| STATISTICAL ANALYSIS PLAN | |
|---|---|
| Study Code | D9487C00001 |
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| Date | 13-Dec-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)

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# LIST OF ABBREVIATIONS

List abbreviations and definitions of specialized or unusual terms, measurements, or units.

| Abbreviation or Specialized Term | Definition |
|---|---|
| AE | Adverse event |
| BMI | Body mass index |
| CEA | |
| CRF | Case Report Form |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| eCDF | Empirical Cumulative Distribution Function |
| ED | Emergency Department |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practice |
| HR | Hazard Ratio |
| IM | Immunogenicity |
| IPD | Important Protocol Deviation |
| ITT | Intent-To-Treat |
| IXRS | Interactive voice/web response system |
| KM | Kaplan-Meier |
| MedDRA | Medical Dictionary for Regulatory Activities |
| LTFU | Lost to follow up |
| PD | Pharmacodynamic |
| PK | Pharmacokinetics |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SS | Safety Set |
| SED | Study End Date |
| SID | Subject ID |
| VF | Ventricular Fibrillation |
| VT | Ventricular Tachycardia |
| WoC | Withdrawal of consent |

# AMENDMENT HISTORY

| CATEGORY<br>Change refers to: | Date | Description of change | In line with CSP? | Rationale |
|---|---|---|---|---|
| N/A | Click or tap here to enter text. | Initial approved SAP | N/A | N/A |
| Interim Analysis | 13-Jan-2022 | Added text to Section 5.0 of the SAP from CSP version 1.0 on interim analysis | Yes | Administrative change |
| Interim Analysis | 19-Apr-2022 | Clarified the planned number of interim analyses, as well as the type I error rate that is planned to use.<br>Added secondary endpoints in interim analysis. | to be updated | The two-sided alpha to be used for the interim analysis relies on timing of the analysis, in terms of Information Fraction at Interim Look. Further clarifications were added.<br>Interim analysis will be conducted and tested for each secondary endpoint. Therefore, more details were provided. |
| Multiplicity/Multiple Comparisons | 19-Apr-2022 | Deleted "Further adjustment to the significance level will be done if more than one formal interim analysis for efficacy is performed (Section 5)." In Section 3.3.4 and clarified how to adjust type I error rate for the final analysis | To be updated | This change is in line with Section Interim Analysis updates. |
| Section 4.2.2.3 Handling of Dropouts and Missing Data | 19-Apr-2022 | Added tipping point analyses for following secondary endpoints:<br>• Time to first occurrence of hospitalization/intervention/ED visit due to arrhythmias (AF, bradycardia, asystole, VT)<br>• Time to SCD<br>• Time to first occurrence of stroke<br>• Time to CV death<br>• Time to death of any cause | Yes | The changes are in line of handling of missing data for those key secondary endpoints |
| Hospitalizations/interventions/ED visits due to arrhythmias (AF, bradycardia, asystole, or VT) | 19-Apr-2022 | Added definition on number of hospitalizations/interventions/ED visits due to arrhythmias (AF, bradycardia, asystole, or VT) in Section 4.2.2.2 | Yes | The definitions were not clearly defined initially. Both the definitions and what constitutes |

| | | | | |
|---|---|---|---|---|
| | | | | intervention have been clarified |
| Sample size determination | 19-Apr-2022 | Added text to Section 3 of the SAP from CSP version 2.0 on Sample size determination | Yes | Administrative change |
| Sample Size | 15-Nov 2023 | Sample size was increased from 2300 to 2800 which is documented in Section 3 | Yes | Sample size modified to accelerate primary event accrual |
| Timing of the final analysis | 15-Nov 2023 | Number of primary events at the final analysis decreased | Yes | To shorten duration of the trial |
| Interim Analysis | 15-Nov 2023 | Two interim analyses were introduced in SAP Edition 4 to replace single interim analysis in SAP Edition 3. The first interim analysis is for futility and the second interim analysis is for efficacy. | Yes | To optimize decision making and allow early stopping for futility and efficacy |
| Section 4.2.2 | 15-Nov 2023 | Sensitivity analysis was added for binary endpoints based on potassium levels at the 12 months | Yes | To assess sensitivity of the result to missing data assumptions |
| Section 4.2.3 Multiplicity/ Multiple Comparisons | 15-Nov 2023 | Significance levels for the efficacy interim and final analyses were updated. | Yes | To account for modification to interim analyses |

# 1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D9487C00001 (DALIZE-Outcomes), supporting the clinical study report. The details of study conduct and data collection are provided in the clinical study protocol (CSP) and the case report form (CRF).

# 2 CHANGES TO PROTOCOL PLANNED ANALYSES

There are no changes to protocol planned analyses. However, safety analysis dataset was renamed as safety set (SS).

# 3 DATA ANALYSIS CONSIDERATIONS

## 3.1 Timing of Analyses

The study involves two interim analyses (the first interim analysis is for futility and the second interim analysis is for efficacy) and the final analysis.

Thus, there are three timepoints for planned analyses in the study: one corresponding to study completion, planned to take place when 730 subjects had an adjudicated primary composite event, and the other two corresponding to interim analyses planned to take place when 292 (40% information fraction) and 511 (70% information fraction) subjects, respectively had an adjudicated primary composite event. The interim analyses will be conducted by independent data monitoring committee (DMC) and will mainly be aimed at evaluating the primary objective of the study with the possibility of early stopping for either futility (at n=292 events) and for efficacy (at n=511 events). In case of an early stopping of the study at efficacy interim analyses, all analyses as specified in this document will be conducted. However, if the study stops for futility, only selected analyses covering key efficacy and safety outcomes will be conducted.

## 3.2 Analysis Populations

Two analysis sets are defined according to International Conference on Harmonization (ICH) E9 guideline.

Full analysis set (FAS) includes all subjects who underwent randomization and received a randomization number, irrespective of their protocol adherence and continued participation in the study. Subjects will be analysed according to their randomized study intervention assignment, irrespective of the treatment actually received. The FAS will be used as the analysis set for all efficacy analyses.

Safety Set (SS) includes all subjects who are randomised and have received at least one dose of study intervention (SZC or Placebo). Subjects will be analysed according to the treatment randomised. The SS will be used as the analysis set for all safety analyses.

## 3.3 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 84.7% statistical power to demonstrate a statistically significant difference at either second interim analysis using two-sided significance level of 1.64% or at the final analysis using two-sided significance level of 4.46%. Based on an assumption that the event rate of the primary composite endpoint is approximately 0.11 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 will be based on blinded event rate data (e.g., observed overall event rate), and study discontinuation rate.

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).

## 3.4 General Considerations

In order to provide an overview of the data, descriptive statistics will be utilized. The type of descriptive statistic will depend on the variable being summarized, with number of patients with available data (n), mean, standard deviation, median, quartiles, minimum, and maximum used to summarize continuous variables, and counts and percentages used to summarize categorical variables.

