**STATISTICAL ANALYSIS PLAN**

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|---|---|
| Study Code | D9485C00001 |
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# A Phase 3b, Multicentre, Prospective, Randomized, Double-Blind, Placebo-Controlled Study to Reduce Incidence of Pre-Dialysis Hyperkalaemia with Sodium Zirconium Cyclosilicate in Chinese Subjects (DIALIZE China)

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| Abbreviation or Specialized Term | Definition |
|---|---|
| AE | Adverse Event |
| ALP | Alkaline Phosphatise |
| ALT | Alanine Transaminase |
| AST | Aspartate Transaminase |
| ATC | Anatomical Therapeutic Chemical |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| CDF | Cumulative Distribution Function |
| CI | Confidence Interval |
| CK | Creatine Kinase |
| c-Lab | Central Laboratory |
| COVID-19 | Coronavirus 2019 |
| CRF | Case Report Form (electronic/paper) |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| DBP | Diastolic Blood Pressure |
| DBL | Database Lock |
| ECG | Electrocardiogram |
| eCRF | electronic Case Report Form |
| EM | Expectation Maximization |
| EOS | End of Study |
| EOT | End of Treatment |
| ESRD | End-Stage Renal Disease |
| FAS | Full Analysis Set |
| FU | Follow-up |
| GGT | Gamma-glutamyl Transferase |
| Hb | Haemoglobin |
| hCG | Human Chorionic Gonadotropin |
| HL | Hy's Law |
| HR | Heart Rate |
| ICF | Informed Consent Form |

| Abbreviation or Specialized Term | Definition |
|---|---|
| ICH | International Conference on Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| IDWG | Interdialytic Weight Gain |
| IP | Investigational Product |
| IPD | Important Protocol Deviation |
| ITT | Intention to Treat |
| LIDI | Long Inter-dialytic Interval |
| LOCF | Last Observation Carried Forward |
| LS | Least Squares |
| MAR | Missing at random |
| MCMC | Markov Chain Monte Carlo |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Multiple Imputation |
| MMRM | Mixed Model Repeated Measures |
| MNAR | Missing not at random |
| OR | Odds Ratio |
| PD | Protocol Deviation |
| PSDV | Premature Study Discontinuation Visit |
| PT | Preferred Term |
| Qb | Blood Flow (dialysis) |
| Qd | Dialysate Flow Rate |
| QTcF | QT interval corrected for heart rate using Friderica's formula |
| RBC | Red Blood Count |
| S-K | Serum Potassium |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Safety Analysis Set |
| SIDI | Short Inter-dialytic Interval |
| SOC | System Organ Class |
| spKt/V | Single-Pool Kt/V (K - dialyzer urea clearance coefficient; t - time on dialysis; V - volume of distribution of urea or total body water). |
| SBP | Systolic Blood Pressure |
| SZC | Sodium Zirconium Cyclosilicate |
| TFL | Table, Figures and Listings |

| Abbreviation or Specialized Term | Definition |
|---|---|
| URR | Urea Reduction Ratio |
| WHO | World Health Organization |

# AMENDMENT HISTORY

| **CATEGORY**<br>**Change refers to:** | **Date** | **Description of change** | **In line with CSP?** | **Rationale** |
|---|---|---|---|---|
| N/A | 9 Feb 2021 | Initial approved SAP | N/A | N/A |
| Derivation of primary endpoint(s) | 02 Nov 2021 | Updated analysis method for primary endpoint, sensitivity analysis 2 to use multiple imputation instead of LOCF (table 3 and section 4.2.1.4). Updated number of burn-in iterations to 1000. Added Risk Difference to presentation. (4.2.1.2) | NA | To improve previous intent |
| Derivation of primary endpoint(s) | 02 Nov 2021 | Updated null and alternative hypothesis to be in terms of OR, updated text and subscripted 0 and 1 in H0/H1 (section 3.3.2) | Yes | Clarification of analysis method |
| Primary endpoint(s) | 02 Nov 2021 | Removed text about presenting difference of proportions between treatment groups (section 4.2.1.4) | NA | To align with TFLs |
| Statistical analysis method for secondary endpoint(s) | 24 Jul 2021 | Updated analysis method for secondary endpoint 1 (table 3 and sections 2, 3.2.2 and 4.2.2) | No | Clarification of analysis method |
| Statistical analysis method for secondary endpoint(s) | 24 Jul 2021 | Updated analysis method for secondary endpoint 2 (table 3 and sections 2 and 4.2.3) | No | Clarification of analysis method |

