Clinical Study Protocol	
Study Intervention	Sodium Zirconium Cyclosilicate (SZC)
Study Code	D9487C00001
Version	3.0
Date	04 April 2023

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)

Sponsor:
AstraZeneca AB, 151 85 Södertälje, Sweden
(Japan) AstraZeneca K.K., 3-1, Ofuka-cho, Kita-ku, Osaka 530-0011, Japan

Regulatory Agency Identifier Numbers:
EudraCT 2020-005561-14

This clinical study protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D9487C00001

Amendment Number: 2

Study Intervention: Sodium Zirconium Cyclosilicate

Study Phase: Phase III

Brief Title: Effect of Sodium Zirconium Cyclosilicate on Arrhythmia-Related Cardiovascular Outcomes in Participants on Chronic Hemodialysis with Recurrent Hyperkalemia

Acronym: DIALIZE-Outcomes

Study Physician Name and Contact Information Will Be Provided Separately

International Coordinating Investigator:

PPD
North Shore University Hospital
True North Dialysis Center, LLC
100 Community Drive, second floor
Great Neck, New York 11021
United States

VERSION HISTORY AND SUMMARY OF CHANGES

Version 1, 13 January 2021

Initial version

Version 2, 05 November 2021
Changes to the protocol amendment are summarized below:

- Primary endpoint and all endpoint language modified where ventricular tachycardia (VT) was originally to all ventricular tachyarrhythmias (VF, VT, etc).
- **Table 1 SoA, Section 4.1, Section 8.2.5**

  Circumstances for omission of visit 3, retests during screening and correction of screening time added.
- **Table 2 SoA**

  Clarification regarding post weight of V9 and V10 and correction of timing of sites visits.
- **Section 5.2**

  Exclusion criterion #8 updated and broken into 2 separate exclusion criteria: 8 clarifies atrial fibrillation exclusion and 17 clarifies ventricular tachycardia exclusion.
- **Exclusion criteria #9 Prior/Concomitant Therapy** and **#10 Prior/Concurrent Clinical Study Experience** – wording clarifications
- **Section 6.1.2**

  Up-titrated changed to titrated and 4 weeks added to weekly.
- **Section 6.3 and 7.1.3**

  Clarification regarding treatment unblinding and how to handle potentially unblinding data has been added.
- **Section 6.5 Table 5**

  Clarification regarding restricted medication added. SZC (Lokelma) and Diuretics have been added to restricted medications.
- **Section 6.5.2**
  "eg." was deleted since Patiromer = Veltassa is the only the one categorized as patiromer.
- **Section 7.1.1**

  The need for long term use of potassium binders added.
- **Section 7.1.3**

  Clarification step added.

- **Section 7.2**

  Clarification regarding use of coded data for future research.
- **Section 10 Appendix 7**

  Clarification regarding time records and documents need to be retained at sites.
- **Section 8.3.7.1 and Appendix B section B2**

  Wording for "congenital abnormality" was changed to "congenital anomaly".
- **Section 9 Statistical Considerations**

  Clarification regarding the estimand for the primary analysis, as well as the type I error rate that is planned to use for the interim analysis.
- **Appendix**

  Primary endpoint reporting functionality deleted. Time of the digital support start corrected from screening to randomization.

Version 3, 04 April 2023
General changes throughout the protocol amendment are as follows:

- Regulatory Agency Identification Number added to synopsis per new template.
- Study being conducted in approximately 26 countries at approximately 330 study sites.
- Sample size increased to 2800 patients throughout, thus participants to be enrolled increased to 5600 throughout.
- The anticipated average treatment period updated throughout to approximately 37 months.
- DMC futility analysis and interim analysis text updated and clarified throughout.
- Two-sided significance level changed to 4.46% throughout.
- Change in study milestones and recruitment timelines throughout.
- Clarity regarding K-binder chronic therapy timeframe added throughout.
- Updates in line with the new CSP template throughout, including appendices.
- Style, grammatical, and spelling corrections throughout.

Additional minor changes to Section 6.1.2, Section 6.5.2, and Section 11 in-line with text added to Section 4.2.1.

Specific changes to sections throughout the protocol amendment are as follows:

- **Table 1 SoA – Screening Phase**

  Laboratory safety variables clarified and accompanying footnote updated.
- **Table 2 SoA – Randomized Study Intervention Phase**

  Laboratory safety variables clarified.

  Study Events questionnaire administration added to IP dispensation visits and followed by an investigator phone visit, if needed.

  Questions clarified.
- **Section 3**

  Per new template, added information regarding primary estimand details.
- **Section 4.2**

  For Hungary-specific Rationale for Study Design, see Appendix E.
- **Section 4.4**

  End of study definition new template text added.
- **Section 5.1**

  Updated inclusion criterion #3 per request of the Local Study Leader from Japan. See Appendix E.

  Updated inclusion criterion #8 per Austrian requirements. See Appendix E.
- **Section 5.2**

  Clarified exclusion criterion #10 per Italy's request. See Appendix E.
- **Section 5.4**

  Added cross reference to guidance for exclusion criterion #9 regarding screen failure patients who have received K-Binder therapy (due to high potassium) within the prior 7 days.
- **Section 6.1.2**

  Added clarity regarding serum potassium measurement 1 week after the dose change.

  Study Events questionnaire administration added to IP dispensation visits and followed by an investigator phone visit, if needed.

  Questions clarified.
- **Section 6.3**

  Deletion of S-K results from local laboratories as a data item with potential to unblind study team members.
- **Section 6.4**

Added that compliance < 80% and > 120% between the scheduled investigational product dispensation visits are considered deviations.

- **Section 6.5, Table 5 Restricted Medications**

  Based on the drug-drug interaction study, tacrolimus and cyclosporin have been included as restricted medications.

  Text added below Table 5 to clarify dosing of SZC and concomitant medications.

- **Section 6.5.2**

  Additional information added regarding recording of rescue medications.

  Regarding rescue therapy for hyperkalemia, included information clarifying potassium binder use and additional rescue therapies included.

  Hungary-specific information in Appendix E.

- **Section 7.1.1**

  To avoid a protocol deviation, clarify that restricted medications are a mandatory requirement for patients who permanently discontinue from investigational product and remain in the study.

  Italy-specific information in Appendix E.

- **Section 7.2**

  Added Patient Follow-Up Checklist Form and Withdrawal of Consent Checklist should be used to document the process for participants withdrawing from the study.

  Text added to clarify the process of participant withdrawal from the study.

- **Section 8.2.5.2**

  Adding text regarding potassium measurement 1 week after dosage change for local laboratory assessments.

- **Section 8.3.8**

  Medication error, drug abuse, and drug misuse sub-sections added per new template.

- **Section 8.3.6**

  Text updated regarding electronic data capture and reporting of SAEs.

- **Section 9.2**

  Sample size determination updates: 730 primary endpoint events will result in approximately 85% power to demonstrate a statistically significant difference at either interim analysis (two-sided significance level of 1.64%) or at final analysis (two-sided significance level of 4.46%).

- **Section 9.5 Interim Analysis**

  Updates regarding the non-binding futility testing to be performed by DMC when 40% of the total adjudicated events have accrued. The threshold for futility has also been updated. Updated interim efficacy analysis plan to occur at 70% accrual and adjudication of 730 total events. Necessary changes applied throughout relevant sections, including Appendix 2.

- **Appendix A6**

  Template text added.

- **Appendix B4**

  Drug abuse and drug misuse template text added.

- **Appendix B5**

  Study Events Questionnaire referred to in Table 1 included for reference.

- **Appendix E**

  Mobile software application will not be used during the study; thus, content is not required and removed from appendix. Reference to Appendix E in Section 8 also removed.

- **Appendix E**

  Local CSPs for Hungary, Japan, Austria, and Italy merged with global CSP per the EU CTR updated policy. All information and text provided in Appendix E.

  – For Hungary, the Ethics Committee for Clinical Pharmacology of the Medical Research Council (ETT- KFEB) of Hungary expressed concern regarding the use of placebo in patients with hyperkalemia in study D9487C00001. Thus, the scientific rationale for study design (Section 4.2) and rescue medicine text (Section 6.5.2) were updated to clarify that investigators have the ability and discretion to use rescue therapy as needed, according to local practice, to treat all participants; plus, the justification for use of placebo added to emphasize safety of participants in both study arms. These updates can be found in Appendix E.

  – For Japan, updated inclusion criterion #3, Section 5.1, by removing, “For participants < 20 years of age and enrolled in Japan, a written informed consent should be obtained from the participant and his or her legally acceptable representative.” Text no longer required due to civil code change.

  – For Austria, change applies to inclusion criterion #8, Section 5.1.

  – For Italy, changes apply to exclusion criterion #10, Section 5.2; and permanent discontinuation of study intervention in Section 7.1.1.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Special Term	Explanation
AE	adverse event
AF	atrial fibrillation
BP	blood pressure
CKD	chronic kidney disease
CPS	calcium polystyrene sulfonate
CSP	clinical study protocol
CSR	clinical study report
CV	cardiovascular
ECG	electrocardiogram
eCRF	electronic case report form
ED	emergency department
EDC	electronic data capture
DMC	Data Monitoring Committee
EOIV	end of study intervention visit
ESRD	end stage renal disease
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice Unless otherwise noted, 'GCP' shall mean 'the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice' (ICH GCP) and the Japanese 'Good Clinical Practice for Trials on Drugs (Ministry of Health, Labor and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications' (GCP Ordinance)
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	intent-to-treat
Kd	dialysate potassium concentration
LIDI	long interdialytic interval
PIDV	premature study intervention discontinuation visit
qd	once daily
QTcF	QT interval corrected by the Fridericia method

Abbreviation or Special Term	Explanation
RTSM	Randomization and Trial Supply Management
S-K	serum potassium
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sudden cardiac death
SCV	study closure visit
SED	study end date
SoA	Schedule of Activities
SPS	sodium polystyrene sulfonate
SZC	sodium zirconium cyclosilicate
TIA	transient ischemic attack

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title

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)

Brief Title

Effect of Sodium Zirconium Cyclosilicate on Arrhythmia-Related Cardiovascular Outcomes in Participants on Chronic Hemodialysis with Recurrent Hyperkalemia

Acronym: DIALIZE-Outcomes

Regulatory Agency Identifier Numbers

EudraCT 2020-005561-14

Rationale

Patients with end stage renal disease (ESRD) on hemodialysis have an increased prevalence of cardiac arrhythmias that predisposes them to a higher risk of sudden cardiac death (SCD) and stroke. Pre-dialysis hyperkalemia and rapid serum potassium (S-K) shifts that occur during hemodialysis may aggravate or trigger these arrhythmias. Clinical studies in patients with hyperkalemia have demonstrated the efficacy of sodium zirconium cyclosilicate (SZC) in the correction of hyperkalemia and maintenance of normokalemia. Specifically, the efficacy of SZC for treatment of hyperkalemia in patients with ESRD on chronic hemodialysis was demonstrated in the DIALIZE study (randomized, placebo-controlled, double-blind study). The current study will evaluate the effect of treatment with SZC on arrhythmia-related cardiovascular (CV) outcomes in patients with ESRD on chronic hemodialysis with recurrent hyperkalemia.

Objectives and Endpoints

Objectives	Endpoints
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/emergency department (ED) visit due to arrhythmias	• Time to first occurrence of SCD, stroke, or hospitalization/intervention/ED visit due to arrhythmias (atrial fibrillation [AF], bradycardia, asystole, ventricular tachyarrhythmia [such as VF, VT, etc]).
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 long interdialytic interval (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, bradycardia, asystole, ventricular tachyarrhythmia [such as VF, VT, etc])
• 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, 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

Objectives	Endpoints
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 adverse events (AEs)/serious adverse events 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: • Interdialytic weight gain • Events of pre-dialysis hypokalemia (S-K < 3.0 mmol/L)

AE adverse event; AF atrial fibrillation; CV cardiovascular; ED emergency department; LIDI long interdialytic interval; SAE serious adverse event; SCD sudden cardiac death; S-K serum potassium; SZC sodium zirconium cyclosilicate; VT ventricular tachyarrhythmias.

For exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design

This is an international, multicenter, event-driven, randomized, double-blind, parallel group, placebo-controlled study, evaluating the utility of SZC versus placebo to reduce the incidence of SCD, stroke, and arrhythmia-related hospitalizations, interventions, and ED visits in participants on chronic hemodialysis with recurrent hyperkalemia. The study will be conducted at approximately 330 study sites in approximately 26 countries.

Disclosure Statement

This is a parallel group treatment study with 2 arms that is participant, investigator, and outcomes assessor and sponsor blinded.

Number of Participants

The primary objective of the study is to evaluate the efficacy of SZC versus placebo in reducing the incidence of the primary composite endpoint. Assuming the true hazard ratio (HR) for SZC versus placebo is 0.8, 730 primary endpoint events will result in approximately 85% power to demonstrate a statistically significant difference at either interim efficacy analysis (two-sided significance level of 1.64%) or at final efficacy analysis (two-sided significance level of 4.46%). Based on an assumption that the event rate of the primary

composite endpoint is approximately 11 per patient-year in the placebo group, it is expected that approximately 2800 participants will need to be randomized.