Missing data will be ignored in the descriptive statistical summaries, and only subjects with non-missing data at the relevant timepoint will be included. For the percentage calculation for the categorical variables, the number of subjects randomized to each of the treatment arms, as well as the total number of subjects in the relevant study population (e.g FAS), will be used as a rule, unless otherwise specified in the detailed analyses descriptions given below.

Kaplan-Meier estimates will be used to illustrate the distribution of time-to-event data. If Cox regressions are used for a more formal time to event analysis, no hazard ratio estimates with confidence interval and p-values will be given when less than 15 events in total are observed during the relevant time period, both treatment groups combined.

All of analyses will be conducted by AstraZeneca using SAS version 9.4 or higher.

### 3.4.1 General Study Level Definitions

#### 3.4.1.1 Study End Date (SED)

The executive committee and AstraZeneca will monitor the accrual of endpoint events and, when appropriate, define the study end date as the date at which the pre-defined target number of 730 subjects are expected to have experienced a primary adjudicated event. The SED will be used as a global censoring time point for all main time to event analyses performed for the study. However, if the study is stopped before the planned stop date (e.g. based on the results of interim analyses), then the SED will be determined as per early stopping decision.

#### 3.4.1.2 Withdrawal of consent (WoC)

Withdrawal of consent (WoC) refers to the date when the patient withdrew their consent for participation in the study.

#### 3.4.1.3 Lost to follow-up (LTFU)

Lost to follow-up (LTFU) refers to the last date of contact with the patient if the contact with the patient was lost during the course of the study.

#### 3.4.1.4 During the study and on-treatment definitions

For every patient, the following definitions will be used in safety analyses.

**During the study**

"During the study" is defined as time from the randomization day to the date of last contact or death.

**On-treatment**

"On-treatment" is defined as the period between the first day of planned intake of study intervention to one day after the day of the last actual dose of study intervention.

#### 3.4.1.5 Others

**Baseline value**

For both efficacy and safety analyses the baseline value for all variables is defined as the last value obtained during screening period on or prior to the date of randomization.

**Geographic Region**

Geographic regions are defined as follows:

- Asia (China, Japan, Taiwan, Vietnam, India, Malaysia, Thailand)
- Europe (Austria, Bulgaria, Czech Republic, Germany, Hungary, Italy, Poland, Russia, Slovakia, Spain, Ukraine, UK, Turkey)

- North America (Canada, US)
- South America (Argentina, Brazil, Mexico, Peru)

The determination of the region will be based on the country recorded in interactive voice/web response system (IxRS) as a stratification factor.

**Incomplete dates**
All efforts should be made to obtain complete dates of clinical assessments and events. For analyses requiring complete dates, partially missing dates will be imputed based on available corroborating information. Appendix 1 presents the dates that will be imputed and the associated rules.

**Study day**
Study day related to event day or censoring day is derived using following formula: (event or censoring date – randomization date) + 1.

### 3.4.2 Visit Window

No visit windowing be applied.

### 3.4.3 Handling of Unscheduled Visits

Data obtained on unscheduled visits (e.g., safety laboratory evaluations) will be excluded from any analyses and presentations that are done for each visit separately. It will, however, be included in analyses of extreme values observed during a particular period of time, such as tabulations of high/low/out-of-range test results observed while a subject was on treatment. Data obtained on unscheduled visits will also be listed.

### 3.4.4 Handling of Protocol Deviations in Study Analysis

The section covers the list of potential Important Protocol Deviations (IPDs) that might potentially impact the results of the analyses and/or are a serious breach of Good Clinical Practice (GCP).

The IPDs will be categorized as follows:

1. Written informed consent not obtained prior to mandatory study specific procedures, sampling and analyses.
2. Received alternative protocol specific therapy than that which they were randomised.
3. Developed discontinuation of study intervention criteria during the study, but remained on the study intervention.
4. Site procedure for unblinding of the subject is not complaint with the CSP.
5. Received prohibited/excluded concomitant medication.

As the main efficacy analyses for the study follow the intention-to-treat principle, presence of protocol deviations for a subject will not imply exclusion of the subject, or any data obtained from the subject, from these analyses. However, supplementary analyses aimed at e.g., evaluating potential efficacy for subjects who remain on the assigned study treatment regimen might be conducted. As such analyses are per protocol in nature, they would exclude data obtained following a protocol deviation, see Section 4.2.

# 4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain (study population, efficacy, safety).

## 4.1 Study Population

This section covers the presentation of subject recruitment, disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical history, prior and concomitant medication, exposure and study drug compliance. Data will be summarised by treatment arm and overall using FAS except for disposition and analysis sets overview.

### 4.1.1 Subject Disposition and recruitment

#### 4.1.1.1 Definitions and Derivations

**Complete follow-up of the primary endpoint**
Subject having experienced the primary endpoint event, or the subject reaching SED is defined as having completed the follow-up for primary endpoint.

**Study completers**
Randomised subjects who stayed in the study until the SED irrespective whether they discontinued IP or had any event will be considered as study completers.

**Vital Status** of subjects at the end of the study will be recorded, if available, as dead or alive in the eCRF, along with the relevant dates. Vital status of the subjects that are lost to follow up (LTFU) will be recorded as 'unknown’.

#### 4.1.1.2 Presentation

**Disposition**

The presentation of patient disposition will include information on enrolment, randomization, receiving at least one dose of IP, completing the treatment and completing the study. It will summarise whether a subject did or did not experience these milestones and, if not, the reason. The presentation will also include the number of subjects with

complete follow-up of the primary endpoint and vital status of subjects at the end of the study (dead, alive or unknown).

The tabulation will include an overview of the number and percentage of subjects experiencing a particular disposition event, per treatment arm and in total, with number of randomized subjects in the respective treatment group, and in total, used as the denominator for the percentage calculation.

Number of subjects enrolled, but not randomized, as well as number of subjects with a certain reason for not being randomized, will only be displayed for all subjects combined, with no percentage calculated.

**Disposition due to Country/Global Situation**

The number, and percentage, of subjects discontinuing treatment and discontinuing study due to Country/Global Situation (e.g. COVID-19), will be presented separately.

**Randomised Subjects**

Randomized subjects by region, country and site will be presented in terms of number and percentage of patients randomized at a particular location, by treatment arm and in total.

### 4.1.2 Analysis Sets

#### 4.1.2.1 Definitions and Derivations

Please refer to Section 3.2 for definitions of analysis sets. Note that only one reason for not being included in SS, while being included in FAS, is possible, namely failing to receive study intervention.

#### 4.1.2.2 Presentation

An overview of the number of subjects included in, and, for SS, excluded from, the respective analysis set will be provided. The reasons for not being randomized, and, consequently, not being included in FAS or SS, will not be included in this presentation.