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|---|---|---|---|---|
| Statistical analysis method for secondary endpoint(s) | 02 Nov 2021 | Added detail of using Bootstrap to obtain 95% CI in secondary endpoint 3 (section 4.2.4.2) | NA | Clarification of analysis method |
| Statistical analysis method for secondary endpoint(s) | 02 Nov 2021 | • Updated text to use GENMOD instead of LOGISTIC<br>• Added baseline as covariate for a generalized linear model for secondary endpoints 1 and 2<br>• Clarified what happens if model fit isn't valid<br>• Added "Maximum" to title<br>• Changed number of burn-in iterations from 200 to 1000<br>(sections 4.2.2 and 4.2.3) | Yes | Clarification of analysis method |
| Statistical analysis method for secondary endpoint(s) | 02 Nov 2021 | Updated null and alternative hypothesis to be in terms of OR, updated text and subscripted 0 and 1 in H0/H1 (section 3.3.2) | Yes | Clarification of analysis method |
| Secondary endpoint(s) | 24 Jul 2021 | Clarification that secondary endpoint 1 is below or equal to 5.5mol/L(table 3 and sections 2, 3.2.2 and 4.2.2). | NA | To improve previous intent |

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|---|---|---|---|---|
| Multiple testing procedure | 24 Jul 2021 | Update secondary endpoint 1 in multiple testing procedure figure (section 3.3.5 and figure 1). | Yes | Clarification of analysis method |
| Multiple testing procedure | 02 Nov 2021 | Clarification added that rescue therapy is the only intercurrent event being considered (section 4.2) | Yes | Clarification of analysis method |
| Data presentation | 24 Jul 2021 | Update to visit window section (section 3.3.3), amended to use one-to-one mapping for visits, since windowing does not apply | NA | To improve previous intent |
| Data presentation | 24 Jul 2021 | Update to handling of unscheduled visits section (section 3.3.4) to clarify how unscheduled visits are handled in TFLs | NA | To improve previous intent |
| Data presentation | 24 Jul 2021 | IPD text updated to confirmed that IPDs will be summarized overall and by COVID-19 related or not (section 4.1.3.2). | NA | To improve previous intent |
| Data presentation | 24 Jul 2021 | Removal of redundant text for compliance rate (section 4.1.9.2). | NA | To align with TFLs |
| Data presentation | 24 Jul 2021 | Included presentation of change from baseline at each visit for bicarbonate (section 4.6.3.2) | NA | To align with TFLs |

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|---|---|---|---|---|
| Data presentation | 24 Jul 2021 | Updated presentation of ECGs to include all ECG variables from eCRF and add additional summary table for QTcF (section 4.6.7) | NA | To align with TFLs |
| Data presentation | 02 Nov 2021 | [redacted] (section 4.2.8.2) | NA | [redacted] |
| Data presentation | 02 Nov 2021 | Added text about AE listing for subjects not randomized | NA | To align with TFLs |
| Data presentation | 02 Nov 2021 | Updated presentation of hematology and clinical chemistry tables to have separate tables for pre-dialysis S-K and bicarbonate and also for Haemoglobin, Magnesium and Calcium (section 4.6.3.2) | NA | To improve previous intent |
| Data presentation | 02 Nov 2021 | Updated presentation of low level S-K to be for pre-dialysis S-K only (section 4.6.2.2) | NA | To improve previous intent |
| Data presentation | 02 Nov 2021 | Updated presentation of vital signs listing to be for all vital signs, not just abnormal (section 4.6.6.2) | NA | To improve previous intent |

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|---|---|---|---|---|
| Data presentation | 02 Nov 2021 | [redacted] (Exploratory endpoint 5 – section 4.2.10.2) | NA | [redacted] |
| Data presentation | 02 Nov 2021 | Updated duration of exposure to be presented for both planned and actual exposure (section 4.6.1.2) | NA | To improve previous intent |
| Data presentation | 02 Nov 2021 | • Updated presentation of AE to be time from previous dose prior to AE start date instead of time from last dose<br>• Updated order AEs presented in tables<br>• Added AEs possible related to study drug and AEs leading to interruption of study treatment<br>• Removed reference to treatment emergent<br>(section 4.6.2.2) | NA | To improve previous intent |
| Other | 24 Jul 2021 | Updated abbreviations table. | NA | To improve previous intent |