Assuming a screen failure rate of 50%, approximately 5600 participants will be enrolled to achieve approximately 2800 participants randomly assigned (1:1) to study intervention (SZC or placebo).

Note: "Enrolled" means a participant's, or his/her legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. "Screen failures" are defined as participants who signed the informed consent form to participate in the clinical study (ie, "enrolled") but did not fulfill the eligibility criteria and, as a consequence, were not subsequently randomized to a treatment group.

Intervention Groups and Duration

The study design will consist of the following planned phases:

- Screening phase (2 to 6 weeks; no study intervention administered). Data required for determination of eligibility are collected and inclusion/exclusion criteria are evaluated.
- Randomized (1:1 ratio) treatment phase (on study intervention until required number of events are accrued). The dose of study intervention will be up-titrated weekly in 5 g increments starting at 5 g once daily (qd) on non-dialysis days (4 doses per week) based on local laboratory pre-dialysis S-K values to achieve and maintain a pre-dialysis S-K between 4.0 and 5.0 mmol/L after the LIDI. The maximum dose of study intervention will be 15 g qd on non-dialysis days. After the initial up-titration, monthly (or more frequent based on clinical judgment) pre-dialysis S-K will be collected after the LIDI at the local laboratory to guide further dose adjustment at any time during the study to achieve and maintain a pre-dialysis S-K between 4.0 to 5.0 mmol/L.

The study is event-driven. The study closure procedures will be initiated when the predetermined number of primary endpoint events are expected to have occurred (730 events). The anticipated recruitment period is planned to be 32 months. The anticipated average treatment period is approximately 37 months, which in practice will be dependent on the actual event rate observed during the study, as the study duration is event-driven. The study duration may be changed if the number of participants enrolled, the event rate, or the randomization rate is different than anticipated. Any decision to increase or decrease participant numbers or extend or shorten the study duration will be based on blinded event rate data.

The Data Monitoring Committee (DMC) will be responsible for monitoring the progress of the study with respect to randomization, 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 all or part of the trial. The DMC will conduct a non-binding futility analysis when 40% of the planned number of primary endpoint events have accrued and have been adjudicated. An interim analysis for efficacy when 70% of the planned number of primary endpoint events have accrued and have been adjudicated is also planned to take place. The DMC will notify the sponsor if the formal stopping criteria for superiority or futility are met.

Data Monitoring Committee: Yes

Statistical Methods

The efficacy analyses will be performed according to the intent-to-treat principle. The Full Analysis Set will be used, which will consist of all randomized participants, regardless of whether participants received study intervention.

The primary endpoint is time to the first occurrence of SCD, stroke, or hospitalization/intervention/ED visit due to arrhythmias (AF, bradycardia, asystole, ventricular fibrillation). The occurrence of intercurrent events (eg, termination of study intervention or initiation of an additional treatment that potentially affects the primary outcome) will be ignored. The only exception to this rule is death: participants who die during the study, for any cause that is not SCD, will be censored at that time point. This would reflect a "hypothetical strategy", the results representing a hypothetical patient population in which a death that is not a SCD does not occur.

The primary hypothesis of no difference between study intervention arms will be evaluated by means of a Cox regression, with time to first event/censoring as response and study intervention arm and geographic region as covariates. Other covariates may also be included as appropriate as specified in the statistical analysis plan. The HR estimate, its standard deviation, 95% confidence interval, and p-value will also be provided. Kaplan-Meier estimates of time to the first occurrence of any event in the composite endpoint will be calculated and plotted.

The following secondary time to event endpoints will be analyzed similarly:

- Time to first occurrence of hospitalization/intervention/ED visit due to arrhythmias (AF, bradycardia, asystole, ventricular tachyarrhythmia such as ventricular fibrillation, ventricular tachycardia, etc)
- Time to first instance of rescue therapy use for hyperkalemia
- Time to SCD
- Time to first occurrence of stroke
- Time to CV death

- Time to death of any cause

A logistic model with the binary variable (yes/no) as response and study intervention arm and geographic region as covariates will be used to evaluate the efficacy of SZC as compared with placebo in the following secondary endpoints. As for the primary endpoint analysis, other covariates may also be included as appropriate. The proportion of participants fulfilling each endpoint criteria will also be presented by study intervention arm. The estimated odds ratio, corresponding 95% confidence interval, and two-sided p-value will be presented.

- S-K of 4.0 to 5.5 mmol/L (yes/no) after the LIDI at the 12-month visit
- S-K > 6.5 mmol/L (yes/no) after the LIDI at the 12-month visit

A negative binomial model with number of events as response and study intervention arm and geographic region as covariates (other covariates included as appropriate) will be used to evaluate the efficacy of SZC as compared with placebo for the following secondary endpoint. 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 occur. Number of events will also be presented by study intervention arm. The estimated rate ratio, corresponding 95% confidence interval, and two-sided p-value will be presented.

- Number of hospitalizations/interventions/ED visits due to arrhythmias (AF, bradycardia, asystole, and ventricular tachyarrhythmia such as ventricular fibrillation, ventricular tachycardia etc)

A non-binding futility analysis will be performed by the DMC when 40% of the planned number of primary endpoint events have accrued and have been adjudicated. The threshold for futility is defined as the estimated hazard ratio at the interim analysis, SZC versus placebo being equal to or larger than 1. This will correspond to a predictive power of < 5.1%.

Additionally, the DMC is also planning an interim analysis for efficacy when 70% of the primary endpoint events have accrued and have been adjudicated, using an O'Brian and Fleming rule (O'Brian P, Fleming T. Cytel Inc. Software Package East 6.5, Copyright 2018). The Type I error rate for the final analysis of the primary endpoint and subsequent secondary endpoints will be adjusted for the interim analysis performed by the DMC.

To control the familywise Type I error rate, a fixed sequence multiple testing procedure for primary and secondary endpoints will be performed. For the primary endpoint the hypothesis of no difference between study intervention arms will be tested at the 4.46% two-sided level (assuming one interim analysis for efficacy). Once the null hypothesis concerning the primary composite efficacy endpoint is rejected, the hypotheses for the secondary efficacy endpoints

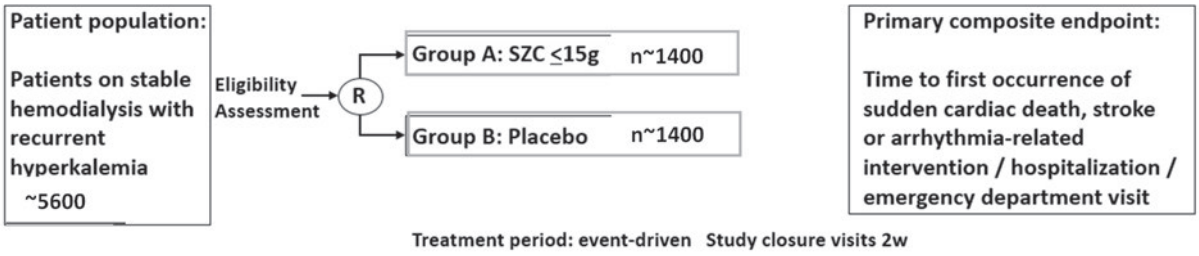
will be tested separately in the order listed in the table above with the same alpha level as the primary endpoint. The testing procedure will continue down the hierarchy if the current endpoint is rejected at a two-sided 4.46% level and will stop if the current endpoint is not rejected at a two-sided 4.46% level.

Safety analyses will be performed using the Safety Analysis Set, defined as all participants who receive at least one dose of study intervention. Safety data will be presented using descriptive statistics unless otherwise specified.

1.2 Schema

The study design is presented in Figure 1.

Figure 1 Study Design



R randomization; SZC sodium zirconium cyclosilicate; w week.

1.3 Schedule of Activities

The SoA to be performed during the screening phase is presented in Table 1. The SoA to be performed during the randomized study intervention phase is presented in Table 2.

Table 1 Schedule of Activities – Screening Phase

Visit	**1**	**2**	**3 (if needed)[a]**	**Details in CSP Section or Appendix**
Study Day (Window)	**-21 (-7 days)**	**-14 (-7 days)**	**-7 (-7 days)**	
	In case retest of lab sample is needed screening may last up to 42 days. Each screening visit can be repeated once.			
Type of Visit	**LIDI**	**LIDI**	**LIDI**	
Informed consent prior to any study specific procedures	X			Section 5.1; Appendix A
Enrollment in IRT/RTSM	X			
Inclusion/exclusion criteria	X			Sections 5.1 and 5.2
Demographics	X			
Medical/surgical history [b, c]	X			
Dialysis prescription [d]	X			
Concomitant Medications	X	X	X	Section 6.5
Pulse and BP [e]	X			Section 8.2.3
Physical examination	X			Section 8.2.1
Height	X			Section 8.2.1
12-lead ECG	X			Section 8.2.4
Pre-dialysis weight	X			Section 8.2.2
Serum HCG pregnancy test (FOCBP only) [f]	X			Section 8.2.5
Pre-dialysis central laboratory safety variables: clinical chemistry (serum) panel (including LIDI S-K)[g]	X	X	X	Section 8.2.5
SAEs	X	X	X	Section 8.3

[a] If S-K measurement criteria are met at V1 and V2 participant should be randomized without performing V3. V3 in this Schedule of Event becomes V4 - the randomization visit because participant has met inclusion criteria. If S-K measurement criteria are not met at V1 and V2 participant should be screen failed without performing V3.

[b] Including dialysis history: (I) dialysis vintage (time since first dialysis in years); (II) type of access: AV fistula, AV graft, tunneled central venous catheter, other (specify).

[c] Including cause of end stage renal disease.

[d] The following parameters will be collected: date when dialysis was initiated; prescribed duration for dialysis; prescribed duration for dialysis unit; dialysate potassium concentration; dialysate potassium concentration unit; blood flow (Qb); blood flow unit; other blood flow unit; dialysate flow (Qd); dialysate flow unit; other dialysiate flow unit, specified; prescribed ultrafiltration; prescribed ultrafiltration unit; dialysis adequacy (spKt/V); and urea removal rate (%).

[e] Pulse and BP should be measured prior to the hemodialysis procedure. Pulse and BP should be measured in triplicate after the participant is comfortably at rest in either supine or seated position quietly for at least 5 minutes.

[f] A suspected pregnancy should be confirmed by increasing levels of serum beta HCG (repeated after one or 2 weeks) or a uterine ultrasound if pregnancy test result is questionable. Repeated serum HCG pregnancy tests may be analyzed by the local laboratory.

[g] If needed laboratory safety variables: clinical chemistry (serum) panel (including LIDI S-K) can be repeated (after LIDI) once for each screening visit. If there is a need to repeat screening visit more than once this needs to be consulted with the Study Physician.

AV arteriovenous; BP blood pressure; CSP clinical study protocol; ECG electrocardiogram; FOCBP females of childbearing potential; HCG human chorionic gonadotropin; IRT/RTSM interactive response technology/randomization and trial supply management; LIDI long interdialytic interval; S-K serum potassium; SAE serious adverse event.

Table 2 Schedule of Activities – Randomized Study Intervention Phase

Visit Description	**Randomization On-site Visit**	**3 months On-site Visit**	**6 months On-site Visit**	**9 months On-site Visit**	**12 months On-site Visit**	**TC/Video/ On-site Visit [a]**	**EOIV or PIDV On-site Visit**	**SCV TC/Video/ On-site Visit [a]**	**Details in CSP Section or Appendix**
Visit	**4**	**5**	**6**	**7**	**8**	**9, 10, 11, etc.**	**EOIV or PIDV [b]**	**SCV [c]**	
Study Day	**1**	**92 ± 7 days**	**183 ± 7 days**	**274 ± 7 days**	**365 ± 7 days**	**Every 3rd Month ± 7 days**			
Type of Visit	**LIDI**	**LIDI**	**LIDI**	**LIDI**	**LIDI**	**LIDI**	**LIDI [b]**		
Pulse and BP [d]	X						X		Section 8.2.3
Physical examination	X						X		Section 8.2.1
12-lead ECG	X								Section 8.2.4
Pre-dialysis weight (measured at the dialysis clinic) [g]	X	X	X	X	X	X	X		Section 8.2.2
Post-dialysis weight after the prior dialysis session (measured at the dialysis clinic) [e, g]	X	X	X	X	X	X	X		Section 8.2.2
Pre-dialysis central laboratory safety variables: clinical chemistry (serum) panel (including LIDI S-K) Hematology/hemostasis (whole blood) panel (only at randomization, Day 1)	X				X				Sections 8.1.2, 8.2.5
Randomization in IRT/RTSM	X								Section 6.3
Study intervention dispensation, compliance reminder, and accountability	Study intervention will be dispensed to the participant at the time of the dose adjustment review: weekly for 4 dispensations and every 4 weeks thereafter. Study intervention may be dispensed more frequently if needed (eg, if the participant's dose is changed per dose adjustment review). Compliance reminder, and accountability check will be done at every dispensation.								Sections 6.1.1, 6.1.2, 6.2, 6.4

Table 2 Schedule of Activities – Randomized Study Intervention Phase

Visit Description	Randomization On-site Visit	3 months On-site Visit	6 months On-site Visit	9 months On-site Visit	12 months On-site Visit	TC/Video/ On-site Visit [a]	EOIV or PIDV On-site Visit	SCV TC/Video/ On-site Visit [a]	Details in CSP Section or Appendix
Visit	**4**	**5**	**6**	**7**	**8**	**9, 10, 11, etc.**	**EOIV or PIDV [b]**	**SCV [c]**	
Study Day	**1**	**92 ± 7 days**	**183 ± 7 days**	**274 ± 7 days**	**365 ± 7 days**	**Every 3rd Month ± 7 days**			
Type of Visit	**LIDI**	**LIDI**	**LIDI**	**LIDI**	**LIDI**	**LIDI**	**LIDI [b]**		
Study Events evaluation/ Study Events Questionnaire [h]	X	X	X	X	X	X	X		Appendix B 5
Concomitant medication	X	X	X	X	X	X	X	X	Section 6.5
Endpoint collection [f]	X	X	X	X	X	X	X	X	Section 8.1
AEs and SAEs	X	X	X	X	X	X	X	X	Section 8.3

[a] Visit can be done via TC, video call or on-site visit, if more convenient.