### 4.1.3 Protocol Deviations

#### 4.1.3.1 Definitions and Derivations

All protocol deviations, regardless of the method of identification (e.g. manual vs programmatic), will be stored in the Veeva Clinical Vault (VCV) system, from which the final protocol deviation data set will be extracted and included as part of the data base. This data set will be the basis for the summaries and listings of protocol deviations.

#### 4.1.3.2 Presentation

The number of subjects with any IPD, as well as the number of subjects experiencing an IPD in a particular category, will be summarized descriptively as categorical variables, as

described in Section 3.3. The presentation will also include the corresponding information specifically on the occurrence of Country/Global Situation related protocol deviations.

### 4.1.4 Demographics

#### 4.1.4.1 Definitions and Derivations

Demographic data is recorded in the eCRF at the Screening Visit. Demographic variables summarized as part of the description of the study population are as follows:

- Age (years) as a continuous variable, and categorically as:
  - ≥18 to 50, 51 to 64, 65 to 84 and ≥85 years
  - <65, 65 to 74, and ≥75 years
  - <65 and ≥65 years
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Geographic region and country as defined in Section 3.4.1.5)

#### 4.1.4.2 Presentation

The demographic attributes as described above will be summarized descriptively as described in Section 3.3.

### 4.1.5 Baseline and Disease Background Characteristics

#### 4.1.5.1 Definitions and Derivations

Baseline characteristics summarized as part of the description of the study population are as follows: height (cm), pre- and post-dialysis weight (kg) and body mass index (BMI) ($kg/m^2$), continuous and categorical (30<, ≥30).

**The BMI ($kg/m^2$)**, defined as post-dialysis weight (kg) / $(\text{height (m)})^2$, will be derived for each subject.

Disease related background characteristics will include pulse (BPM), blood pressure (BP), S-K (mmol/L), continuous and categorical (<5.5, 5.5-6.5, >6.5) and inter-dialytic weight gain (IDWG).

**Interdialytic weight gain (IDWG)** will be calculated as the difference between current pre-dialysis weight and the previous post-dialysis weight (measured at preceding dialysis session prior to the visit) in kilograms. If current pre-dialysis weight or previous post-dialysis weight is missing, no interdialytic weight gain will be derived.

#### 4.1.5.2 Presentation

The presentation of the baseline characteristic will follow the same rules as that for demographics.

### 4.1.6 Disease Related Medical and Surgical History

#### 4.1.6.1 Definitions and Derivations

Disease related medical and surgical history will be coded using the version Medical Dictionary for Regulatory Activities (MedDRA) implemented in the study at the time of database lock.

#### 4.1.6.2 Presentation

Presence of disease related medical or surgical history will be summarized descriptively by system organ class and preferred term, as a categorical variable, as described in Section 3.3. The MedDRA version used will be included in the relevant outputs as a footnote.

### 4.1.7 Dialysis History

#### 4.1.7.1 Definitions and derivations

Dialysis history recorded on the eCRF at screening visit includes: (I) dialysis vintage (time since first dialysis in years); (II) type of access: AV fistula, AV graft, tunneled central venous catheter, other (specify).

#### 4.1.7.2 Presentation

Time since first dialysis (years) will be summarized as a continuous variable and dialysis access type as a categorical variable, as described in Section 3.3.

### 4.1.8 Prior and Concomitant Medications

#### 4.1.8.1 Definitions and Derivations

**Concomitant medication** is defined as a medication taken by the subject after the date of randomization, regardless of when it has been initiated.

Please see Appendix 1 for imputation rules for missing medication start and stop dates.

**Disallowed medication** is defined as a potassium binder that is taken post-randomization and is not identifiable as rescue therapy. Potassium binders are defined by the ATC terms listed in Appendix 3.

**Rescue** is defined as any potassium lowering treatment (e.g. a medication, an extra dialysis, a change in dialysate K concentration in the existing dialysis regimen) given in connection to an adverse event (AE) of hyperkalaemia requiring rescue.

#### 4.1.8.2 Presentation

All concomitant medications and disallowed medications will be summarized separately in a descriptive manner, by presenting the number and percentage of subjects receiving the medication by ATC classification and generic drug name. Rescue treatments will be similarly summarized, the presentation including additional categories for dialysis initiation and change in dialysate K concentration.

### 4.1.9 Study Drug Compliance

#### 4.1.9.1 Definitions and Derivations

Compliance will be derived from an estimate of the actual exposure (in grams of IP), obtained through sachet counts, and the planned exposure to IP as indicated by the investigator (also in grams of IP), from first planned dose date to last planned dose date, accounting for dose interruptions. No compliance will be derived for subjects who did not receive study treatment. The last planned dose for subjects who withdraw from the study or withdraw from the treatment is the date of respective withdrawal.

Compliance will be analysed as a continuous variable, as well as a categorical variable, with categories defined as <80%, 80% to 120% and >120%.

#### 4.1.9.2 Presentation

Compliance during the study will be presented by means of descriptive summary statistics, as described in Section 3.3.

### 4.1.10 Duration of follow-up

#### 4.1.10.1 Definitions and Derivations

**Time in study to SED (months)** is defined as:
(min(withdrawal of consent, death, LTFU, SED) date – randomization date + 1) / 30.4

#### 4.1.10.2 Presentation

Duration of follow-up as described above will be summarized using descriptive statistics, as a continuous variable. Empirical Cumulative Distribution Function (eCDF) plots will also be produced, by treatment group.

### 4.1.11 Exposure

#### 4.1.11.1 Definitions and Derivations

The duration of total planned exposure (months) to study drug is defined as the length of period on study drug, calculated for each subject as (date of last actual dose – date of first planned dose +1)/30.4.

The duration of planned exposure excluding interruptions (months) to study drug is defined as total planned exposure (months) minus total interruptions. Interruptions will be identified from eCRF EX module. Similarly, duration of exposure to a particular dose will be defined as the time the dose was prescribed to the date it was dose stop plus one day.

#### 4.1.11.2 Presentation

Duration of exposure and exposure excluding interruptions will be summarized using descriptive statistics as described in Section 3.3 by treatment group. Duration of exposure to a particular dose level will be summarized in a similar manner, by treatment group and dose level.

Number of subjects (%) with any treatment interruption, as well as reasons for interruption, will be summarized descriptively based on the SS data set for each treatment group.

A figure with number of subjects on study drug vs days from randomisation will be produced.

A plot of the proportion of subjects on each dose (including dose 0) over time will be produced by treatment group. This will be complimented by a table summarizing the average doses the subjects receive during the course of the study, as well as a one presenting the proportions of time a subject spends on each dose level.

A listing of subjects by batch number of study medication and dosage over time will be generated.

## 4.2 Endpoint Analyses

This section covers details related to endpoints, intercurrent event strategies, handling of missing data and analyses pre-specified for the efficacy objectives. All defined analyses will be performed using FAS if not otherwise stated. This implies that the population to which the results are generalizable is the population of all subjects that satisfy inclusion and exclusion criteria. For all analyses, the treatments, or, in terms of estimands, “treatment conditions”, will be SZC or Placebo administrated according to the dosing regimen, as detailed in CSP Section 6.1.2.