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|---|---|---|---|---|
| Other | 24 Jul 2021 | Minor cosmetic update to display BMI on separate line from dry-weight (section 4.1.5.1) | NA | Minor / cosmetic |
| Other | 24 Jul 2021 | Updated section references in endpoint analyses Table at beginning of section 4.2 | NA | Minor / cosmetic |
| Other | 24 Jul 2021 | Clarification that records which are not considered "true LIDI" should be excluded for all analyses unless otherwise stated (section 4.2). | NA | To improve previous intent |
| Other | 24 Jul 2021 | [redacted] (sections 4.2.6, 4.2.7, 4.2.12 and table 3). | Yes | [redacted] |
| Other | 24 Jul 2021 | Minor cosmetic update to remove typo (full stop) in section 4.2.4.2 | NA | Minor / cosmetic |
| Other | 24 Jul 2021 | [redacted] (sections 4.2.8.2, 4.2.9.2, 4.2.10.2, 4.2.11.2, 4.2.13.2 and 4.2.14.2). | NA | [redacted] |
| Other | 02 Nov 2021 | Added derivation for time since first dialysis (years) | N/A | To improve previous intent |

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|---|---|---|---|---|
| Other | 02 Nov 2021 | Added PD and LS to list of abbreviations. Abbreviations added in section 4.1 and 4.1.3.1/2 | N/A | To improve previous intent |
| Other | 02 Nov 2021 | Added title of study to Introduction | N/A | Minor / cosmetic |
| Other | 02 Nov 2021 | Removed unnecessary sentence in changes to Protocol Planned Analysis (section 2) | N/A | To improve previous intent |
| Other | 02 Nov 2021 | Removed section 4.2.6.3 and replaced with text in section 4.2.6.2 | N/A | Minor / cosmetic |
| Other | 02 Nov 2021 | Updated definition of non-true LIDI to use time of next dialysis, not pre-dialysis (section 4.2, 4.2.1.1, 4.2.2.2) | Yes | To improve previous intent |
| Other | 02 Nov 2021 | Updated instance of "K-Shift" to "S-K Shift" (table 3) | Yes | Minor / cosmetic |
| Other | 02 Nov 2021 | Remove reference to treatment emergent, clarify which AEs are presented in tables (sections 3.3.1.3 and 4.6.2.2) | NA | To improve previous intent |
| Other | 02 Nov 2021 | Updated ECG categories to be "abnormal, borderline" instead of "borderline abnormal" (sections 4.6.7 and 4.6.7.2) | Yes | To improve previous intent |

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|---|---|---|---|---|
| Other | 02 Nov 2021 | Updated definitions of baseline for IDWG (section 3.3.1.1) | NA | To improve previous intent |
| Other | 02 Nov 2021 | Updated definitions of pre-treatment and concomitant medications (section 4.1.8) | NA | To improve previous intent |
| Other | 02 Nov 2021 | [redacted] (sections 4.2.6 and 4.2.12) | NA | [redacted] |
| Other | 02 Nov 2021 | [redacted] (section 4.2.8.2) | NA | [redacted] |
| Other | 02 Nov 2021 | [redacted] (section 4.2.12) | NA | [redacted] |

# 1 INTRODUCTION

This statistical analysis plan (SAP) contains a more detailed description of the analyses in the clinical study protocol (CSP) for the DIALIZE China study and is based on version 2.0 of the CSP. Refer to the CSP and the case report form (CRF) for details of study conduct and data collection.

This SAP applies to the phase 3b, multicentre, prospective, randomized, double-blind, placebo-controlled study to reduce incidence of pre-dialysis hyperkalaemia with sodium zirconium cyclosilicate (SZC) in Chinese subjects (DIALIZE China).

Refer to the CSP for a detailed description of the rationale for this study.

# 2 CHANGES TO PROTOCOL PLANNED ANALYSES

The following exploratory objective, which is not included in the CSP, is included within the SAP and addressed as outlined in section 4.2.14:

- [redacted]

Contrary to the statement regarding exploratory endpoints that "No formal statistical tests will be performed" (see section 9.4.1.5 of the CSP)), formal statistical analysis is performed for the following exploratory endpoints:

- [redacted]
- [redacted]
- [redacted]

The analysis method outlined for secondary endpoints 1 and 2 differs from method described in the CSP (v3.0). The probability estimation is updated from the previous method to multiple imputation based approach combined with a generalized linear model. Refer to sections 4.2.2 and 4.2.3 for further details.