[b] Refer to Section 7.1.5 for further details on the EOIV. Refer to Sections 7.1 and 7.1.4 for further details on the PIDV. The PIDV is not required to be performed at a LIDI visit.

[c] Refer to Section 7.1.6 for further details on the SCV.

[d] Pulse and BP should be measured prior to the hemodialysis procedure. Pulse and BP should be measured in triplicate after the participant is comfortably at rest in either supine or seated position quietly for at least 5 minutes.

[e] The prior session post-dialysis weight measured at dialysis session immediately prior to the study visit will be used in the calculation of interdialytic weight gain.

[f] Potential endpoints will be collected from randomization throughout the study until and including the participant's last visit.

[g] Pre and post-dialysis weight not to be collected if the visit is done via TC/ video.

[h] Study Events evaluation to be done during study intervention dispensation visit. Study Events Questionnaire to be used to facilitate the evaluation. In case Study Events evaluation is not done by the Investigator/ Sub-investigator and there is positive answer to any of the question unscheduled follow up visit/ phone visit should be done by Investigator/ Sub-investigator within a week to complete Study Event evaluation and to report AEs. In case an SAE needs to be reported, timelines for SAE reporting apply. Refer to Appendix B 5 Study Events Questionnaire.

AE adverse event; BP blood pressure; CSP clinical study protocol; ECG electrocardiogram; EOIV end of study intervention visit; IP investigational product; IRT/RTSM interactive response technology/randomization and trial supply management; LIDI long interdialytic interval; PIDV premature study intervention discontinuation visit; S-K serum potassium; SAE serious adverse event; SCV study closure visit; TC telephone call.

2 INTRODUCTION

Sodium zirconium cyclosilicate, hereafter abbreviated as SZC, is an oral, non-polymer inorganic cation-exchanger that represents a novel therapy for the treatment of hyperkalemia. SZC selectively captures potassium ions in exchange for hydrogen and sodium ions in the gastrointestinal tract, thereby reducing S-K concentration and removing potassium from the body through increased fecal excretion. SZC exerts its effect locally and it is not absorbed systemically.

2.1 Study Rationale

Patients with ESRD on hemodialysis have an increased prevalence of cardiac arrhythmias that predisposes them to a higher risk of SCD and stroke (Foley et al 2011, Jadoul et al 2012, Seliger et al 2003). Pre-dialysis hyperkalemia and rapid S-K shifts that occur during hemodialysis may aggravate or trigger these arrhythmias. Clinical studies in patients with hyperkalemia have demonstrated the efficacy of SZC in the correction of hyperkalemia and maintenance of normokalemia. Specifically, the efficacy of SZC for treatment of hyperkalemia in patients with ESRD on chronic hemodialysis was demonstrated in the DIALIZE study (randomized, placebo-controlled, double-blind study; Fishbane et al 2019). The current study will evaluate the effect of treatment with SZC on arrhythmia-related CV outcomes in patients with ESRD on chronic hemodialysis with recurrent hyperkalemia.

2.2 Background

With the progression of CKD to ESRD the ability of the kidneys to eliminate potassium is eventually lost resulting in the need for renal replacement therapy to maintain a normal S-K. While kidney transplantation is the preferred treatment option for most patients with ESRD, dialysis remains the global standard of care for those awaiting, or not being eligible for, transplantation. Hemodialysis is the most common modality and is usually performed 3 times a week, with a Kd of 2.0 to 2.5 mmol/L being the most commonly used prescription (Karaboyas et al 2017). However, despite dialysis, hyperkalemia remains common in this population (62.9 per 100 patient-months at the end of the LIDI) (Yusuf et al 2016). These patients are therefore chronically exposed to the pro-arrhythmic effects of potassium, and at higher risk of SCD, which accounts for 26% of all deaths in the ESRD population (Jadoul et al 2012). Recent studies have shown that S-K levels above 5.6 mmol/L are associated with increased CV and all-cause mortality (Kovesdy et al 2007, Yusuf et al 2016).

Further, cardiac conduction disorders and arrhythmias are common in hemodialysis patients. The reported annualized event rate for arrhythmias requiring hospitalization is 13.6 per 100 person-years with 25.9% of hemodialysis patients having an admission for an arrhythmia event during a follow-up period of 2.2 years (Foley et al 2011).

Atrial fibrillation is one of the strongest risk factors for ischemic stroke and an independent predictor of death in the general population (Benjamin et al 1998, Dries et al 1998, Sankaranarayanan et al 2015, Wolf et al 1998). The estimated prevalence of AF among patients with ESRD in observational studies has been reported to be as high as 27% (Genovesi et al 2005, Soliman et al 2010). Rates of hospitalized stroke are reportedly 5- to 10-fold higher in dialysis patients when compared to non-ESRD patients, with ischemic strokes being the most common (Seliger et al 2003, Sozio et al 2009).

Recent studies using continuous heart rhythm monitoring with implantable loop recorders for up to 21 months in patients with ESRD on hemodialysis have shown a prevalence of AF between 21% and 42% (Roy-Chaudhury et al 2018, Sacher et al 2018, Wong et al 2015). The highest rates of AF occur during the dialysis session, but a significantly increased AF event rate is also observed at the end of the LIDI and during the 12 hours following completion of a dialysis session (Roy-Chaudhury et al 2018, Wong et al 2015). The mechanisms for the increased frequency of AF surrounding dialysis sessions are unknown, but sudden shifts in S-K resulting from a large gradient between pre-dialysis S-K and Kd have been proposed to play a role (Roy-Chaudhury et al 2018). A decrease in S-K during hemodialysis is associated with modifications of atrial electrophysiology that can favor AF onset, namely a decrease in atrial conduction velocity and a decrease in atrial cell effective refractory period; decreased P-wave conductivity is a known risk factor for AF (Severi et al 2010). Therefore, reducing large, sudden shifts in S-K during dialysis by achieving pre-dialysis normokalemia and a smaller S-K-Kd gradient can potentially decrease abnormalities in atrial electrophysiology and reduce susceptibility to AF.

Another important finding in hemodialysis patients is the occurrence of high rates of atrio-ventricular conduction disorders, bradycardia, and periods of asystole (Roy-Chaudhury et al 2018, Sacher et al 2018, Wong et al 2015). The availability of implantable loop recorders for continuous heart monitoring has provided compelling evidence that bradyarrhythmias, rather than tachyarrhythmias, are the pre-eminent arrhythmic associations of SCD and fatal events (Kalra et al 2018). In one study, prolonged episodes of bradycardia leading to asystole and SCD were documented in several patients (Wong et al 2015).

The LIDI has been associated with the highest incidence of SCD (Foley et al 2011). In one study using implantable loop recorders, the LIDI was found to be the highest-risk period for all forms of arrhythmias and SCD (Wong et al 2015). In another study, the LIDI was the highest-risk period for bradyarrhythmias and asystole (Roy-Chaudhury et al 2018). A pre-dialysis S-K > 5.0 mmol/L was associated with a higher risk of conduction disorders, which may lead to bradyarrhythmias and asystole (Sacher et al 2018). A reduction in interdialytic hyperkalemia may therefore potentially decrease the susceptibility to conduction disorders, bradycardia, and asystole.

Potassium-binding resins (SPS and CPS) are used in some instances to treat hyperkalemia in dialysis patients; however, these agents have not been extensively studied, are not universally used, and have no specific indications in this population. Moreover, even after dynamic management of Kd (more frequent prescription of 2.0 mmol/L) and potassium binder treatment (increasing the dose), only 6.3% of patients become normokalemic within 3 months after an S-K of > 5.5 mmol/L (Rossignol et al 2017). There is, therefore, a medical need for a pharmacological treatment that can effectively correct and maintain S-K levels within the normokalemic range during the interdialytic intervals in this segment of the hyperkalemia patient population.

The effect of SZC in reducing S-K has consistently been demonstrated in the clinical development program. In randomized, double-blind, placebo-controlled studies in non-dialysis patients, SZC rapidly, effectively, and safely reduced S-K into the normokalemic range across a broad population of patients with hyperkalemia and with various underlying comorbidities, concomitant treatments, and demographic characteristics. Furthermore, continued SZC administration effectively maintained normokalemia for up to 12 months. Importantly, the DIALIZE study demonstrated that SZC is effective in maintaining normokalemia during the LIDI in the segment of the hyperkalemia patient population on chronic hemodialysis. It is hypothesized in this study that treatment with SZC may reduce the occurrence of SCD, stroke, or hospitalizations, interventions, or ED visits due to arrhythmias and potentially reduce morbidity and mortality in patients on chronic hemodialysis with hyperkalemia.

A detailed description of the chemistry, pharmacology, efficacy, and safety of SZC is provided in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

The primary benefit for participants randomized to SZC treatment is expected to be the maintenance of normokalemia during the LIDI, in line with what was observed in the DIALIZE study. Further, should the study hypothesis prove true, this may bring a consequent improvement in arrhythmia-related CV outcomes and urgent ED/hospital visits for hyperkalemia-related arrhythmias. 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.

Participants treated with placebo may not obtain any benefit in terms of hyperkalemia correction and maintenance but may benefit from the closer follow-up. Participants will receive alternative therapies whenever clinically indicated.

An established dose adjustment algorithm will be used during the study to titrate SZC doses to enable participants to achieve and maintain pre-dialysis normokalemia (S-K between 4.0 to 5.0 mmol/L) after the LIDI (Section 6.1.2). In accordance with the algorithm, the dose may be

increased, reduced, or kept unchanged, depending on the current potassium concentration, adapting the dosing regimen to each participant and preventing unnecessarily high exposure to the product.

The risks identified with SZC treatment include hypokalemia and edema-related events (includes fluid overload, fluid retention, generalized edema, hypervolemia, localized edema, edema, peripheral edema, peripheral swelling). In this study, the risk for hypokalemia is mitigated by periodic monitoring of potassium and adjustment of the SZC dose as necessary. Edema can be managed by conservative measures in line with standard clinical practice. No additional safety risks were identified in the DIALIZE study.

In conclusion, the favorable benefit-risk ratio that has been established for SZC in the clinical development program remains positive when SZC is used to treat hyperkalemia in participants on chronic hemodialysis, as shown in the DIALIZE study.

More detailed information about the known and expected benefits and potential risks of SZC may be found in the Investigator's Brochure.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

The objectives of the study, as well as the associated endpoints, are listed in Table 3. For a detailed discussion of these analyses, see Section 9.

Table 3 Objectives and Endpoints

Objectives	Endpoints
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	• Time to first occurrence of SCD, stroke, or hospitalization/intervention/ED visit due to arrhythmias (AF, bradycardia, asystole, ventricular tachyarrhythmia [such as VF, VT, etc]).
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, bradycardia, asystole, ventricular tachyarrhythmia [such as VF, VT, etc]).
• 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, bradycardia, asystole, or ventricular tachyarrhythmia [such as VF, VT, etc])

Table 3 Objectives and Endpoints

Objectives	Endpoints
• 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: • Interdialytic weight gain • Events of pre-dialysis hypokalemia (S-K < 3.0 mmol/L)
Exploratory	
• To evaluate the efficacy of SZC compared with placebo in maintaining normokalemia at one year	• S-K of 4.0-5.0 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, all stroke, or hospitalization/intervention/ED visit due to arrhythmias, or of the need for rescue therapy for hyperkalemia	• Time to first occurrence of SCD, stroke, or hospitalization/intervention/ED visit due to arrhythmias (AF, bradycardia, asystole, ventricular tachyarrhythmia [such as VF, VT etc]), or use of rescue therapy
• To evaluate the use of rescue therapy for SZC compared to placebo	• Number of events of rescue therapy use for hyperkalemia

AE adverse event; AF atrial fibrillation; CV cardiovascular; ED emergency department; LIDI long interdialytic interval; SAE serious adverse event; SCD sudden cardiac death; S-K serum potassium; SZC sodium zirconium cyclosilicate; VT ventricular tachyarrhythmias.