Unless otherwise specified, for all analyses for which a statistical test is performed, the null hypothesis corresponds to no difference between SZC and Placebo treatment arms.

The unit of time for all time to event analysis will be days.

Endpoints, intercurrent event strategies and censoring rules, as well as population level summaries, are given in Table 1 for primary objective, Table 2 for secondary objectives, and Table 3 for exploratory objectives.

## Table 1 Summary of endpoints, intercurrent event strategy, and population level summary for the primary objective

| Purpose | Endpoint | Intercurrent event strategy and censoring rules | Population level summary |
|---|---|---|---|
| Primary objective: To evaluate the efficacy of SZC compared with placebo in reducing the time event of the primary composite endpoint of SCD, all stroke, or hospitalization/intervention/ED visit due to arrhythmias | | | |
| Establishing the efficacy of treatment with regards to risk for the occurrence of the primary endpoint events | Time to first occurrence of SCD, stroke, or hospitalization /intervention /ED visit due to arrhythmias (atrial fibrillation [AF], bradycardia, asystole, ventricular tachyarrhythmias [such as VF, VT, etc]) | Events included in analysis regardless of treatment discontinuation and additional therapy (treatment policy).<br><br>Patients censored at the earliest of death that is non-SCD, WoC, LTFU, study discontinuation for other reason, and SED. | Hazard Ratio (SZC/placebo) |
| **Sensitivity analyses of primary analysis.** Details in Section 4.2.1.5 | | | |
| Sensitivity to classification of cause of death | Time to the first occurrence of SCD or death adjudicated as undetermined, stroke, or hospitalization /intervention /ED visit due to arrhythmias (atrial fibrillation [AF], bradycardia, asystole, ventricular tachyarrhythmias [VT]). | Events included in analysis regardless of treatment discontinuation and additional therapy (treatment policy).<br><br>Patients censored at the earliest of death that is non-SCD and has a known cause, WoC, LTFU, study discontinuation for other reason, and SED. | Hazard Ratio (SZC/placebo) |
| Sensitivity to inclusion of post-SED events | Time to first occurrence of a primary endpoint event | Events included in analysis regardless of treatment discontinuation and additional therapy (treatment policy).<br><br>Patients not censored at SED. All other censoring rules used in the main analysis apply. | Hazard Ratio (SZC/placebo) |
| Supplementary analyses of the primary objective. Details in Section 4.2.1.6 | | | |

| Purpose | Endpoint | Intercurrent event strategy and censoring rules | Population level summary |
|---|---|---|---|
| Impact of non-SCD as a component in the primary endpoint composite | Time to first occurrence of all cause death, stroke, or hospitalization /intervention /ED visit due to arrhythmias (atrial fibrillation [AF], bradycardia, asystole, ventricular tachyarrhythmias [VT]) | Events included in analysis regardless of treatment discontinuation and additional therapy (treatment policy).<br><br>Patients censored at the earliest of WoC, LTFU, study discontinuation for other reason, and SED. | Hazard Ratio (SZC/placebo) |
| Impact of drop-in (patients starting treatment with non-protocolized SZC during study) | Time to first occurrence of a primary endpoint event | Events occurring post "drop-in" excluded from the analysis (while not on non-protocolised SZC).<br><br>Patients censored at the earliest of non-SCD, WoC, LTFU, study discontinuation for other reason, SED and the time of initiation of non-protocolized SZC, if such occurs. | Hazard Ratio (SZC/placebo) |

Further details can be found in Section 4.2.1

## Table 2 Summary of secondary endpoints, intercurrent event strategy, and population level summary for the secondary objectives (endpoints are listed in statistical testing order)

| Testing Order | Endpoint | Intercurrent event strategy and censoring rules | Population level summary |
|---|---|---|---|
| 1 | S-K of 4.0-5.5 mmol/L (yes/no) after the long interdialytic interval (LIDI) at the 12-month visit | Observations included in analysis regardless of treatment discontinuation and additional therapy (treatment policy) | Odds Ratio (SZC/placebo) |
| 2 | Time to first occurrence of hospitalization/intervention/ED visit due to arrhythmias (AF, bradycardia, asystole, ventricular tachyarrhythmias [such as VF, VT, etc]). | Observations included in analysis regardless of treatment discontinuation and additional therapy (treatment policy).<br><br>Patients censored at the earliest of death, WoC, LTFU, Other reasons of discontinuation and SED. | Hazard Ratio (SZC/placebo) |

| Testing Order | Endpoint | Intercurrent event strategy and censoring rules | Population level summary |
|---|---|---|---|
| 3 | Number of hospitalizations/interventions /ED visits due to arrhythmias (AF, bradycardia, asystole, or VT [such as VF, VT, etc]) | Observations included in analysis regardless of treatment discontinuation and additional therapy (treatment policy)<br>Patients censored at the earliest of death, WoC, LTFU, Other reasons of discontinuation or SED. | Rate ratio (SZC/placebo) |
| 4 | Time to first instance of rescue therapy use for hyperkalemia | Observations included in analysis regardless of treatment discontinuation and additional therapy (treatment policy).<br>Patients censored at the earliest of death, WoC, LTFU, Other reasons of discontinuation and SED | Hazard Ratio (SZC/placebo) |
| 5 | S-K > 6.5 mmol/L (yes/no) after the LIDI at the 12-month visit | Observations included in analysis regardless of treatment discontinuation and additional therapy (treatment policy) | Odds Ratio (SZC/placebo) |
| 6 | Time to SCD | Observations included in analysis regardless of treatment discontinuation and additional therapy (treatment policy).<br>Patients censored at the earliest of non-SCD, WoC, LTFU, Other reasons of discontinuation and SED | Hazard Ratio (SZC/placebo) |
| 7 | Time to first occurrence of stroke | Observations included in analysis regardless of treatment discontinuation and additional therapy (treatment policy),<br>Patients censored at the earliest of death, WoC, LTFU, Other reasons of discontinuation and SED | Hazard Ratio (SZC/placebo) |
| 8 | Time to CV death | Observations included in analysis regardless of treatment discontinuation and additional therapy (treatment policy),<br>Patients censored at the earliest of non-CV death, WoC, LTFU, Other reasons of discontinuation and SED | Hazard Ratio (SZC/placebo) |
| 9 | Time to death of any cause | Observations included in analysis regardless of treatment discontinuation and additional therapy (treatment policy),<br>Patients censored at the earliest of WoC, LTFU, Other reasons of discontinuation and SED | Hazard Ratio (SZC/placebo) |