# 3 DATA ANALYSIS CONSIDERATIONS

## 3.1 Timing of Analyses

The primary analysis is performed after the database lock (DBL). There are no interim analyses for this study.

## 3.2 Analysis Populations

### 3.2.1 Enrolled set

All subjects who sign the informed consent form (ICF).

### 3.2.2 Full analysis set

The full analysis set (FAS) includes all randomized subjects. The FAS is used for all efficacy analyses. Treatment arms are compared on the basis of randomized study treatment, regardless of the treatment actually received. Subjects who were randomized but did not subsequently go on to receive study treatment are included in the analysis in the treatment arm to which they were randomized. The analysis of data using the FAS therefore follows the principles of intention to treat (ITT).

### 3.2.3 Safety analysis set

The safety analysis set (SAS) consists of all randomized subjects who received at least 1 dose of study treatment (SZC or placebo). Safety data is not formally analyzed but summarized descriptively using the SAS, according to the treatment received. Throughout the safety results sections, erroneously treated subjects (subjects randomized to one of the treatment groups but actually given the other treatment) are accounted for in the actual treatment group. Subjects with erroneous treatment are analyzed according to that treatment only if they only received the erroneous treatment and none of the correct treatment. Subjects who receive more than one treatment are analysed according to their randomized treatment.

### 3.2.4 Summary of outcome variables and analysis populations

**Table 1: Summary of outcome variables and analysis populations**

| Outcome variable | Analysis set |
|---|---|
| **Efficacy Data** | |
| Primary endpoint | Full analysis set |
| Secondary endpoints | Full analysis set |
| Exploratory endpoints | Full analysis set |
| **Study Population /Demography Data** | |
| Demography characteristics | Full analysis set |
| Baseline and disease characteristics | Full analysis set |
| Important protocol deviations | Full analysis set |
| Medical/surgical history | Full analysis set |
| Concomitant medications | Full analysis set |
| Compliance | Full analysis set |
| Dialysis history | Full analysis set |
| Dialysate K | Full analysis set |
| **Safety Data** | |
| Exposure | Safety analysis set |
| AEs | Safety analysis set |
| Laboratory measurements | Safety analysis set |
| Physical examinations and vital signs | Safety analysis set |
| ECGs | Safety analysis set |

AE Adverse event; ECG Electrocardiogram.

## 3.3 General Considerations

Efficacy data is summarized and analyzed based upon the FAS. Safety data is summarized based upon the SAS. Study population and demographic data are summarized based upon the FAS.

The below mentioned general principles are followed throughout the study:

- All analyses and reporting are by treatment arm.
- Descriptive statistics are used for all variables, as appropriate. Continuous variables are summarized by the number of observations, mean, standard deviation, median, upper and lower quartiles, minimum, and maximum. Categorical variables are summarized by frequency counts and percentages for each category.

- Unless otherwise stated, percentages are calculated out of the population total and for each treatment group. Overall totals are calculated for baseline summaries only.

- For continuous data, the mean and median are rounded to 1 additional decimal place compared to the original data. The standard deviation is rounded to 2 additional decimal places compared to the original data. Minimum and maximum are displayed with the same accuracy as the original data. In instances when 1st and 3rd quartiles are presented these are rounded to 1 additional decimal place than the original data.

- For categorical data, percentages are rounded to 1 decimal place.

- P-values are presented to 3 decimal places and p-values less than 0.001 are presented as <0.001 in Tables, Figures and Listings (TFLs).

- SAS® version 9.4 will be used for all analyses.

## 3.3.1 General Study Level Definitions

### 3.3.1.1 Definition of Baseline

**Efficacy Endpoints**

In general, for efficacy endpoints the last observed measurement prior to randomization is considered the baseline measurement. However, if an evaluable assessment is only available after randomization but before the first dose of randomized treatment then this assessment is used as baseline.

**Safety Endpoints**

For safety endpoints the last observation before the first dose of study treatment is considered the baseline measurement unless otherwise specified. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, serves as sufficient evidence that the assessment occurred prior to first dose. Assessments on the day of the first dose where neither time nor a nominal pre-dose indicator are captured are considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose.