PRIMARY ESTIMAND DETAILS

Primary clinical question: Can SZC, compared to placebo, reduce the incidence of SCD/stroke/arrhythmia-related hospitalizations/interventions/ED visits in participants receiving chronic hemodialysis with recurrent hyperkalemia?

The hazard ratio for SZC versus placebo will be estimated regardless of treatment discontinuation and additional therapy (treatment policy) for the time to the first event of SCD/stroke/arrhythmias in participants receiving chronic hemodialysis with recurrent hyperkalemia.

Targeted population: All participants receiving chronic hemodialysis with recurrent hyperkalemia and satisfying other inclusion exclusion criteria.

Endpoint: Time to the first occurrence of adjudicated events of SCD, stroke, or arrhythmia-related hospitalizations/interventions/ED visits.

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.

Population-level summary: Hazard ratio for SZC versus placebo.

Rationale for estimand: The rationale for the population and treatment condition is explained in Section 2.1. Hazard ratio is the target of estimation as per standard approach to time to event analysis. Treatment policy approach is in line with the standard intention to treat principle and corresponds to a conservative evaluation of treatment effect.

For secondary endpoints, a similar approach of adopting the treatment policy strategy will be applied.

4 STUDY DESIGN

4.1 Overall Design

This is an international, multicenter, event-driven, randomized, double-blind, parallel group, placebo-controlled study, evaluating the utility of SZC versus placebo to reduce the incidence

of SCD, stroke, and arrhythmia-related hospitalizations, interventions, and ED visits in participants on chronic hemodialysis with recurrent hyperkalemia.

It is estimated that approximately 5600 participants at about 330 study sites in about 26 countries will be enrolled to reach the target of 2800 participants randomized (1:1) to study intervention (SZC or placebo).

The study design will consist of the following planned phases:

- Screening phase (2 to 6 weeks; no study intervention administered). Data required for determination of eligibility are collected and inclusion/exclusion criteria are evaluated.
- Randomized (1:1 ratio) treatment phase (on study intervention until required number of events are accrued). The dose of study intervention will be up-titrated weekly in 5 g increments starting at 5 g qd on non-dialysis days (4 doses per week) based on local laboratory pre-dialysis S-K values to achieve and maintain a pre-dialysis S-K between 4.0 and 5.0 mmol/L after the LIDI. The maximum dose of study intervention will be 15 g qd on non-dialysis days. After the initial up-titration, monthly (or more frequent based on clinical judgment) pre-dialysis S-K will be collected after the LIDI at the local laboratory to guide further dose adjustment at any time during the study to achieve and maintain a pre-dialysis S-K between 4.0 to 5.0 mmol/L.

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

The study is designed and will be directed and published by an Executive Committee. The following additional committees will be selected: a National Lead Investigator Committee, an Adjudication Committee, and an independent DMC (Appendix A 5). The DMC will be responsible for monitoring the progress of the study with respect to randomization, 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 all or part of the trial. A non-binding futility analysis will be undertaken when 40% of the planned number of primary endpoint events have accrued and have been adjudicated

(Section 9.5). The DMC will also conduct an interim analysis for efficacy when 70% of the planned number of primary endpoint events have accrued and have been adjudicated. The DMC will notify the sponsor if the formal stopping criteria for superiority or futility are met.

The overall study design is presented in Figure 1.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimize risks to study integrity.

Where permissible by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following:

- Obtaining consent for the mitigation procedures and document this in the source data
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix D.

4.2 Scientific Rationale for Study Design

This is a randomized, double-blind, placebo-controlled parallel-group event-driven study. Randomization and double-blinding will minimize potential bias.

The study includes hemodialysis participants who have been on dialysis for a minimum of 4 months and receive treatment 3 times a week and who have at least 2 out of 2 or 2 out of 3 pre-dialysis S-K values $\geq$ 5.5 mmol/L at the end of the LIDI during screening. No clinically justified therapy for severe acute hyperkalemia will be withheld from study participants. Choice of rescue therapy will be available according to local practice patterns. Furthermore,

since the hypothesis that reducing LIDI hyperkalemia will reduce patient-experienced outcomes, which is the purpose of this study, has not been proven, placebo is deemed to be the appropriate comparator in this study.

Sudden cardiac death, stroke, and increased hospitalizations, ED visits and therapeutic interventions can result from arrhythmias associated with interdialytic hyperkalemia (ie, bradyarrhythmias and asystole) and rapid S-K fluxes during hemodialysis (ie, AF) (Section 2.2). Therefore, a composite of SCD, stroke, and hospitalizations, interventions, and ED visits due to these arrhythmias is selected as the primary endpoint. Such interventions may be pharmacological or non-pharmacological. All of the components of the primary endpoint will be adjudicated.

While the key objective of the study is to demonstrate benefit on clinical outcomes, evidence of successful hyperkalemia management long-term is deemed clinically relevant. Additionally, hospitalizations due to arrhythmias as well as from any cause are important outcomes from a patient and health resource utilization perspective and help further describe the clinical benefit of SZC.

The Hungary-specific rationale is included in Appendix E.

4.3 Justification for Dose

The recommended starting dose in this study in participants on chronic hemodialysis is 5 g qd on non-dialysis days. To establish normokalemia, the dose should be titrated up or down weekly based on pre-dialysis S-K after the LIDI in increments of 5 g up to a maximum of 15 g qd on non-dialysis days. SZC will be dosed and titrated in this study according to the approved label in the dialysis population (US PI, SmPC).

For details regarding the dosing regimen, see Section 6.1.

4.4 End of Study Definition

For Clinical Trial Transparency (CTT) the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last participant for any protocol related activity.

Food and Drug Administration requirements defines 2 completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with

different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

The Executive Committee and AstraZeneca will monitor the accrual of endpoint events and when appropriate define the SED at which time at least the pre-defined target number of 730 participants are anticipated to have had events for the primary composite endpoint. The study sites will be instructed to plan for EOIVs and SCVs.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor (Appendix A 9).

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

In this protocol, "enrolled" means a participant's, or his/her legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. "Randomized" participants are defined as those who undergo randomization and receive a randomization number (Section 6.3). "Screen failures" are defined in Section 5.4.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Informed Consent

1 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

2 Provision of signed and dated, written ICF prior to any mandatory study-specific procedures, sampling, and analyses (Appendix A).

Age

3 Must be ≥ 18 years of age, at the time of signing the ICF (see Appendix E for Japan-specific update).

Type of Participant and Disease Characteristics

4 Receiving hemodialysis (or hemodiafiltration) 3 times a week for treatment of ESRD for ≥ 4 months before enrollment

5 Must have hemodialysis access consisting of an arteriovenous fistula, arteriovenous graft, or tunneled (permanent) catheter which is expected to remain in place for the entire duration of the study

6 At least 2 out of 2 or 2 out of 3 pre-dialysis S-K values ≥ 5.5 mmol/L after the LIDI during screening

Contraception and Reproduction

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

7 Negative pregnancy test for female participants of childbearing potential

8 Female participants must be 1 year postmenopausal, surgically sterile, or using one highly effective form of birth control (defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly). They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study and willing to remain on the birth control until 12 weeks after the last dose. See Section 5.3.4. See Appendix E for Austria-specific update.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Pseudohyperkalemia secondary to hemolyzed blood specimen (this situation is not considered a screening failure: sampling or full screening can be postponed to a later time as applicable)

2 Presence of cardiac arrhythmias or conduction defects that require immediate treatment

3 Participants who have a pacemaker or implantable cardiac defibrillator

4 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, confound safety or efficacy assessment and jeopardize the quality of the data, or interfere with study participation, or any other restrictions or contraindications in the local prescribing information for SZC

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

6 Congenital long QT syndrome

7 QTcF > 550 msec

8 Atrial fibrillation requiring immediate/urgent intervention at screening or randomizations.

Prior/Concomitant Therapy

9 Treated with sodium polystyrene sulfonate (SPS, Kayexalate, Resonium), calcium polystyrene sulfonate (CPS Resonium Calcium), patiromer (Veltassa), or SZC (Lokelma) within 7 days before screening or anticipated requiring chronic use of any of these agents during the study. If a participant requires rescue therapy (potassium binder or dialysate S-K change during screening period, see Section 6.5.2), the participant will be screen failed.

Prior/Concurrent Clinical Study Experience

10 Participation in another clinical study with an investigational product, device, or non-standard hemodialysis procedure administered within one month before screening. See Appendix E for Italy-specific update.

Other Exclusions

11 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

12 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

13 Previous randomization in the present study

14 Females who are pregnant (confirmed with positive pregnancy test or a uterine ultrasound if pregnancy test result is questionable), breastfeeding, or planning to become pregnant during the study.

15 Known hypersensitivity or previous anaphylaxis to SZC or to components thereof.

16 Scheduled date for living donor kidney transplant.

Medical Conditions continuation

17. Sustained Ventricular Tachycardia > 30 seconds requiring assessment / intervention.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Dialysis clinics included in the study should provide participants with dietary advice. Although details may vary across sites, the overall approach should be to give participants dietary advice targeted to maintain low potassium intake (limited amount of high-potassium food, restrictions on raw vegetables) while maintaining adequate nutrition in terms of protein and caloric intake. The use of print educational materials to educate participants is encouraged.

5.3.2 Caffeine, Alcohol, and Tobacco

No restrictions regarding caffeine, alcohol, or tobacco intake, beyond those specified by dietary counselling as described above.

5.3.3 Activity

No physical activity restrictions.

5.3.4 Contraception

Female participants of childbearing potential must have a negative pregnancy test during screening (before first dose of study intervention).

Female participants of childbearing potential must use one highly effective form of birth control. They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study and willing to remain on the birth control until 12 weeks after the last dose. Women who are surgically sterile or those who are postmenopausal are not considered to be of childbearing potential.

- Surgical sterilization includes: hysterectomy, bilateral oophorectomy, or bilateral salpingectomy.
- Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause.
- Highly effective birth control methods (defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:
  - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
  - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
  - Intrauterine device
  - Intrauterine hormone-releasing system
  - Bilateral tubal occlusion
  - Vasectomized partner
  - Sexual abstinence (true abstinence in line with the participant's preferred and usual lifestyle; however, periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of exposure to the study intervention, and withdrawal are not acceptable methods of contraception)

Serum levels of beta HCG can be elevated in ESRD patients on dialysis in the absence of pregnancy. A suspected pregnancy should be confirmed by increasing levels of serum beta HCG (repeated after one or 2 weeks) or a uterine ultrasound. Repeated serum HCG pregnancy tests may be analyzed by the local laboratory.

5.4 Screen Failures

Screen failures are defined as participants who signed the ICF to participate in the clinical study (ie, "enrolled") but did not fulfill the eligibility criteria and, as a consequence, were not subsequently randomized to a treatment group via the IRT/RTSM. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any SAE, and information necessary to link laboratory assessments with central laboratory data.

Individuals who do not meet the S-K criteria for participation in this study during the screening period (screen failure) may be rescreened once, if the cause of the S-K ineligibility is thought to be transient in the opinion of the investigator; the participant must have the 2 or 3 weekly S-K measurements repeated when the transient condition is resolved in the opinion of the investigator (refer to Section 5.2, exclusion criterion #9).

Rescreened participants will keep the originally assigned enrollment number and are not required to sign another ICF if the rescreening occurs within 60 days from the previous ICF signature date (Appendix A 3). Repeated assessments will be documented as rescreening visits in the eCRF.

Enrolled participants who are not randomized (eg, due to screen failure or participant decision) should have the reason for study withdrawal recorded in the eCRF.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol. Study intervention in this study refers to SZC or placebo.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

The study intervention (investigational products) to be administered in this study are presented in Table 4.

Table 4 Investigational Products

Arm Name	**Arm A**	**Arm B**
Intervention Name	**SZC**	**SZC Placebo**
Type	Drug	Drug
Dose formulation	Powder for oral suspension in a sachet	Powder for oral suspension in a sachet
Unit dose strength(s)	5 g or 10 g SZC	5 g or 10 g SZC placebo
Dosage level(s)	Single dose contains 5 to 15 g SZC that should be suspended in 45 mL of water by participant and administered qd on non-dialysis days.	Single dose contains 5 to 15 g SZC placebo that should be suspended in 45 mL of water by participant and administered qd on non-dialysis days.
Route of administration	Oral	Oral
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labeling	Study intervention will be provided in sachet. Each sachet will be labeled in accordance with GMP Annex 13 and per country regulatory requirement. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil1 GMP Annex 13 requirements for labeling. Label text will be translated into local language. For Japan: Labels will be prepared in accordance with GCP Ordinance. Details are specified in the document explaining the reconstitution procedures and other handling procedures for the investigational products.	