**Table 3 Summary of endpoints, intercurrent event strategy, and population level summaries for the exploratory objectives**

| Endpoint | Intercurrent event strategy | Population level summary |
|---|---|---|
| S-K of 4.0-5.0 mmol/L (yes/no) after the LIDI at the 12-month visit | Observations included in analysis regardless of treatment discontinuation and additional therapy (treatment policy) | Odds Ratio (SZC/placebo) |
| Time to first occurrence of SCD, stroke, or hospitalization/intervention/ED visit due to arrhythmias (AF, bradycardia, asystole, VT [such as VF, VT, etc]), or use of rescue therapy | Observations included in analysis regardless of treatment discontinuation and additional therapy (treatment policy).<br><br>Patients censored at the earliest of non-SCD, WoC, LTFU, other reasons of discontinuation and SED. | Hazard Ratio (SZC/placebo) |
| Number of events of rescue therapy use for hyperkalemia | Observations included in analysis regardless of treatment discontinuation and additional therapy (treatment policy).<br><br>Patients censored at the earliest of death, WoC, LTFU, other reasons of discontinuation or SED. | Rate ratio (SZC/placebo) |

## 4.2.1 Primary Endpoint

### 4.2.1.1 Definition

The primary endpoint is the composite endpoint of time to first occurrence of adjudicated events of SCD, stroke, or hospitalization/ intervention/ ED visit due to arrhythmias (AF, bradycardia, asystole, ventricular tachyarrhythmia [VT, VF etc.]). The potential components of the primary endpoint will be individually adjudicated by an independent committee. Only events that are positively adjudicated will be used in deriving the primary composite endpoint and the individual components.

### 4.2.1.2 Derivations

**Censoring:** See Table 1 for the censoring rules for the different analyses.

**Time to event or censoring:** See Section 3.3.1.5 for the definition of the study day.

### 4.2.1.3 Handling of Dropouts and Missing Data

The missing data in the context of the main analysis of the primary objective are potential events that might have occurred after subjects have been prematurely censored (i.e. due to causes other than SED). Since the time-to-event analysis using the Cox regression depends on the assumption of noninformative censoring, corresponding to the missing-at-random

missing data pattern, sensitivity analyses will be performed to assess the robustness of the results with regards to this assumption. Explicitly, in case of a statistically significant result, a 'tipping point' analysis, where the risk of censored subjects in the SZC group experiencing an event post-censoring is increased until the statistical significance is lost, will be performed. Appendix 2 provides the technical details of the tipping point analysis.

The missing data will also be described in terms of the number and percentage of subjects in the respective treatment arm that do not experience a primary endpoint event and that are censored before the SED, as well as reasons for censoring.

#### 4.2.1.4 Main Analysis of the Primary Endpoint

The analysis of the primary composite endpoint will be based on a Cox regression model that includes the following factors/covariates: treatment group, geographic region. The Efron method for handling ties will be used.

The estimate of the HR corresponding to the difference between treatment arms, the corresponding 95% two-sided confidence interval (CI) as well as the two-sided p-value for the null hypothesis of no difference will be reported. If the p-value falls below the significance limit as specified in Section 4.2.3 , the null hypothesis will be rejected.

The contribution of each component of the primary composite endpoint to the overall treatment effect will be assessed. In the analysis of the components, all first events of the given type will be included, irrespective of any preceding non-fatal component of a different type. Each component in the composite endpoint will be analysed similarly to the composite primary endpoint, i.e. by means of a Cox regression.

Kaplan-Meier estimates will be calculated and plotted, both for the composite endpoint and for individual components. The KM estimate at 12, 24 and 36 months will be included in the tabular presentation of the primary endpoint analysis.

#### 4.2.1.5 Sensitivity analyses of the Primary Endpoint

The majority of the sensitivity, and supplementary, analyses will be performed by means of replicating the main analysis using different censoring rules and different event definitions. For all such analyses, no KM plots of the CDFs will be produced, but the KM estimates for the two treatment arms evaluated at particular timepoints will be included in the tabular presentation.

**Undetermined cause of death**

Deaths adjudicated as 'undetermined' cause will be included in the composite endpoint, along with the components used for the main analysis of the primary endpoint. The Cox regression analysis as described in Section 4.2.1.4 will then be replicated using this endpoint.

**Events occurring post SED**
The main analysis will be replicated using the entire follow-up time available for a patient, i.e. including events occurring post SED.

#### 4.2.1.6 Supplementary Analyses of the Primary Endpoint

**Non-SCD events**
All the deaths will be included in the composite endpoint along with the rest of the components, used for the main analysis of the primary endpoint. The Cox regression analysis as described in Section 4.2.1.5 will be replicated using this endpoint.

**Drop-in**
The sensitivity of the results observed in the main analysis to the "drop-in", i.e. instances of patients starting on non-protocolized SZC, will be examined. This will be done by censoring such patients at the time of drop-in, correspondingly ignoring events that occur after the fact, and replicating the main analysis using the resulting time to event / censoring.

**Assumption of proportional hazards for Cox model**
The underlying assumption of proportional hazards for Cox model will be assessed. The assessments will include: visual examination of the negative logarithms of the KM curves, with a crossing of the curves indicating that the assumption is not met, and by introducing, and testing, the significance of a time-dependent covariate in the Cox regression model, with a significant interaction indicating that the assumption is not met. This will be done for the main analysis of the primary endpoint only.

#### 4.2.1.7 Subgroup Analyses

The consistency of the treatment effect observed in the main analysis will be evaluated with respect to the following demographic/baseline characteristic and prognostic factors:

- Sex
- Age at baseline
  - categorization 1 (<65, 65 - 84, ≥ 85)
  - categorization 2 (<65, 65 - 74, ≥ 75)
  - categorization 3 (<65, ≥65)

- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, Not reported)
- Geographic Region (Asia, Europe, North America, South America)
- Region (USA, Non-USA)
- Baseline S-K (<5.5, 5.5-6.5, >6.5)
- BMI (<30, ≥ 30 kg/m²)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Haemodialysis access type (Arteriovenous Fistula, Arteriovenous Graft, Tunnelled Catheter, Other)

- Historical arrhythmia (yes/no) at baseline.
- Prior History of
    - Atrial Fibrillation (Yes, No)
    - Ventricular Tachycardia (Yes, No)
    - Ventricular Fibrillation (Yes, No)
    - Stroke/TIA (Yes, No)

The Cox proportional hazards model used for the primary analysis (Section 4.2.1.4), including a factor for the relevant subgroup and the treatment-by-subgroup interaction, will be used for each subgroup analysis. HR for each level of the subgroup will be estimated separately.

The presentation of the results will include the estimate of the HR between treatment arms in the respective sub-group, the corresponding 95% CI and the p-value for the interaction term.

Results will also be plotted using a forest plot.

### 4.2.2 Secondary and Exploratory Objectives

**Potassium levels at 12 months visit**
The primary analyses of potassium levels at 12 months will be based on the available data (i.e. no imputation performed).

**Normokalemia**
Two definitions of normokalemic will be used to assess the likelihood of a patient being normokalemic at the 12 months visit. For the purpose of analyzing the corresponding secondary objective, normokalemia will be defined as:

- S-K of 4.0-5.5 mmol/L (yes/no), as measured by the central lab, after the long interdialytic interval (LIDI).