If two visits are equally eligible to assess subject status at baseline (e.g., screening and baseline assessments both on the same date prior to the first dose with no other intervention in the screening period), the average is used as the baseline value. For non-numeric laboratory tests where taking the average is not possible, the best value is taken as baseline as this is most conservative. In the scenario where there are two assessments recorded on the day, one with time recorded and the other without time recorded, the one with the time recorded is selected as baseline. Where safety data are summarized over time, time on study is calculated in relation to date of first study treatment.

For weight baseline is defined as the latest pre-dialysis weight prior to first dose of treatment. For Interdialytic Weight Gain (IDWG) baseline is the latest IDWG prior to first dose of treatment.

For subjects randomized and not treated, randomization date will be used instead of first dose to assign baseline measurement .

#### 3.3.1.2 Definition of Study Period

The study will consist of four study periods as follows:

**Screening period**, one week. This period starts on visit 1 and ends on the day prior to randomization day. At screening, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects can be re-screened once during the clinical trial period, see CSP Section 5.4 “Screen failures” for details.

**Dose Adjustment period**, four weeks. This period starts with visit 4, when randomization takes place, and ends at visit 14. During this period, the dose is titrated to achieve and maintain pre-dialysis after-LIDI S-K between 4.0 and 5.0 mmol/L. The maximum allowable investigation product (IP) dose is 15g. See CSP Section 6.1 “Treatments administered” for details.

**Evaluation period**, four weeks. This period starts day after visit 14 and ends with visit 22 (end of treatment visit, EOT). During evaluation period the dose is held stable. This is the period that will be used for the majority of the efficacy evaluations.

**Follow-up period**, approximately two weeks. This is an off-treatment period that starts day after visit 22 and ends with visit 23 (end of study visit, EOS), with the primary purpose of capturing potential post-treatment safety issues.

The following visits are of special importance:

**Visit 1, enrolment**. This is the very first visit of the study on which the informed consent form (ICF) should be signed and first study procedure undertaken. Premature signing of ICF, i.e. signing before visit 1, should be avoided. A subject will be considered as enrolled in the study from the time the first ICF is signed (signing multiple ICFs might be necessary e.g. in case of re-screening). See CSP Appendix A2 “Informed consent process” for further information regarding ICF.

**Visit 4, randomization**. This is the visit at which the randomization code is obtained, and a subject is randomized to either SZC or Placebo, provided they have fulfilled the eligibility criteria and were not withdrawn (e.g. subject decision). For further information regarding randomization process, see CSP Sections Section 4.2.2 “Methods for blinding and

unblinding" 6.3 "Measures to minimise bias: randomization and blinding" and 7.4 "Procedure for erroneously randomized subjects".

**Visit 22, end of treatment (EOT)**. This is the last visit of the evaluation period, as well as treatment period overall. If no premature treatment discontinuation occurred, this is also the day after which no IP should be taken. For details on the process of premature treatment discontinuation see CSP Section 7.1 "Discontinuation of study treatment".

**Visit 23, end of study (EOS)**. This is the very last scheduled visit of the study with no assessments planned to take place after it. It should take place 14 +/- 3 days after the EOT visit to match the dialysis schedule.

**Extra visit, premature study discontinuation visit (PSDV)**. This visit is only relevant for subjects that are withdrawn from the study (note that this differs from treatment discontinuation). It might occur at any point during the study and no information should be collected after the visit takes place. In particular, such subjects will not have an EOS visit, with the premature study discontinuation visit replacing it. For further details on the process of premature study discontinuation see CSP Section 7.3 "Withdrawal from the study".

#### 3.3.1.3 Definition of Treatment Emergent

In the reporting of laboratory parameters, a treatment emergent change is defined as compared to baseline a change that occurs during the treatment period (dose adjustment and evaluation period) or follow-up period.

#### 3.3.1.4 Handling of missing data

Missing safety data is generally not imputed. However, safety assessments of the form of "<x" (i.e., below the lower limit of quantification) or ">x" (i.e., above the upper limit of quantification) are imputed as "x" in the calculation of summary statistics but are displayed as "<x" or ">x" in the listings.

See section 4.2 Endpoint Analyses and respective subsections for how missing data is handled in the analysis of efficacy endpoints.

For missing start dates for AEs and concomitant medications/procedures, the following is applied:

- Missing day: Impute the 1st of the month unless month is the same as month of the first dose of study drug then impute first dose date.