GCP Good Clinical Practice; GMP Good Manufacturing Practice; IMP investigational medicinal product; NIMP non-investigational medicinal product; qd once daily; SZC sodium zirconium cyclosilicate.

6.1.2 Dose and Treatment Regimens

SZC or placebo will be suspended in 45 ml of water and administered orally on non-dialysis days.

For participants on dialysis, study intervention should only be dosed on non-dialysis days. The recommended starting dose is 5 g once daily. To establish normokalaemia (4.0 to 5.0 mmol/L based on local laboratory pre-dialysis S-K values), the dose should be titrated weekly based on the pre-dialysis serum potassium value after the LIDI.

The dose should be adjusted at intervals of 1 week in increments of 5 g up to 15 g once daily on non-dialysis days. In case of dose adjustment serum potassium must be measured one week after the dosage change. After the initial titration and once normokalaemia is established, potassium should be monitored regularly (eg, monthly, or more frequently based on clinical judgment including changes in dietary potassium or medication affecting serum potassium).

Once normokalaemia is established, pre-dialysis S-K will be collected after the LIDI at the local laboratory and the study intervention dose adjusted depending on the current potassium value to achieve and maintain a pre-dialysis S-K between 4.0 to 5.0 mmol/L. The maximum dose of study intervention will be 15 g qd on non-dialysis days.

Study intervention will be dispensed to the participant at the time of the dose adjustment review: weekly for 4 dispensations and every 4 weeks thereafter. Study intervention may be dispensed more frequently if needed (eg, if the participant's dose is changed per dose adjustment review). The Study Events questionnaire will be administered at each dispensation visit and followed by an investigator follow-up/phone visit, if needed (refer to Table 2 and Appendix B 5). Compliance reminders and accountability checks will also be performed at every dispensation (Sections 6.2 and 6.4).

Rescue therapy should be guided by local clinical practice patterns. Rescue therapy should be followed by the appropriate dose adjustment if appropriate and proper documentation of the event (Section 6.5.2).

6.2 Preparation/Handling/Storage/Accountability

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. All study intervention should be kept in a secure place under appropriate storage conditions. The study intervention label specifies the appropriate storage.

3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

All participants who fulfill eligibility criteria will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log-in information and directions for the RTSM will be provided to each site.

The randomization codes will be computer generated in blocks using the AstraZeneca Global Randomization System in a way that ensures approximate balance (1:1) between the 2 intervention arms.

The randomization will be stratified by country.

If a participant withdraws from the study, then his/her enrollment/randomization code cannot be reused. Withdrawn participants will not be replaced.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the intervention randomization. The IRT/RTSM programmed with blind-breaking instructions will be available at all times. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to AstraZeneca, without revealing the study intervention given to the participant to the AstraZeneca staff. The actual result of the S-K sample taken at the 12-month visit will be blinded to the investigator site and the AstraZeneca study team. The S-K values that fall outside of the reference range at this visit with potential critical implications for the participant, will be notified to the principal investigator and a pre-identified sponsor contact.

Information on study drug dose adjustment has the potential to unblind study team members and therefore requires special handling (EX/DA modules and IRT reports are redacted). The local Study Team, AZ IRT Lead and IQVIA DM Team will be unblinded to that data. Information about dosing information must not be shared with the Global Study Team (not to be included in the MV reports, Follow up Letters, Q&A logs or other kind of communication with the Global Study Team).

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study intervention and that potentially require expedited reporting to regulatory authorities. Care should be taken to maintain the blinding to the Executive Committee and AstraZeneca Study Team conducting the trial. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

Routines for all measures listed in this section will be described in the IRT/RTSM user manual that will be provided to each center.

6.4 Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed. Compliance will be assessed by counting returned sachets and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

The rule to be followed regarding study intervention compliance is: < 80% and > 120% (including dose adjustments) between the study intervention dispensation visits should be considered deviations. For lost/unreturned study intervention < 80% of returned study intervention sachets are to be considered deviations.

A record of the number of study intervention sachets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the eCRF.

6.5 Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy. The medications listed in Table 5 are restricted during the study.

Restricted medications taken outside the conditions as specified in the “Usage” column, due to, eg, compelling medical reasons that necessitate such an action, will be considered as disallowed medications, the use of which constitutes a protocol deviation.

Table 5 Restricted Medications

Restricted Medication/Class of Drug	Usage
Potassium Binders: SPS (Kayexalate, Resonium), CPS (Resonium Calcium), or patiromer (Veltassa)	These drugs should be avoided during the study and can only be used as rescue therapy (Section 6.5.2).

Table 5 Restricted Medications

Restricted Medication/Class of Drug	Usage
Loop Diuretics: Bumex (bumetanide), Edecrin (ethacrynic acid), Lasix (furosemide), Demadex (torsemide)	Changes to loop diuretics (including adding a new changing the dose or discontinuation or switching of loop diuretics) during the study are discouraged. If changes in loop diuretics are clinically indicated this should be documented in the electronic case report form.
SZC (Lokelma)	Once the participant has been enrolled in the study, SZC cannot be used for rescue therapy.

CPS calcium polystyrene sulfonate; SPS Sodium polystyrene sulfonate.

Effect of Other Medicinal Products on SZC

As SZC is not absorbed or metabolized by the body, there are no clinically significant drug-drug interactions with other medicinal products on the pharmacological action of SZC.

Effect of SZC on Other Medicinal Products

As SZC is not absorbed or metabolized by the body and does not meaningfully bind other medicinal products, there are limited effects on other medicinal products.

SZC can transiently increase gastric pH by absorbing hydrogen ions that can lead to changes in solubility and absorption kinetics for co-administrated drugs with pH-dependent bioavailability. Therefore, the study intervention should be administered at least 2 hours before or 2 hours after oral medications with gastric pH-dependent bioavailability to mitigate the risk of drug interactions.

SZC can be co-administered with oral medications that do not exhibit pH-dependent bioavailability without spacing of dosing times.

Examples of drugs that should be taken 2 hours before or after SZC to avoid possible raised gastric pH drug interaction are listed in Table 6.

Table 6 Drug Interactions

Class of Drug	Drugs
Azole antifungals	ketoconazole, itraconazole, posaconazole
Anti-HIV drugs	atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir, rilpivirine
Tyrosine kinase inhibitors	erlotinib, dasatinib, nilotinib
Immunosuppressives	tacrolimus

HIV human immunodeficiency virus.

SZC/placebo can be co-administered without spacing of dosing times with oral medications that do not exhibit pH-dependent bioavailability.

In a clinical drug-drug interaction study conducted in healthy subjects, co-administration of SZC with amlodipine, dabigatran, clopidogrel, atorvastatin, furosemide, glipizide, warfarin, losartan, or levothyroxine did not result in clinically meaningful drug-drug interactions. No dose adjustments or separation of the time of dosing are required for these drugs.

In another drug-drug interaction study in healthy volunteers, co-administration of SZC 15 g with tacrolimus 5 mg resulted in a decreased tacrolimus area under the concentration-time curve and maximum observed concentration by 37% and 29%, respectively. Therefore, tacrolimus should be taken at least 2 hours before or after SZC/placebo. In the same study, co-administration of SZC and cyclosporin did not show a clinically meaningful interaction.

6.5.1 Other Concomitant Therapy

Medication other than that described above, which is considered necessary for the participant's safety and wellbeing, may be given at the discretion of the investigator, and recorded in the appropriate sections of the eCRF.

6.5.2 Rescue Medicine

Rescue therapy for controlling hyperkalemia is defined as any short-term (24 to 48 hours) therapeutic intervention during the study, that is considered necessary per the investigator's judgment and in accordance with local practice patterns to reduce S-K in the setting of an AE of severe hyperkalemia. See Hungary-specific text in Appendix E.

Rescue Therapy Permissible in Dialize-Outcomes Study

Specifically, rescue therapy applies only to short-term (24 to 48 hours) therapy to treat an AE of severe hyperkalemia as defined in the CSP. Note that rescue medications indicated for treatment of severe hyperkalemia encompass primarily rapid-acting IV or inhalable drugs that reduce serum potassium within a few hours (eg, insulin/glucose, beta adrenergic agonists, sodium bicarbonate); these drugs must take precedence over oral potassium binders in such acute setting given that oral binders have delayed onset of action and lack approval for life-threatening hyperkalemia. Potassium binders (other than SZC) should only be used for short periods of time (24 to 48 hours) to complement the action of rapid acting hyperkalemia rescue drugs. Potassium binders (other than SZC IP) are restricted medications and must not be used recurrently or for chronic treatment during the study.

The date and time of rescue medication administration, as well as the name and dosage regimen of the rescue medication, must be recorded. Rescue medication for hyperkalemia will not be provided as part of study medications (Table 5).

Rescue therapy includes, but is not limited to, any of the following:

1 Insulin/glucose, beta-adrenergic agonist, sodium bicarbonate, etc.

2 Other potassium binders: SPS (eg, Kayexalate, Resonium), CPS (eg, Resonium Calcium) and patiromer (Veltassa) (Table 5).
NOTE: All potassium binders other than SZC are considered restricted medications and can be used only for short-term rescue (24 to 48 hours). Once the participant has been enrolled in the study, SZC cannot be used for rescue therapy. SZC/placebo must be temporarily discontinued while rescue therapy is administered. Table 5 lists medications restricted during the study.

3 Any additional dialysis or other forms of renal replacement treatments when used specifically for the treatment of severe hyperkalemia.

4 Any reduction in the Kd that is prescribed for the treatment of severe hyperkalemia during the study.

Rescue therapy should be guided by local clinical practice patterns and limited to the setting of severe hyperkalemia. Rescue therapy is recommended for treatment of S-K > 6.0 mmol/L, if clinically justified, however investigators are allowed to treat hyperkalemia at lower levels (5.5 mmol/L or greater) if there are signs or symptoms of hyperkalemia or in any instance if it is judged clinically warranted. Rescue therapy should be followed by the appropriate dose adjustment of SZC/placebo study intervention if appropriate and proper documentation of the event. Refer to Appendix E for Hungary-specific rescue therapy text.

All hyperkalemia events that require rescue therapy will be reported as an AE.

6.6 Dose Modification

As outlined in Section 6.1.2 the study intervention dose will be titrated in 5 g increments from 5 g up to 15 g qd on non-dialysis days depending on the current potassium value as measured after the LIDI at the local laboratory to achieve and maintain a pre-dialysis S-K between 4.0 to 5.0 mmol/L.

It is recommended that if S-K is < 3.0 mmol/L on any non-dialysis day or pre-dialysis, study intervention should be withheld, and hypokalemia should be managed as per standard practice. The participant should be evaluated for any intercurrent illness or comorbidity that may increase the risk of hypokalemia. Study intervention administration can be resumed if indicated but only after the intercurrent medical condition that precipitated the hypokalemia has improved and S-K has returned to the target range of normal levels (4.0 to 5.0 mmol/L). It is suggested to resume treatment at a dose of 5 g or per investigator discretion.

Treatment with study intervention on dialysis days should be judged as a medication error and reported in the eCRF (Section 8.3.8). The S-K should be monitored for safety and if S-K

< 3.0 mmol/L, study intervention should be withheld, and hypokalemia managed as noted above. The participants should receive clear instructions regarding intake of study drug.

6.7 Intervention After the End of the Study

Not applicable. Individual physicians may treat each of their randomized participants according to local laboratory values and the local standard of care.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

At any time, participants are free to discontinue study intervention or withdraw from the study, without prejudice to further treatment.

7.1 Discontinuation of Study Intervention

7.1.1 Permanent Discontinuation of Study Intervention

Participants may be discontinued from study intervention in the following situations. Note that discontinuation from study intervention is NOT the same thing as a complete withdrawal from the study.

- Participant decision. The participant is free at any time to discontinue treatment, without prejudice to further treatment.
- Incorrectly randomized participant in whom the inclusion/exclusion criteria violation would put the participant at undue risk.
- The need for long term chronic/continual use of potassium binders (Section 6.5.2).
- Adverse event for which the investigator judges continued treatment may put the participant at undue risk.
- Severe noncompliance with the CSP.
- Pregnancy.
- Renal transplant.
- QT prolongation: If an absolute QTc > 550 msec, or an increase in QTc interval > 60 msec from baseline to more than 500 msec is reached, the participant should immediately receive appropriate medical intervention and be discontinued from the study intervention. The QTcF algorithm (QT interval corrected by the Fridericia method) is recommended. All participants meeting the QTc > 500 msec criterion on study intervention should immediately have potassium assessed, if not already done within 1 hour of performing the ECG. See Appendix E for Italy-specific update.

Participants who permanently discontinue study intervention, but remain in the study, must continue to adhere to the restricted medications requirements; not doing so would be a protocol deviation.

See the SoA (Section 1.3) and Section 7.1.4 for data to be collected at the time of discontinuation from study intervention and follow-up and for any further evaluations that need to be completed.