For the purpose of analyzing the corresponding exploratory objective, normokalemia will be defined as:

- S-K of 4.0-5.0 mmol/L (yes/no), as measured by the central lab, after the long interdialytic interval (LIDI).

A logistic regression model with the binary variable (yes/no) as response and the same covariates as for the main analysis of the primary objective described in Section 4.2.1.4 will be used. The estimated odds ratio, corresponding 95% confidence interval, and two-sided p-value will be presented. The proportion of normokalemic subjects in each treatment arm

will also be presented, with the number of patients with available SK data in the respective treatment arms used as the denominator.

**Severe hyperkalemia**
Severe hyperkalemia will be defined as S-K > 6.5 mmol/L (yes/no) after the LIDI. The same analysis as for the classification of potassium into normal / abnormal (i.e. a logistic regression) will be performed.

**Sensitivity Analysis**

To assess sensitivity of the result to missing data assumptions, binary endpoints based on potassium levels at the 12 months will be analysed using Full Analysis Set (all randomized subjects). Subjects with missing values will be considered as non-responders. For severe hyperkalemia endpoint (S-K > 6.5 mmol/L (yes/no)), subjects with missing values will be considered as having severe hyperkalemia.

**Supplementary analyses**
The distribution of the SK values at the 12 months visit, as well as at baseline, in each treatment arm, will be illustrated by means of a box plot. A complimentary table presenting the summary statistics (mean, SD, median, min, max, quartiles) describing the distribution of SK, as well as the distribution of difference in SK as compared to baseline, per treatment arm, will also be provided.

#### 4.2.2.1 Time to first event analyses

In addition to the main analysis of the composite primary endpoint, and its components, the difference between the two treatment arms in time to the following events (in days) will be analyzed:

- Time to first instance of use of rescue therapy for hyperkalemia
- Time to CV death
- Time to death from any cause
- Time to first occurrence of SCD, stroke, or hospitalization/intervention/ED visit due to arrhythmias (AF, bradycardia, asystole, VT), or use of rescue therapy (exploratory objective)

For all of these endpoints, the analysis described in Section 4.2.1.4 (i.e. the main analysis of the primary objective) will be replicated, with the censoring rules given in Table 2 and Table 3. KM estimates of the CDF in the respective treatment arms will be plotted as a supportive illustration.

**Sensitivity analyses**
A sensitivity analysis of the analysis of time to CV death, where deaths adjudicated as ‘undetermined’ cause are included as endpoint events, instead of being treated as censoring

events, will be performed using the same approach as for the main analysis of time to CV death. No plots of KM estimates will be produced.

#### 4.2.2.2 Number of events analyses

Two analyses aimed at examining the difference in the expected number of events of interest, per a unit of time, between treatment arms will be performed. In the first analysis, aimed at evaluating the corresponding secondary objective, the events of interest are hospitalizations /interventions /ED visits due to arrhythmias. Only arrhythmias events that are positively adjudicated will be considered. Multiple hospitalizations /interventions /ED visits due to a single positively adjudicated arrhythmias will be counted as one event. In the second analysis, aimed at evaluating the corresponding exploratory objective, the events of interest are use of rescue therapy for hyperkalemia.

For both of these endpoints, a negative binomial regression model with number of events as response and the same covariates as in the main analysis of the primary endpoint (Section 4.2.1.4) will be used. The logarithm of the subject's corresponding follow-up time will be used as an offset variable in the model to adjust for subjects having different follow-up times during which the events can occur. See Table 2 and 3 for the definition of the follow-up time (censoring).

The estimated event rate in the respective treatment arm, rate ratio between these, corresponding 95% confidence interval, and two-sided p-value will be presented. Total number of events that occurred up to the point of censoring will also be presented, by treatment group.

Time to event analysis for recurrent events may be conducted as a supplementary analysis.

### 4.2.3 Multiplicity/Multiple Comparisons

Testing for efficacy will be performed at two time points, first at 0.7 information fraction and at the final analysis. The significance levels for the interim and the final analyses will be adjusted to control the overall type I error rate at two-sided 5%. At the efficacy interim analysis, the hypothesis for the primary endpoint will be tested at two-sided 1.64% significance level (O'Brian and Fleming method implemented by East 6.5, Copyright © 2018 Cytel Inc.). If the outcome of the interim analysis is to stop the trial for efficacy, then the interim analysis results will be considered as the primary efficacy results. However, a supplementary analysis will be performed with the additional data up to the study termination.

If the trial does not stop at any interim, then the final analysis planned at 730 adjudicated events, will be performed at a two-sided significance level of 4.46%. If the actual information fraction at the efficacy interim look deviates from 0.70, the significance level

for the final analysis will be adjusted based on the actual number of adjudicated primary events at the interim and final analyses.

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:

H0: HR[SZC:placebo] = 1

Versus

H1: HR[SZC:placebo] ≠ 1

If study is terminated early prior to conducting efficacy and futility interim analyses and for reasons unrelated to efficacy, primary endpoint will be tested at 5% two-sided significance level.

Once the null hypothesis concerning the primary efficacy endpoint is rejected, the hypotheses for the secondary efficacy endpoints will be tested separately in the order listed in Table 2, with the same alpha level as the primary endpoint. The testing procedure will continue down the hierarchy if the current endpoint is rejected and will stop if the current endpoint is not rejected.

No multiplicity correction will be applied to the family of exploratory analyses. Hence, the results obtained from these should be regarded as hypothesis generating, rather than confirmatory.

### 4.2.4 Handling of Dropouts and Missing Data

Missing data imputation will not be adopted for secondary, or exploratory endpoints and no supplementary analyses of the same type as the tipping point analysis described in Section 4.2.1.3 will be performed.

The missing data will also be described in terms of the number and percentage of subjects in the respective treatment arm that do not experience an endpoint event and that are censored before the SED, as well as reasons for censoring.

## 4.3 Pharmacodynamic Endpoint(s)

Not applicable.

#### 4.3.1.1 Pharmacokinetics

Not applicable.

## 4.4 Immunogenicity

Not applicable.

## 4.5 Safety Analyses

The domain safety covers adverse events, clinical laboratory, vital signs, and ECG.

Tables and listings are, as a rule, provided for the SS, except for an SAE listing that displays SAEs for non-randomised subjects that occur during screening.

The primary method for presentation of summary of safety will be "during the study" (see Section 3.3.1.4 for the definition of this time period), reflecting the ITT approach used for the efficacy analyses. However, a selection of tabulations will be replicated for "on treatment" period, as supportive information.

### 4.5.1 Adverse Events

Occurrence of AEs during the course of the study will be summarized descriptively, using frequencies and percentages.

#### 4.5.1.1 Definitions and Derivations

Adverse events will be coded using the latest version of MedDRA implemented at the time of database lock. The MedDRA version will be stated in a footnote in the relevant outputs.

