillation; VT, ventricular tachycardia.

hyperkalaemia occurring within the control group can be treated in accordance with clinically justified therapy.

Objectives and endpoints

The study objectives and endpoints are listed in [table 2](#). The primary objective is to evaluate the efficacy of SZC compared with placebo in reducing the incidence of the primary composite endpoint of sudden cardiac death, stroke or hospitalisation, intervention or emergency department visits due to arrhythmias. This study is event driven, and study closure procedures will be initiated when the predetermined number of 770 primary endpoint events is expected to have occurred. The events comprising the primary composite endpoint were selected due to their prevalence within the haemodialysis population,^{3–7} and to fully capture the potential benefits of SZC on cardiovascular and arrhythmia-related outcomes. In addition, reductions in hospitalisations due to arrhythmias, as well as from any cause, are important outcomes from a patient and healthcare resource utilisation perspective.³⁰

Secondary objectives include evaluating the efficacy of SZC compared with placebo in maintaining normokalaemia (serum K⁺ concentration of 4.0–5.5 mmol/L), reducing the need for rescue therapy for hyperkalaemia, preventing severe hyperkalaemia (serum K⁺ concentration >6.5 mmol/L 12 months post randomisation) and reducing the incidence of individual cardiovascular outcomes (eg, cardiovascular-related death) ([table 2](#)).

Rescue therapy is defined as any intervention needed for the control of an adverse event (AE) of severe hyperkalaemia (eg, serum K⁺ concentration >6.5 mmol/L or a patient with signs or symptoms of hyperkalaemia) and is allowed at any time during the study; this is not a studied intervention. No clinically justified therapy for severe acute hyperkalaemia is withheld from study participants. Choice of rescue therapy is available according to local practice patterns.

The safety and tolerability of SZC will be evaluated through ascertainment of AEs, laboratory safety assessments (ie, serum chemistry and whole blood haematology/haemostasis measures, performed by central laboratory), interdialytic weight gain and events of predialysis hypokalaemia (serum K⁺ concentration <3.0 mmol/L) ([table 2](#)). Interdialytic weight gain is predominantly the result of salt and water intake between dialysis sessions,³¹ therefore it is considered relevant as a safety parameter as SZC comprises ~10% sodium. However, no safety concerns were reported regarding this during the DIALIZE study.²⁹

Study procedures

The schedule of study assessment is summarised in [table 3](#). The screening period comprises three on-site visits at days –21 (visit 1), –14 (visit 2) and –7 (visit 3). Each screening visit can be repeated once, meaning that screening can last up to 6 weeks. If serum K⁺ measurement criteria are met at visits 1 and 2, the patient will be randomised without

Table 3 Schedule of study assessments

	Screening				R (on-site)	On-site visits at 3, 6, 9 and 12 months	TC/video/on-site	EOIV or PIDV (on-site)	SCV (TC/video/ on-site)
Study day	-21	-14	-7	1		91, 182, 273, 364 (each ± 7 days)	Every third month (± 7 days)		
Visit	1	2	3*	4		5, 6, 7, 8	9, 10, 11, etc.		
Informed consent	X								
Inclusion/exclusion criteria	X								
Randomisation				X					
Physical examination	X			X				X	
Pulse and BP†	X			X				X	
ECG	X			X					
Predialysis and postdialysis weight‡	X§			X		X	X	X	
Laboratory predialysis serum K ⁺ ¶	X	X	X	X					
Endpoint collection**				X		X	X	X	X
AEs and SAEs	X††	X††	X††	X		X	X	X	X

*If serum K⁺ measurement criteria are met at visits 1 and 2, patient will be randomised without performing visit 3. Visit 3 in this schedule of events becomes visit 4: the randomisation visit. If serum K⁺ measurement criteria are not met at visits 1 and 2, patient will be screen failed without performing visit 3.

†Pulse and BP will be measured prior to the haemodialysis procedure and will be measured in triplicate after the participant is comfortably at rest in either supine or seated position quietly for ≥ 5 min.

‡Predialysis and postdialysis weight will not be collected if the appointment is done via TC or video.

§On study day -21 during prescreening, only predialysis weight is collected.

¶To be measured also on study day 364 (visit 8). If required, the laboratory chemistry panel will be repeated (after the LIDI) once for each screening visit. If there is a need to repeat the screening visit more than once, the study physician will be consulted.

**Potential endpoints will be collected from randomisation throughout the study until and including the participant's last visit.

††For all prescreening visits, only SAEs are collected.

AE, adverse event; BP, blood pressure; ECG, electrocardiogram; EOIV, end-of-study intervention visit; K⁺, potassium; LIDI, long interdialytic interval; PIDV, premature study intervention discontinuation visit; R, randomisation; SAE, serious adverse event; SCV, study closure visit; TC, teleconference.

performing visit 3. If serum K⁺ measurement criteria are not met at visits 1 and 2, the patient will be 'screen failed' without performing visit 3. The randomised treatment period comprises the following: an on-site randomisation visit (day 1; LIDI); four on-site visits at days 91, 182, 273 and 364 (all ± 7 days; LIDI), and teleconferences or on-site visits every third month (± 7 days; LIDI) thereafter until study completion. On study completion, an on-site end-of-study intervention visit and a teleconference or on-site study closure visit takes place (table 3). In the event of premature discontinuation of study intervention, an on-site premature study intervention discontinuation visit is performed at the earliest possible dialysis visit after the last dose of study intervention (table 3).