7.1.2 Temporary Discontinuation

Participants who have temporarily discontinued study intervention for reasons other than hypokalemia can resume treatment as soon as, in the opinion of the investigator, the participant's condition is stable, and the participant wishes to resume. No minimum time period is necessary before treatment can resume. Whenever possible, restart of randomized study intervention should be encouraged. Refer to Section 6.6 for details on hypokalemia (S-K < 3.0 mmol/L).

7.1.3 Procedure for Erroneously Randomized Participants

A situation might arise where, despite every effort, a participant is randomized into the study while not fulfilling one or several of the inclusion/exclusion criteria. In this case, the following steps should be undertaken:

1 The Study Physician should be contacted for an assessment of whether study intervention could pose a risk to the participant in light of the new information.
2 If yes, the participant should be immediately discontinued from study intervention (not to be confused with study discontinuation).
3 If no, the Study Physician should carefully review the specific Inclusion/Exclusion criterion which was not met. If discontinuation of study treatment is deemed detrimental to the participant, the study medication will be continued and the decision documented. If discontinuation of study medication is not detrimental to the participant, it will be discontinued, the participant followed according to the study protocol, and the decision documented.
4 The occurrence should be documented as appropriate (Important/Major Protocol Deviation).

7.1.4 Procedures for Premature Study Intervention Discontinuation Visit

The investigator should instruct the participant to contact the site before or at the time study intervention is stopped. Participants who prematurely and permanently discontinue study intervention should return for a PIDV, which should be performed at the earliest possible dialysis visit after the last dose of study intervention. See the SoA (Section 1.3) for assessments to be performed at the PIDV.

A participant who decides to discontinue study intervention will always be asked about the reason(s). The date of last dose of study intervention should be documented in the eCRF, as well as the date of study intervention discontinuation. All study intervention should be returned by the participant, and drug accountability should be checked and documented in the eCRF.

Discontinuation of study intervention, for any reason, does not impact on the participant´s participation in the study. The participant should, if possible, continue attending subsequent study visits, including the SCV, and data collection should continue according to the study protocol. If, upon discontinuation of study intervention, the participant choses to withdraw from the study entirely, procedures described in Section 7.2 should be followed.

Data collection and procedures should continue according to the study protocol until study closure. If the participant does not agree to this option (which must be documented), a modified follow-up (eg, regular telephone contacts or a contact at study closure) should be arranged, if agreed to by the participant and in compliance with local data privacy laws/practices in order to collect at least the study endpoint information. If the participant does not allow the site to call him/her but allows the site to review the participant's medical records it should be done following the protocol-specified visit schedule or at least every 6 months until the study closure, to ensure collection of study endpoint information.

After stopping study intervention, the investigator should ensure that the participant is treated according to standard clinical practice and ascertain there is a proper medical follow-up plan in place.

7.1.5 Procedures for End of Study Intervention Visit

All participants who are still on study intervention at the SED will be asked to return for an EOIV, which should be performed at the earliest possible LIDI dialysis visit but no later than 3 weeks after the SED. At this visit the participant will be taken off the study intervention. See the SoA (Section 1.3) for assessments to be performed at the EOIV.

The date of last dose of study intervention should be documented in the eCRF. All study intervention should be returned by the participant, and drug accountability should be checked and documented in the eCRF.

After stopping study intervention, the investigator should ensure that the participant is treated according to standard clinical practice and ascertain there is a proper medical follow-up plan in place.

7.1.6 Procedures for Study Closure Visit

When the SED is determined, all participants (including any participants who have discontinued study intervention) will be asked to return for a SCV. For participants who did

not discontinue prematurely, the SCV should be performed 14 days (± 7 days) after the participant's EOIV visit. For participants who discontinued prematurely, the SCV should occur as soon as possible but no later than 3 weeks after the SED. See the SoA (Section 1.3) for assessments to be performed at the SCV.

If the participant who discontinued prematurely decides to withdraw from the study between the time of the discontinuation of study intervention and study closure, the SCV should be performed for this participant at the earliest possible dialysis visit after the participant has decided to withdraw from the study.

7.2 Participant Withdrawal from the Study

- A participant may withdraw consent from the study at any time at his/her own request without prejudice to further treatment. In exceptional circumstances, the participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- A participant who considers withdrawing consent from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records). Participant Follow-Up Checklist Form and Withdrawal of Consent Checklist should be used to document the process.
- At the time of withdrawal from the study, if possible and agreed by the patient, a PIDV should be conducted at the earliest possible dialysis visit after the last dose of study intervention; refer to Section 7.1.4 and the SoA (Section 1.3) for data to be collected at the time of study withdrawal. A follow-up visit should be performed 14 days (± 7 days) after last dose of the study intervention/ PIDV if agreed by the patient. This visit will be considered SCV. Date of SCV, if performed, will be considered date of withdrawal of consent.
  - If the patient does not agree to have PIDV, follow-up visit/ SCV performed, it will not be performed, and the date of participant's consent withdrawal will be documented by the Investigator in the source data and EDC.
- At the time of withdrawal of consent from the study, if possible, a PIDV should be conducted at the earliest possible dialysis visit after the last dose of study intervention; refer to Section 7.1.4 and the SoA (Section 1.3) for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed. The SCV should be performed 14 days (± 7 days) after the participant's PIDV.
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws consent from the study, it should be confirmed if he/she still agrees for use of participant's coded data for future research in line with the original consent, if applicable in the country. The investigator must document the decision on use of existing coded data for future research in the site study records and inform the Global Study Team.
- To ensure validity of study data, it is very important to collect as much data as possible throughout the study and especially vital status (dead or alive) at study closure (also for participants who have withdrawn their informed consent). The investigator will therefore attempt to collect information on all participants' vital status from publicly available sources at study closure, even if informed consent has been withdrawn completely, in compliance with local privacy laws/practices.

7.3 Lost to Follow-up

The term lost to follow-up will be limited to only participants with unknown vital status at study end (if not dead, participants need to have a date last known alive after randomization).

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Efforts to reach the participant should continue until the end of the study
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
  - Unscheduled Visits: An unscheduled visit may occur in-between scheduled visits eg, to follow up on potential endpoint or safety events.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

8.1 Efficacy Assessments

8.1.1 Adjudicated Endpoint Reporting Overview

Potential endpoints will be identified through clinical evaluations, questioning the participants about their overall health and symptoms, or through information received through standard medical practice. Investigators will be encouraged to have a low threshold to submit any potential/possible event that might represent an endpoint.

The information for potential endpoints will be recorded in the eCRF and submitted for central adjudication if they are assessed by the investigator as potentially representing endpoint-related events. The investigator should also make a high-level characterization of the event and as to whether the event fulfills the criteria for the endpoint definition.

- All Deaths
  - The investigator will assess cause of death, CV/non-CV/unknown, and if this was a SCD.
- Stroke (including TIA)
  - For potential stroke and TIA events, the investigator will assess the stroke, and whether the stroke is ischemic/hemorrhagic, or unknown.

- Hospitalization, intervention, or ED visits due to arrhythmia-related events (defined as AF, bradycardia, asystole, and ventricular tachyarrhythmia [such as VF, VT, etc]).
  - For potential hospitalizations, interventions, and ED visits due to arrhythmias, the investigator will assess the type of arrhythmia and will note any interventions for the event.

For each potential endpoint, the investigator or delegate will record the endpoint specific information in the eCRF. If the event is subject to adjudication, relevant source documents will be assembled. The source documents and relevant eCRF data will be sent for central adjudication. Detailed instructions regarding endpoint reporting will be provided to the study sites. Additional details about the evaluations/definitions of potential endpoints will be described in the Adjudication Committee charter and will be provided to the investigator.

All endpoints will also be reported as AEs.

8.1.1.1 Death

The Adjudication Committee members will adjudicate and classify all deaths based on definitions described in the Committee's charter. For the efficacy analysis, deaths will be subclassified by SCD, CV death, non-CV death, or undetermined cause of death.

8.1.1.2 Stroke

The Adjudication Committee members will adjudicate and classify all strokes and TIAs based on definitions described in the Committee's charter.

8.1.1.3 Hospitalizations, Interventions, or Emergency Department Visits

The Adjudication Committee members will adjudicate all potential hospitalizations, interventions, or ED visits due to arrhythmias (AF, bradycardia, asystole, and ventricular tachyarrhythmia [such as VF, VT, etc]) as specified in the Committee's Charter.

8.1.2 Serum Potassium Measurements

Blood samples for determination of potassium for the efficacy endpoint will be taken at the time points specified in the SoA (Section 1.3). Analyses will be performed at a central laboratory contracted by AstraZeneca. Refer to Section 8.2.5 for further details.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations and Height

A brief physical examination (including height) will be performed at time points specified in the SoA (Section 1.3), and will include, at a minimum, assessments of the lungs, CV system, abdomen, and a brief neurological examination.

8.2.2 Weight and Interdialytic Weight Gain

Weight must be measured at the dialysis clinic.

Post-dialysis weight from the previous dialysis session will be collected at time points specified in the SoA (Section 1.3).

Weight will be assessed pre-dialysis at time points specified in the SoA (Section 1.3).

Interdialytic weight gain will be calculated as the difference between current pre-dialysis weight minus previous post-dialysis weight (measured at immediate dialysis session prior to the visit) in kilograms. The calculation will be performed as part of the analysis.

8.2.3 Vital Signs

Vital signs (pulse and BP) will be assessed at time points specified in the SoA (Section 1.3). Pulse and BP should be measured prior to the hemodialysis procedure and should be measured in triplicate after the participant is comfortably at rest in either supine or seated position quietly for at least 5 minutes.

8.2.4 Electrocardiograms

A 12-lead ECG will be performed at time points specified in the SoA (Section 1.3). The ECG data should be recorded in the eCRF, including QTcF.

The ECGs should be made available to the Adjudication Committee upon request, to facilitate adjudication of potential cardiac events.

8.2.5 Clinical Safety Laboratory Assessments

8.2.5.1 Central Laboratory Assessments

Blood samples for determination of clinical chemistry for the study database will be taken at the time points specified in the SoA (Section 1.3). All serum samples should be examined and any hemolyzed samples MUST be re-drawn. Sample re-tests are allowed for each screening visit but there should not be more than one re-test for one screening visit.

Analyses will be performed at a central laboratory contracted by AstraZeneca. Sites will be provided with ready-to-use laboratory kits, as well as appropriate instructions/manuals. Procedures for collection, processing, and sending samples to the central laboratory will be provided in laboratory manuals. Table 7 lists the laboratory variables to be measured.

Table 7 Laboratory Safety Variables

Clinical Chemistry (Serum)	Hematology/Hemostasis (Whole Blood)
S-Potassium	B-Erythrocyte count (RBC) [a]
S-Calcium, total	B-Hemoglobin [a]

Table 7 Laboratory Safety Variables

Clinical Chemistry (Serum)	Hematology/Hemostasis (Whole Blood)
S-Sodium	B-Leukocyte count [a]
S-Bicarbonate	B-Leukocyte differential count (absolute count and %) [a]
S-Phosphate	B-Platelet count [a]
S-Blood urea nitrogen	
S-Magnesium	
S-Creatinine [a]	
S-Bilirubin, total [a]	
S-Alkaline phosphatase [a]	
S-Aspartate transaminase [a]	
S-Alanine transaminase [a]	
S-Gamma-glutamyl transferase [a]	
S-Albumin [a]	
S-Chloride [a]	
S-Creatine kinase [a]	
S-Glucose [a]	
S-Lactate dehydrogenase [a]	
S-Total protein [a]	
S-Pregnancy test (serum HCG) [b]	

Blood B; Human chorionic gonadotropin HCG; Red blood cell RBC; Serum S.
[a] Randomization/Day 1 Visit 4 only.
[b] Screening Visit 1 only. Repeated serum HCG pregnancy tests may be analyzed by the local laboratory.

8.2.5.2 Local Laboratory Assessments

Routine laboratory assessments are to be collected as per usual care for participant management. This includes weekly potassium tests at the end of the LIDI during the initial up-titration and at least monthly (or more frequent based on clinical judgment), for adjustment of the dose of SZC. Additional samples may be collected if clinically indicated at the discretion of the investigator (refer to Section 6.1.2). In case of dose adjustment, potassium must be measured 1 week after the dosage change. The maximum dose of study intervention will be 15 g qd on non-dialysis days. Unless important for AE/endpoint data collection, routine laboratory assessments should not be reported in the eCRF.

8.3 Adverse Events and Serious Adverse Events

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

All potential endpoints (Section 8.1.1) will also be reported as AEs.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

Adverse events will be collected from the time of randomization, throughout the treatment period, and including the follow-up period.

Serious AEs will be recorded from the time of signing of the ICF.

If the investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of Adverse Events and Serious Adverse Events

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse Event Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the study intervention (yes or no)
- Action taken with regard to study intervention
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between study intervention and each AE , and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the study intervention?'

For SAEs, causal relationship should also be assessed for other medications and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention, or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as

to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

Hyperkalemia requiring rescue therapy (see Section 6.5.2) should be reported as an AE regardless of whether there are associated signs and symptoms.