**Oedema-related** events are defined as AEs with the following PT terms: Fluid overload, Fluid retention, Generalised oedema, Hypervolemia, Localised oedema, Oedema, Oedema Peripheral, Peripheral swelling.

**Pre-dialysis hypokalemia** (S-K < 3.0 mmol/L based on local laboratory assessment) will be reported as an AE regardless of whether there are associated signs and symptoms, and is indicated directly by the investigator in the appropriate eCRF form (note that hypokalemia could also be determined based on the central lab potassium evaluation, and would then be reported separately, see Section 4.6.2.1).

**Pre-dialysis hyperkalemia requiring rescue** is collected as an adverse event, and is indicated directly by the investigator in the appropriate eCRF form.

**Dialysis adequacy (Kt/V)** will be collected in eCRF only in Indian sites during visit 1 (screening), visit 4 (randomization) and thereafter during subsequent protocol specified onsite visits until the end of study intervention visit (EOIV) or premature study intervention discontinuation visit (PIDV).

**Duration variables** to be presented, where applicable (e.g. key subject information tables), are defined as follows:

- Time from planned treatment start date to onset of AE (days)
- Time from planned treatment start date to death (days)
- Time from planned treatment start date to AE becoming serious (days)
- Time from planned treatment start date to discontinuation of IP (days)
- Time from actual last dose date to death (days)
- Time from actual last dose date to AE start date (days)

The derivations for these variables will be the difference between the two dates stated above + 1 day.

#### 4.5.1.2 Presentation

**Overall overview**

An AE overview table will be created, with AEs falling within the following categories summarized by treatment group.

- Any AE
- Any SAE
- Any AE with outcome death
- Any AE leading to discontinuation of IP
- Any AE possibly related to IP
- Any event of hypokalaemia
- Any event of hyperkalemia requiring rescue therapy

This summary will be replicated for on-treatment analysis period.

**AEs, SAEs, DAEs and deaths, by system organ class and preferred term**

A detailed overview of number, and percentage, of subjects with AEs, SAEs, DAEs and deaths in a particular SOC and PT class will be presented. In addition, for AEs and SAEs, a corresponding overview of the number of AEs in a particular SOC/PT class, and the rate of AEs, will be created.

The summaries of SAEs and DAEs will be replicated for on-treatment analysis period.

**Most common AEs**

A tabulation of the PT terms for most common AEs, i.e. AE PT terms that occur in more than 10% of the patient population (both treatment arms combined), will be provided. It will be replicated for the on-treatment study period.

**Intensity of AEs**
An overview of the number and the percentage of subjects with AEs in a particular SOC, PT and intensity class (mild, moderate, severe) will be created. Subjects will be counted only once in each category. A subject with two AE in the same SOC and PT class of e.g. both high and moderate intensity will be assigned the "high" intensity category, i.e. the more severe class.

**Causality of AEs**
Number and percentage of subjects with AEs considered as possibly related to IP will be tabulated by SOC and PT.

**Events of special interest: oedema, hypokalemia and hyperkalemia**
An overview of oedema-related AEs, with number and percentage of subjects with an event with a particular PT term, will be presented.

Number of subjects with AE classified as hypokalemia, or hyperkalemia requiring rescue, will be tabulated in a similar manner.

Both of these overviews, oedema-related AEs and hypo-hyperkalemia AEs, will be replicated for the on-treatment period as well as during study.

**Dialysis adequacy (Kt/V)** as a continuous variable will be summarized descriptively as described in Section 3.3.

**Key subject information tables**
Key subject information will be provided for all SAEs, AEs with an outcome of death, and all AEs leading to IP discontinuation. This will include e.g. the duration variables defined in the beginning of this section, outcome of an AE and action taken with respect to IP.

**Listings**

The listings provided will include, but may not be limited to:

- All AE
- All AE of hypokalemia. The listing will e.g. include information on the actual SK value observed during the AE.
- SAE for enrolled, but not randomized, subjects.

All listings will be created for during the study time period, and will include planned treatment arm, actual treatment arm, planned dose, actual dose and time since the actual last IP administration date.

### 4.5.2 Clinical Laboratory, Vital Signs and ECG

Blood samples will be taken at Visit 1, 2, 3, 4 (randomization), and 8 (12-month) for the determination of clinical chemistry by a central laboratory; a full list of the laboratory variables for this study is provided in Table 7 of the CSP. For the definition of baseline, see Section 3.3.1.5.

Vital signs (pulse and BP) will be assessed at Visit 1, 4 (randomization) and end of study intervention visit (EOIV) or premature study intervention discontinuation visit (PIDV).

A 12-lead ECG will be performed at Visit 1 and 4 (randomization). That is, only the baseline ECG value will be available for this study.

#### 4.5.2.1 Definitions and Derivations

All summaries of clinical chemistry and hematology variables will be based on samples analyzed at the central laboratory and presented in SI units.

**Hyper- and hypokalemia:** Based on the S-K obtained from the central laboratory at visit 8, a set of classification variables reflecting different degrees of hyperkalemia (> 5.0, > 5.5, > 6.0 mmol/L, > 6.5 mmol/L) and hypokalemia (< 3.5, < 3.0, < 2.5 mmol/L) will be created.

**Lab abnormalities:** Abnormality status (“low”, “high”) of the laboratory values will be derived based on the normality ranges provided by the central laboratory.

**Vital signs abnormalities:** Abnormal vital signs will be indicated directly in the eCRF by the investigator.

#### 4.5.2.2 Presentations

**Summary of measurements over time**

The result and the change from baseline of each clinical chemistry and vital sign variable will be summarized, by treatment group, at baseline and 12-month visit (for labs) or EOIV/PIDV (for vital signs), using descriptive statistics as appropriate for continuous variables. For the ECG variables, only the baseline measurements will be presented, with no change from baseline, as there are no planned post-baseline ECG measurement occasions. The absolute values, as well as the changes, will also be illustrated by means of box plots.

**Haematology, clinical chemistry and vital signs, treatment emergent abnormalities**
The number, and percentage, of subjects falling into the different categories as defined above, at any post-baseline visit including unscheduled, for each variable, will be tabulated. The number of subjects with a baseline and a post-baseline value in the respective treatment arms will be used as the denominator for the calculation of the percentages.

The tabulations will be replicated for on-treatment time period.

**Instances of hyper- and hypokalemia**
Number, and percentage, of subjects experiencing different degrees of hyper- and hypokalemia at the 12-month visit, as defined above, will be tabulated. The number of subjects with observations available at visit 8 in the respective treatment arm will be used as the denominator for the percentages.

**Listings**

The listings provided will include, but may not be limited to:

- Instances of lab measurements classified as abnormal.
- Instances of vital sign measurements classified as abnormal.

## 4.5.3 Other Safety Assessments

### 4.5.3.1 Definitions and Derivations

Pre-dialysis weight will be collected at Visit 1, 4 (randomization), and all the visits specified in the protocol. Post-dialysis weight from the previous dialysis session will be collected at Visit 4 (randomization), and all other visits specified in the protocol, except SCV.