Efficacy endpoints are identified through clinical evaluations, interviewing the participants about their overall health and symptoms or through information received through standard medical practice. For events that comprise the primary composite endpoint, the investigator will submit their assessment and details about the event for review by the trial adjudication committee for adjudication and classification. Investigators are encouraged to have a low threshold to submit any potential or possible event that might represent an endpoint. The adjudication committee comprises five members, as follows:

two cardiologists/electrophysiologists, one nephrologist and two stroke neurologists for stroke events. Adjudication of the events occurs in a blinded manner. Events are adjudicated on the basis of strict application of event definitions developed by the Standardized Data Collection for Cardiovascular Trials Initiative and the US Food and Drug Administration.³² However, the clinical likelihood that a suspected event has occurred is individually assessed even in the absence of fulfilment of all criteria specified in the event definition, recognising that information may at times be difficult to interpret due to missing or incomplete data. All endpoint events are also reported as AEs.

Blood samples for determination of serum K⁺ concentration for the secondary efficacy endpoint are obtained at randomisation and at the 12-month visit. All serum samples are examined visually, and any haemolysed samples will be redrawn. Sample retests are allowed for each screening and 12-month visit, but there should not be more than one retest per screening visit. Analyses are performed at a central laboratory contracted by Astra-Zeneca. As part of the safety and tolerability assessments, predialysis and postdialysis weight is measured at the dialysis clinic at each on-site visit (except for the study closure visit); values will not be collected if the visit is performed via teleconference. Interdialytic weight gain is calculated

as the difference between the current predialysis weight and the postdialysis weight in kilograms, measured at the dialysis session immediately prior to the visit. AEs and serious AEs will be assessed at each study visit, and a 12-lead ECG will be performed at the randomisation visit. Vital signs will be monitored, with pulse and blood pressure measured in triplicate prior to the haemodialysis procedure after the participant is comfortably at rest in either supine or seated position quietly for at least 5 minutes. A physical examination will be performed at the randomisation and end-of-study intervention visits, and includes, at a minimum, measurement of height and assessment of the lungs, cardiovascular system and abdomen, as well as a brief neurological examination.

Patient and public involvement statement

Patients and study participants were not involved in the study design or recruitment. A summary of the study results will be disseminated to participants at the end of the study.

Statistical analysis

Sample size determination

Assuming the true HR for SZC versus placebo is 0.8, 770 primary endpoint events will result in 87% power to demonstrate a statistically significant difference at a two-sided significance level of 4.8% at the final analysis. Based on an assumption that the event rate of the primary composite endpoint is ~0.222 per person-year in the placebo group,^{4 33} it is expected that ~2300 participants will need to be randomised. The anticipated average time in the study of ~25 months will depend on the actual event rate, and any decision to increase or decrease the study duration will be based on blinded event-rate data. Assuming a screen failure rate of 50%, ~4600 participants will be screened to achieve the ~2300 participants randomly assigned (1:1) to the study intervention.

The DMC will conduct an unblinded, formal interim analysis for efficacy when 50% of the total number of primary endpoint events have accrued and are adjudicated (ie, a minimum of 385 events). If the interim analysis occurs at 50% of the total number of primary endpoint events, the hypothesis for the primary endpoint at interim will be tested at the two-sided 0.52% level ($p < 0.0052$). The type I error rate for the final analysis of the primary endpoint and subsequent secondary endpoints will be adjusted for the interim analysis and will be tested at the 4.8% two-sided level, assuming one formal interim analysis for efficacy. At the time of the planned formal interim analysis for efficacy, a non-binding futility analysis will be performed by the DMC. The threshold for futility is defined as a predictive power of <10%.

Analytical methods

Efficacy endpoints will be analysed according to the intention-to-treat principle using the full analysis set (all participants who undergo randomisation and receive a randomisation number). For the main analysis of the

primary objective, the primary hypothesis of no difference between study intervention arms will be evaluated using a Cox regression model with time to first event or censoring, as well as the event indicator as the response, and the study intervention arm and geographic region as covariates. The HR estimate, its SD, 95% CI and p value will be provided. Kaplan–Meier estimates of time to first occurrence of any event in the composite endpoint will be calculated and plotted. Participants will be censored at the study end date or at the time of withdrawal of consent, or death not determined as sudden cardiac death.

For the main analyses of the secondary objectives, time to event of secondary endpoints will be analysed similarly to the primary endpoint (Cox regression model). Serum K^+ concentration endpoints will be analysed using a logistic regression model with a binary variable (serum K^+ concentration of 4.0–5.5 mmol/L, yes or no; serum K^+ concentration of >6.5 mmol/L, yes or no) as the response and the study intervention arm and geographic region as covariates. The estimated OR, corresponding 95% CI and two-sided p value will be presented. The number of hospitalisations, interventions or emergency department visits due to arrhythmias will be analysed using a negative binomial regression model, with the number of events as the response, and the study intervention arm and geographic region as covariates. The logarithm of the participant's corresponding follow-up time will be used as an offset variable in the model to adjust for participants having different exposure times during which the events could potentially occur. The estimated rate ratio, corresponding 95% CI and two-sided p value will be presented.

Safety analyses will be performed using the safety analysis set (all randomised participants who have received at least one dose of study intervention) and will be presented using descriptive statistics, such as mean and SD for continuous variables, and number and percentage for discrete variables.

Ethics and dissemination

This study is conducted in accordance with the consensus ethical principles derived from the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines and the International Council for Harmonisation Good Clinical Practice Guidelines. The protocol, informed consent form, other relevant documents and any amendments required approval by the relevant institutional review board/independent ethics committee from each participating site (online supplemental information). This study will be submitted for publication in a peer-reviewed journal and oral presentations at international conferences. Authorships will be determined based on the International Committee of Medical Journal Editors guidelines.

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