Pre-dialysis hypokalemia (S-K < 3.0 mmol/L based on local laboratory assessment) should be reported as an AE regardless of whether there are associated signs and symptoms.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

8.3.6 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs during the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within 1 day, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone, email or as per local approved process.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the Investigator's Brochure.

8.3.7 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

8.3.7.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the intervention under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies /birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (Section 8.3.6) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

8.3.7.2 Paternal Exposure

There is no restriction on fathering children or donating sperm during the study.

8.3.8 Medication Error, Drug Abuse, and Drug Misuse

8.3.8.1 Timelines

If a medication error occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (Section 8.3.6) and **within 30 days** for all other medication errors.

8.3.8.2 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The definition of a Medication Error can be found in Appendix B 4.

8.3.8.3 Drug Abuse

Drug abuse is the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The definition of a Medication Error can be found in Appendix B 4.

8.3.8.4 Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The definition of a Medication Error can be found in Appendix B 4.

8.4 Overdose

For this study, any dose of study intervention greater than 15 g per day on non-dialysis days will be considered an overdose. Treatment with study intervention on dialysis days should be judged as a medication error and reported in the eCRF (Sections 6.6 and 8.3.8).

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (Section 8.3.6) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples for the central laboratory will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples, see Appendix C.

8.5.1 Pharmacokinetics

Pharmacokinetic samples are not collected in this study.

8.5.2 Immunogenicity Assessments

Immunogenicity samples are not collected in this study.

8.5.3 Pharmacodynamics

Pharmacodynamic samples are not collected in this study.

8.6 Human Biological Sample Biomarkers

Biomarker samples are not collected in this study.

8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

8.8 Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters/data are not collected in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

All personnel involved with the analysis of the study will remain blinded until database lock has occurred, and protocol violations have been identified and documented.

Control of Type I Error at the final analysis

The Type I error rate for the final analysis of the primary endpoint and subsequent secondary endpoints will be adjusted for the interim analysis performed by the DMC. A two-sided significance level of 4.46% will be used, assuming one interim analysis for efficacy will be conducted (Section 9.5).

To control the familywise Type I error rate, a fixed sequence multiple testing procedure for primary and secondary endpoints will be performed.

For the primary endpoint, the following hypothesis will be tested:

H_0: HR[SZC:placebo] = 1
Versus
H_1: HR[SZC:placebo] ≠ 1

During the final analysis, once the null hypothesis concerning the primary composite efficacy endpoint is rejected, the hypotheses for the secondary efficacy endpoints will be tested separately in the order listed in Table 3 (HR for time to event endpoints, odds ratio for binary (yes/no) endpoints, and rate ratio for number of event endpoints [Section 9.4.2]) with the same alpha level as the primary endpoint. The testing procedure will continue down the hierarchy if the current endpoint is rejected at a two-sided 4.46% level and will stop if the current endpoint is not rejected at a two-sided 4.46% level.

The final significance level will be adjusted if the actual timing of the interim analysis does not correspond to half of the information obtained during the trial, eg, due to the total number of events deviating from the planned 730 events.

9.2 Sample Size Determination

The study is event-driven. The primary objective of the study is to evaluate the efficacy of SZC versus placebo in reducing the incidence of the primary composite endpoint. Assuming the true HR for SZC versus placebo is 0.8, 730 primary endpoint events will result in approximately 85% power to demonstrate a statistically significant difference at either interim analysis (two-sided significance level of 1.64%) or at final analysis (two-sided significance level of 4.46%). Based on an assumption that the event rate of the primary composite endpoint is approximately 11 per patient-year in the placebo group, it is expected that approximately

2800 participants will need to be randomized. The anticipated recruitment period is planned to be 32 months. The anticipated average treatment period is approximately 37 months, which in practice will be dependent on the actual event rate observed during the study, as the study duration is event-driven. Any decision to increase or decrease participant numbers or extend or shorten study duration will be based on blinded event rate data.

Assuming a screen failure rate of 50%, approximately 5600 participants will be enrolled to achieve approximately 2800 participants randomly assigned (1:1) to study intervention (SZC or placebo).

9.3 Populations for Analyses

The following populations are defined in Table 8:

Table 8 Populations for Analysis

Population/Analysis Set	Description
Full Analysis Set (FAS)	All participants who undergo randomization and receive a randomization number
Safety Analysis Set (SAS)	All participants who have received at least one dose of study intervention

9.4 Statistical Analyses

An SAP will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses for the primary and secondary endpoints.

9.4.1 General Considerations

All hypothesis testing will be conducted using two-sided tests as specified in Section 9.1.

9.4.2 Efficacy

The efficacy analyses will be performed according to the ITT principle. Thus, the population to which the study results will be generalizable are the participants who fulfill inclusion/exclusion criteria and are suitable to be randomized.

9.4.2.1 Primary Endpoint(s)

The primary endpoint is time to the first occurrence of SCD, stroke, or hospitalization/intervention/ED visit due to arrhythmias (AF, bradycardia, asystole, ventricular tachyarrhythmia [such as VF, VT, etc]). In accordance with the ITT principle, participants will be censored at the common SED or at the time of withdrawal of informed consent.

Although numerous intercurrent events, including, eg, termination of study intervention or initiation of an additional treatment that potentially affects the primary outcome, exist in this

setting, the analysis will follow "Treatment Policy Strategy" (ICH E9(R1) 2020). That is, the occurrence of such intercurrent events will be ignored. The only exception to this rule is death not adjudicated as SCD: participants will be censored at that time point.

The primary hypothesis of no difference between study intervention arms will be evaluated by means of a Cox regression, with time to first event/censoring as response and study intervention arm and geographic region as covariates. Other covariates may also be included as appropriate; further details of the statistical model will be specified in the SAP. The HR estimate, its standard deviation, 95% confidence interval, and p-value will be provided. Kaplan-Meier estimates of time to the first occurrence of any event in the composite endpoint will be calculated and plotted.

The homogeneity of effect with regards to subgroups (eg, gender, age-groups, etc) will be examined as specified in the SAP.

9.4.2.2 Secondary Endpoint(s)

As for the primary endpoint, the secondary endpoints will be analyzed according to the ITT principle (ie, the same analysis set as for evaluation of the primary endpoint will be used).

The following time to event endpoints will be analyzed similarly to the primary endpoint (Cox regression; Section 9.4.2.1).

- Time to first occurrence of hospitalization/intervention/ED visit due to arrhythmias (AF, bradycardia, asystole, ventricular tachyarrhythmia [such as VF, VT, etc]).
- Time to first instance of rescue therapy use for hyperkalemia
- Time to SCD
- Time to first occurrence of stroke
- Time to CV death
- Time to death of any cause

A logistic model with the binary variable (yes/no) as response and study intervention arm and geographic region as covariates will be used to evaluate the efficacy of SZC as compared with placebo in the following secondary endpoints. As for the primary endpoint analysis, other covariates may also be included as appropriate. The proportion of participants fulfilling each endpoint criteria will also be presented by study intervention arm. The estimated odds ratio, corresponding 95% confidence interval, and two-sided p-value will be presented.

- S-K of 4.0 to 5.5 mmol/L (yes/no) after the LIDI at the 12-month visit
- S-K > 6.5 mmol/L (yes/no) after the LIDI at the 12-month visit.

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) will be used to evaluate the efficacy of SZC as compared with placebo for the following secondary endpoint. 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 occur. Number of events will also be presented by study intervention arm. The estimated rate ratio, corresponding 95% confidence interval, and two-sided p-value will be presented.

- Number of hospitalizations/interventions/ED visits due to arrhythmias (AF, bradycardia, asystole, and ventricular tachyarrhythmia [such as VF, VT, etc])

The homogeneity of effect with regards to subgroups (eg, gender, age-groups, etc) may be examined as specified in the SAP.

9.4.2.3 Tertiary/Exploratory Endpoint(s)

Analysis of the exploratory endpoints will be presented in the SAP.

9.4.3 Safety

Safety analyses will be performed using the Safety Analysis Set. Safety data will be presented using descriptive statistics unless otherwise specified in the SAP.

An overview of AEs will be presented for each study intervention arm: the number and percentage of participants with any AE, AEs with outcome of death, SAEs, and AEs leading to discontinuation of study intervention. Additionally, for each study intervention arm, AEs will be summarized by system organ class/preferred term, intensity, and causality as assessed by the investigator. Laboratory data (including instances of hypokalemia), vital signs, and interdialytic weight gain measurements will be tabulated by study intervention arm. Full details of safety analyses will be provided in the SAP.

9.4.4 Other Analyses

Details of sensitivity analysis will be provided in the SAP.

9.5 Interim Analysis

A non-binding futility analysis will be performed by the DMC when 40% of the total number of primary endpoint events have accrued and have been adjudicated. The threshold for futility is defined as the estimated hazard ratio at the interim analysis, SZC versus placebo being equal to or larger than 1. This will correspond to a predictive power of < 5.1%.

An interim analysis is also planned for efficacy by the DMC when 70% of the total number of primary endpoint events have accrued and have been adjudicated (ie, a minimum of

511 events). If the interim occurs at 70% of the total number of primary endpoint events (participants), the hypothesis for the primary endpoint at interim will be tested at the two-sided 1.64% level (O'Brian P, Fleming T. Cytel Inc. Software Package East 6.5, Copyright 2018).

The DMC will notify the sponsor if the formal stopping criteria for superiority or futility are met.

Additional details for the interim analysis will be provided in the DMC charter.

9.6 Data Monitoring Committee

For details on the Executive Committee, National Lead Investigator Committee, Adjudication Committee, and DMC, refer to Appendix A 5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organization, but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of a serious adverse event (SAE) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach.
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial

certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 60 days from the previous ICF signature date.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of the participant's data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

A 5.1 Executive Committee

Together with AstraZeneca, the Executive Committee will be responsible for the final overall study design, including the development of the study protocol and electronic case report form (eCRF), and any protocol amendments needed during the study, liaison with the Adjudication Committee and Data Monitoring Committee (DMC), as needed, development of the statistical analysis plan, and supervision, interpretation, and reporting (presentations at international congresses and publications in peer reviewed journals) of the study.

The Executive Committee will make recommendations to AstraZeneca with regard to early stopping or modifications of the study based on the information received from the DMC. The Executive Committee will be comprised of designated international academic leaders and non-voting members of the sponsor and will operate under an Executive Committee charter.

A 5.2 National Lead Investigator Committee

The National Lead Investigator (NLI) Committee will be comprised of NLIs from each country where the study is conducted and will be supervized by the Executive Committee. Members of the committee will be responsible for providing clinical guidance on study implementation and conduct in their respective country.

A 5.3 Adjudication Committee

An independent Adjudication Committee will be appointed and will adjudicate potential endpoint events of death to determine if they are sudden cardiac death or other (cardiovascular death, non-cardiovascular death, or unknown), all stroke and transient ischemic attacks, and arrhythmia-related hospitalizations, interventions, and emergency department visits. The committee members will not have access to individual treatment codes for any participant or clinical efficacy and safety event. The precise responsibilities and procedures applicable for the Adjudication Committee will be detailed in a separate Adjudication Committee charter.

A 5.4 Data Monitoring Committee

An independent DMC will be appointed. The DMC will be responsible for monitoring the progress of the study with respect to randomization, 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 all or part of the trial. The DMC will conduct a non-binding futility analysis when 40% of the number of primary endpoint events have accrued and have been adjudicated. In addition, the DMC is planning an interim analysis for efficacy when 70% of the planned number of primary endpoint events have accrued and have been adjudicated (Section 9.5). The DMC will notify the sponsor if the formal stopping criteria for superiority or futility are met. A DMC charter

will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the Executive Committee.

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in ICH GCP Section 1.52 Source Documents.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site opened and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites may have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An adverse event (AE) is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Hyperkalemia requiring rescue therapy should be reported as an AE regardless of whether there are associated signs and symptoms.

Pre-dialysis hypokalemia (serum potassium < 3.0 mmol/L based on local laboratory assessment) should be reported as an AE regardless of whether there are associated signs and symptoms.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

The AEs for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the

malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality, consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- **Was identified and** intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature

- Wrong participant received the medication (excluding Interactive Response Technology [IRT]/Randomization and Trial Supply Management [RTSM] errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product.

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

B 5 Study Event Questionnaire

Study Events Questionnaire:

1 During the past month, have you been hospitalized, visited the emergency room, or had any medical procedures for a new condition?
    - If they respond yes, ask the reason for the visit or procedure.
2 During the past month, have you been told by a doctor or other healthcare provider that you have had a stroke?
3 During the past month, have you been told by a doctor or other healthcare provider that you have an abnormal heart rhythm?

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their life cycle.

The investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented, and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to them occurs, are capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.

Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging. (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.

Appendix D Management of Study Procedures During the COVID-19 Pandemic

D 1 Introduction

Safeguarding the health and wellbeing of our participants and ensuring the continued supply of our medicines to participants remains of paramount importance for AstraZeneca through the ongoing COVID-19 outbreak.