**Interdialytic weight gain (IDWG)** will be calculated as the difference between current pre-dialysis weight and the previous post-dialysis weight (measured at proceeding dialysis session prior to the visit) in kilograms. If current pre-dialysis weight or previous post-dialysis weight is missing, no interdialytic weight gain will be derived.

### 4.5.3.2 Presentations

An overview of pre-dialysis weight and IDWG over time will be created. That is, the result obtained at baseline and each scheduled post-baseline visit, as well as the change from baseline, will be summarized by treatment group as appropriate for continuous variables. The IDWG profile over time will also be illustrated by means of box plots.

# 5 INTERIM ANALYSES

The DMC will conduct interim analyses for futility and efficacy when respectively 40%, and 70% of the total number of primary endpoint events have accrued and have been adjudicated (i.e, a minimum of 292 and 511 events).

The futility threshold for non-binding futility analysis is defined as the estimated hazard ratio, SZC versus placebo being equal to or larger than 1. This will correspond to a predictive power of < 5.1%.

At the efficacy interim analysis, the hypothesis for the primary endpoint will be tested at the two-sided 1.64% level ($p < 0.0164$) (O'Brian and Fleming, East 6.5, Copyright © 2018 Cytel Inc.) given that information fraction at the efficacy interim analysis is equal to 0.70. The actual information fraction for the efficacy interim will be recalculated at the final analysis as number of adjudicated primary events at the interim divided by total number of actual primary events for the trial. The two-sided $\alpha$ level for the final analysis will be recalculated using East 6.5 if information fraction rounded to 2 decimal places is not equal to 0.70.

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

# 6 REFERENCES

**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.
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf.

# 7 APPENDIX 1: MISSING DATE IMPUTATION RULES

(a) Missing data imputation for AEs

| Missing scenario | Imputation rule |
|---|---|
| If only the day part of the AE onset date is missing | If the month and year are the same as that of first dose of study medication, the date of first dose of study medication will be used as the onset date of the AE. Otherwise, the first day of the month will be used to complete the onset date of the AE |
| If the day and month parts of the AE onset date are missing | If the year is the same as that of the first dose of study medication, the date of the first dose of study medication will be used as the onset date of the AE. Otherwise, January 1st will be used to complete the onset date of the AE. |
| If the AE onset date is completely missing and end date missing, or after first dose of study medication | The date of the first dose of study medication will be used as the onset date of the AE. |
| If only the day part of the AE end date is missing | The last day of the month will be used to complete the end date of the AE. |
| If the day and month parts of the AE end date are missing | December 31st will be used to complete the end date of the AE. |
| If the end date of the AE is completely missing and the AE is not ongoing, and the onset date of the AE occurs after the date of the first dose of study medication | Then the onset date of the AE will be used as the AE end date. Otherwise, the date of the first dose of study medication will be used as the AE end date. |

(b) Missing data imputation for concomitant medications dates

| Start Date | Stop Date | Imputation rule |
|---|---|---|
| Known | Partial | Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown). |
| Known | Missing | Assume on-going |
| Partial | Known | Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown) |
| Partial | Partial | Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown) |
| Partial | Missing | Assume on-going |
| Missing | Known | If stop date ≥ randomisation date, assign as concomitant |
| Missing | Partial | Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown) |
| Missing | Missing | Assume on-going |

# APPENDIX 2: TIPPING POINT ANALYSIS

Missing data in the context of the primary analysis is defined as the time interval between the premature censoring date and SED or date of non-sudden cardiac death, whichever came first. Tipping point analysis will be conducted to assess the robustness of the statistically significant results of the primary endpoint. Following steps will be used in tipping point analysis.

**Step 1. Identification of patients and time interval requiring imputation**
Randomized patients (the FAS population) with a censoring date prior to SED, regardless of the reason for incomplete follow-up (except death), will be flagged as requiring imputation. The time interval subjected to imputation will be defined by the censoring date and SED or date of death, whichever was earlier.

**Step 2. Estimation of placebo and SZC event rates**
The placebo event rate will be estimated based on available follow-up data among all placebo patients using accelerated failure time model (LIFEREG in SAS). Based on the estimated placebo event rate, the SZC event rate will be estimated as placebo event rate multiplied by the estimated hazard ratio in the primary analysis.

The estimated event rates will be used to inform the time to event in the next step.

**Step 3. Estimation of event time**
For patients requiring imputation, the event time will be estimated separately within placebo and active treatment groups, based on exponential distribution using corresponding rate parameters. A seed will be used in exponential random generator of event time.

Simulated follow-up time (placebo) $= 360^* (RV / ER_{placebo})$

Simulated follow-up time (SZC) $= 360^* (RV / (ER_{placebo}^* \text{Hazard Ratio}))$

Where RV = exponential random variate ($\lambda=1$), $ER_{placebo}$= Placebo event rate, Hazard Ratio=hazard ratio from primary analysis.

**Step 4. Imputation of events**
A simulated date of event is defined as the original censoring date plus the simulated time to event. If the simulated date of event is prior to both SED and the date of death, if applicable, an event will be imputed for this patient with the new time to event calculated based on the simulated date of event. Otherwise the patient will be censored at SED or the date of death, whichever is earlier.

**Step 5. Combining results from imputations**

Step 4 will be repeated 1000 times, generating 1000 imputed datasets. Each of the imputed dataset together with the observed data for the patients with complete follow-up will be analyzed using the same Cox proportional hazards model as the primary analysis. The 1000 hazard ratio estimates will be then combined using the Rubin's combination rule (PROC MIANALYZE). Hazard ratio, 95% CI and p-value will be reported.

**Step 6. Identifying the tipping point**

The imputations in Step 4 will be repeated while SZC event rates will be systematically increased in small increments from observed rates. Placebo event rates will be held at observed rates. The p-value from the combined results will be compared to the alpha threshold for primary analysis. The process will be repeated until the tipping point, as expressed as the ratio of the assumed event rate between the active and placebo groups, is found where the statistical significance is lost.

# APPENDIX 3: ATC TERMS FOR POTASSIUM BINDERS

| ATC CODE | RECNO | SEQNO1 | SEQNO2 | INGREDIENTS |
|---|---|---|---|---|
| V03AE | 000677 | 01 | 001 | SODIUM POLYSTYRENE SULFONATE |
| V03AE | 003281 | 01 | 001 | CALCIUM POLYSTYRENE SULFONATE |
| V03AE | 075390 | 01 | 001 | PATIROMER |
| V03AE | 075390 | 02 | 001 | PATIROMER CALCIUM |
| V03AE | 075390 | 03 | 001 | PATIROMER SORBITEX CALCIUM |
| V03AE | 087714 | 01 | 001 | SODIUM ZIRCONIUM CYCLOSILICATE |

# SIGNATURE PAGE

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