D 2 Risk Assessment for COVID-19 Pandemic

Sodium Zirconium Cyclosilicate (SZC) is a potassium binder acting in the gastrointestinal tract and is not absorbed. No additional risk from COVID-19 is expected due to SZC. However, the risk of exposure to infected people cannot be completely excluded during study participation as the participants may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff).

D 2.1 Measures to Mitigate the Risks Associated with COVID-19

- National laws and local recommendations for regarding the pandemic will be strictly adhered to.
- Site is encouraged to contact the participant within one day prior to a study visit; see next section.

D 3 COVID-19 Prior to Enrollment

It is important that participants with possible ongoing or not completely resolved COVID-19 infection are not to be enrolled in the study. If the participant has evidence of COVID-19 within 2 weeks prior to enrollment (eg, a positive COVID-19 test or a clinical risk that has not been satisfactorily excluded), the participant cannot be enrolled and will be treated according to standard of care.

D 4 Suspected COVID-19 After Enrollment

D 4.1 Participant is Severely Ill or Hospitalized

If the participant becomes symptomatic after enrollment and has suspected COVID-19 (regardless of any SARS-Cov-2 test results that may be available), and is severely ill and/or hospitalized, the participant may temporarily or permanently discontinue study intervention at the discretion of the site investigator.

D 4.2 Participant is NOT Severely Ill or Hospitalized

If the participant becomes symptomatic after enrollment and has suspected COVID-19 (regardless of whether any SARS-Cov-2 test results are available or not), and is NOT severely

ill and/or hospitalized the investigator should determine if continuation of treatment with study intervention is in the best interest of the participant.

Regardless of if study intervention is continued or not, the participant is encouraged to attend the study visits according to schedule.

D 5 COVID-19 During the Study

D 5.1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete on-site study visits and assessments and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Section D 5.2. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note: in the case of verbal reconsent, the informed consent form should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

D 5.2 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix the term telemedicine visit refers to remote contact with the study participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, visits that are scheduled to be on-site may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow adverse events, concomitant medication, and potential endpoints to be reported and documented.

D 5.3 Data Capture During Telemedicine Visits

Data collected during telemedicine visits will be captured by the qualified healthcare professional from the study site.

Appendix E Country-specific Changes

HUNGARY-SPECIFIC SCIENTIFIC RATIONALE FOR STUDY DESIGN

Justification for use of Placebo

The DIALIZE-Outcomes study tests the unproven hypothesis that treatment of hyperkalemia with SZC reduces the risk of arrhythmia-related adverse outcomes in patients on chronic hemodialysis. SZC is already established as an effective treatment of hyperkalemia in this patient population. While potassium-binding resins (sodium polystyrene sulfonate and calcium polystyrene sulfonate) are routinely used in some European countries to manage hyperkalemia in patients on chronic hemodialysis, these agents have not been extensively studied, are not universally used, and have no established efficacy in the control of hyperkalemia when used routinely in this population. Indeed, a prospective, observational study conducted in France, which followed 527 chronic hemodialysis patients for 2 years, reported that even after dynamic management of Kd (more frequent prescription of 2.0 mmol/L) and potassium binder treatment (increasing the dose), only 6.3% of patients became normokalaemic within 3 months after a serum potassium (S-K) of > 5.5 mmol/L at baseline (Rossignol et al 2017).

To date there is no data from interventional studies demonstrating that chronic treatment of hyperkalemia reduces the risk of arrhythmia-related outcomes (or any other hard outcomes) in the hemodialysis population. Therefore, the hypothesis to be tested is whether reducing interdialytic hyperkalemia in a prospective, controlled clinical study reduces the risk of arrhythmia-related outcomes. To clarify, the study is not intended to show whether SZC has a direct effect on arrhythmia-related outcomes. Given the above, an active control treatment, even ignoring that there is no well-established and reliably efficacious treatment for interdialytic hyperkalemia available, would be contrary to the purpose of the study.

Importantly, Investigators have the ability/discretion to use hyperkalemia rescue therapy (extra hemodialysis sessions, changing potassium concentration in dialysate bath or pharmacotherapy like potassium binding resins or other medications) as needed to treat all patients requiring acute hyperkalemia treatment in the DIALIZE-Outcomes trial.

Testing the hypothesis requires comparison between a group with well-controlled S-K (SZC group) and another with less good control (placebo) - as it stands there is no evidence to suggest superiority of well-controlled S-K regarding the primary endpoint. Investigators have discretion to use rescue therapy in either arm as needed to keep patients safe.

AstraZeneca applied for scientific advice with the European Medicines Agency concerning the design of the study in 2 rounds in 2020 and 2021 respectively.

Follow up Scientific Advice received by AstraZeneca from the European Medicines Agency (Case No: EMA/SA/0000053941, dated 22 April 2021) concerning the study design stated the following:

> "Placebo control is considered acceptable to test the hypothesis that strict control of serum potassium will reduce arrhythmia-related adverse outcome. In such a study, less intense potassium control is expected in placebo-arm. The strict rescue criterion of serum potassium of ≥ 6.0 mmol/L for treatment with potassium binders is considered to be too high."

Use of rescue therapy is permitted by this protocol when it is needed by investigator judgment and according to local clinical practice (Section 6.5.2). This protocol allows for treatment at S-K > 6.0 mmol/L, if clinically justified, however investigators are allowed to treat hyperkalemia at lower levels (5.5 mmol/L or greater) if there are signs or symptoms of hyperkalemia or in any instance if it is judged clinically warranted. A pre-LIDI S-K may be managed by the HD session (increasing treatment time, reducing the potassium content of concentrate). The protocol also permits modification of the dialysate K (this would be considered "rescue therapy" if K^+ decreased) as the investigator warrants to manage the participant longer term. This applies to both arms of the study.

JAPAN-SPECIFIC INCLUSION CRITERIA

3 Must be ≥ 18 years of age, at the time of signing the ICF.
Updated inclusion criterion #3 by removing, "For participants < 20 years of age and enrolled in Japan, a written informed consent should be obtained from the participant and his or her legally acceptable representative." Text no longer required due to civil code change.

AUSTRIA-SPECIFIC INCLUSION CRITERIA

8 Female participants must be 1 year postmenopausal or surgically sterile. (Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause. Surgical sterilization includes: hysterectomy, bilateral oophorectomy, or bilateral salpingectomy.)

ITALY-SPECIFIC EXCLUSION CRITERIA

10 Participation in another clinical study with an investigational product administered within one month before screening or 5 IMP half-lives, whichever is longer.

HUNGARY-SPECIFIC RESCUE THERAPY UPDATE

Rescue therapy should be guided by local clinical practice patterns and limited to the setting of severe hyperkalemia. Rescue therapy is recommended for treatment of S K > 6.0 mmol/L, if clinically justified, however investigators are allowed to treat hyperkalemia at lower levels (5.5 mmol/L or greater) if there are signs or symptoms of hyperkalemia or in any instance if it is judged clinically warranted. The use of rescue medications is permissible at any time during the study." There is no strict rescue criterion.

ITALY-SPECIFIC PERMANENT DISCONTINUATION OF STUDY INTERVENTION

Participants may be discontinued from study intervention in the following situations. Note that discontinuation from study intervention is NOT the same thing as a complete withdrawal from the study.

- QT prolongation: If an absolute QTc > 550 msec, or an increase in QTc interval > 60 msec from baseline to more than 500 msec is reached, or more than 470 msec based upon investigator judgment, the participant should immediately receive appropriate medical intervention and be discontinued from the study intervention. The QTcF algorithm (QT interval corrected by the Fridericia method) is recommended. All participants meeting the QTc > 500 msec criterion on study intervention should immediately have potassium assessed, if not already done within 1 hour of performing the ECG.

11 REFERENCES

Benjamin et al 1998
Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946-52.

Dries et al 1998
Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, et al. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. J Am Coll Cardiol 1998;32:695-703.

Fishbane et al 2019
Fishbane S, Ford M, Fukagawa M, McCafferty K, Rastogi A, Spinowitz B, et al. A Phase 3b, Randomized, Double-Blind, Placebo-Controlled Study of Sodium Zirconium Cyclosilicate for Reducing the Incidence of Predialysis Hyperkalemia. J Am Soc Nephrol 2019;30(9):1723-33.

Foley et al 2011
Foley RN, Gilbertson DT, Murray T, Collins AJ. Long interdialytic interval and mortality among patients receiving hemodialysis. N Engl J Med 2011;365:1099-107.

Genovesi et al 2005
Genovesi S, Pogliani D, Faini A, Valsecchi MG, Riva A, et al. Prevalence of atrial fibrillation and associated factors in a population of long-term hemodialysis patients. Am J Kidney Dis 2005;46:897-902.

ICH E9(R1) 2020
ICH E9 (R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf.

Jadoul et al 2012
Jadoul M, Thumma J, Fuller DS, Tentori F, Li Y, et al. Modifiable practices associated with sudden death among hemodialysis patients in the Dialysis Outcomes and Practice Patterns study. Clin J Am Soc Nephrol 2012;7(5):765-74.

Kalra et al 2018
Kalra PA, Green D, Poulikakos D. Arrhythmia in hemodialysis patients and its relation to sudden death. Kidney Int 2018;93(4):781-3.

Karaboyas et al 2017
Karaboyas A, Zee J, Brunelli SM, Usvyat LA, Weiner DE, Maddux FW, et al. Dialysate potassium, serum potassium, mortality, and arrhythmia events in hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 2017;69(2):266-77.

Kovesdy et al 2007
Kovesdy CP, Regidor DL, Mehrotra R, Jing J, McAllister CJ, Greenland S, et al. Serum and dialysate potassium concentrations and survival in hemodialysis patients. Clin J Am Soc Nephrol 2007;2:999-1007.

Rossignol et al 2017
Rossignol P, Lamiral Z, Frimat L, Girerd N, Duarte K, Ferreira J, et al. Hyperkalaemia prevalence, recurrence and management in chronic haemodialysis: a prospective multicentre French regional registry 2-year survey. Nephrol Dial Transplant 2017;32(12):2112-8.

Roy-Chaudhury et al 2018
Roy-Chaudhury P, Tumlin JA, Koplan BA, Costea AI, Kher V, et al. Primary outcomes of the Monitoring in Dialysis Study indicate that clinically significant arrhythmias are common in hemodialysis patients and related to dialytic cycle. Kidney Int 2018;93(4):941-51.

Sacher et al 2018
Sacher F, Jesel L, Borni-Duval C, De Precigout V, Borudenx LF, et al. Cardiac rhythm disturbances in hemodialysis patients: early detection using an implantable loop recorder and correlation with biologic and dialysis parameters. JACC Clin Electrophysiol 2018;4(3):397-408.

Sankaranarayanan et al 2015
Sankaranarayanan R, Kirkwood G, Visweswariah R, Fox DJ. How does chronic atrial fibrillation influence mortality in the modern treatment era? Curr Cardiol Rev 2015;11(3):190-8.

Seliger et al 2003
Seliger SL, Gillen DL, Longstreth WT, Kestenbaum B, Stehman-Breen CO. Elevated risk of stroke among patients with end-stage renal disease. Kidney Int 2003;64(2):603-9.

Severi et al 2010
Severi S, Pogliani D, Fantini G, Fabbrini P, Viganò MR, et al. Alterations of atrial electrophysiology induced by electrolyte variations: combined computational and P-wave analysis. Europace 2010;12(6):842-9.

Soliman et al 2010
Soliman EZ, Prineas RJ, Go AS, Xie D, Lash JP, et al. Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). Am Heart J 2010;159:1102-7.

Sozio et al 2009
Sozio SM, Armstrong PA, Coresh J, Jaar BG, Fink NE, et al. Cerebrovascular disease incidence, characteristics, and outcomes inpatients initiating dialysis: the choices for healthy outcomes in caring for ESRD (CHOICE) study. Am J Kidney Dis 2009;54(3):468-77.

Wolf et al 1998
Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. Arch Intern Med 1998;158:229-34.

Wong et al 2015
Wong MC, Kalman JM, Pedagogos E, Toussaint N, Vohra JK, et al. Temporal distribution of arrhythmic events in chronic kidney disease: highest incidence in the long interdialytic period. Heart Rhythm 2015;12(10):2047-55.

Yusuf et al 2016
Yusuf AA, Hu Y, Singh B, Menoyo JA, Wetmore JB. Serum potassium levels and mortality in hemodialysis patients: a retrospective cohort study. Am J Nephrol 2016;44:179-86.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d9487c00001-csp-v3		
Document Title:	D9487C00001 Clinical Study Protocol version 3	
Document ID:	Doc ID-004401116	
Version Label:	3.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
13-Apr-2023 20:21 UTC	PPD	Content Approval
19-Apr-2023 10:29 UTC	PPD	Content Approval
17-Apr-2023 12:58 UTC	PPD	Content Approval
13-Apr-2023 17:33 UTC	PPD	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.