- Missing day and month: Impute 1st January unless year is the same as first dose date then impute first dose date.

- Completely missing date: Impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

When imputing a start date, ensure that the new imputed date is sensible e.g., prior to the end date of the AE.

For missing stop dates of AEs or concomitant medications/procedures, the following is applied:

- Missing day: Impute the last day of the month unless month is the same as month of last dose of study drug then impute last dose date.

- Missing day and month: Impute 31st December unless year is the same as last dose date then impute last dose date.

- Completely missing: If an AE/medication has a completely missing end date then it is treated as ongoing. Flags are retained in the database indicating where any programmatic imputation has been applied, and in such cases, any durations are not calculated.

If a subject is known to have died where only a partial death date is available, then the date of death is imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided:

- Missing day only: Using the 1st of the month.

- Missing day and month: Using the 1st January.

Subjects with a partial date of birth (i.e., for those cases where year of birth only is given) have 1st of the month imputed if the day is missing, and 1st Jan imputed if the day and month is missing.

### 3.3.2 Hypothesis Testing

For the primary comparisons, the null hypothesis is that the response rate of subjects in the SZC arm is equal to that of subjects in the placebo arm. The alternative hypothesis is that the response rate of subjects in the SZC arm is different from that of subjects in the placebo arm.

$H_0$: $OR_{SZC\ vs\ Placebo} = 1$
$H_1$: $OR_{SZC\ vs\ Placebo} \neq 1$

Secondary endpoint 1: Maximum S-K below or equal to 5.5 mmol/L

The null hypothesis is that there is no difference in probability of the maximum S-K value during the evaluation period (LIDI and SIDI) being smaller or equal to 5.5 mmol/L between the SZC arm and the placebo arm. The alternative hypothesis is that the probability of the maximum S-K value during the evaluation period (LIDI and SIDI) being smaller or equal to 5.5 mmol/L is different in the SZC arm from the placebo arm.

$H_0$: $OR_{SZC\ vs\ Placebo} = 1$
$H_1$: $OR_{SZC\ vs\ Placebo} \neq 1$

Secondary endpoint 2: Maximum S-K between 3.5 and 5.5 mmol/L

The null hypothesis is that there is no difference in probability of the maximum S-K value during the evaluation period (LIDI visits) being greater or equal to 3.5 and smaller or equal to 5.5 mmol/L between the SZC arm and the placebo arm. The alternative hypothesis isthat the probability of the maximum S-K value during the evaluation period (LIDI visits) being greater or equal to 3.5 and smaller or equal to 5.5 mmol/L is different in the SZC arm from the placebo arm.

$H_0$: $OR_{SZC\ vs\ Placebo} = 1$
$H_1$: $OR_{SZC\ vs\ Placebo} \neq 1$

Secondary endpoint 3: Number of normokalaemia instances

The null hypothesis is that there is no difference in expected number pre-dialysis post-LIDI S-K concentration between 4.0 and 5.0 mmol/L during the evaluation period between the SZC arm and the placebo arm. The alternative hypothesis is that the expected number pre-dialysis post-LIDI S-K concentration between 4.0 and 5.0 mmol/L during the evaluation period is different in the SZC arm from the placebo arm.

$H_0$: $OR_{SZC\ vs\ Placebo} = 1$
$H_1$: $OR_{SZC\ vs\ Placebo} \neq 1$

Secondary endpoint 4: Potassium gradient

The null hypothesis is that there is no difference in probability of a potassium gradient of < 3.0 mmol/L after a LIDI during the evaluation period between the SZC arm and the placebo arm. The alternative hypothesis is that the in probability of a potassium gradient of < 3.0 mmol/L after a LIDI during the evaluation period is different in the SZC arm from the placebo arm.

$H_0$: $OR_{SZC\ vs\ Placebo} = 1$
$H_1$: $OR_{SZC\ vs\ Placebo} \neq 1$

### 3.3.3 Visit Window

Visits are defined for all presentations of safety data that summarize values by visit according to the following conventions:

- The visits are assigned in such a way that there is a one-to-one mapping between visits contained in the raw data to visits in the analysis data, as outlined in Table 2.

**Table 2: One-to-one mapping between raw visits and visits in analysis data**

| VISITNUM | AVISITN / AVISIT |
|---|---|
| 1 | 1 / Visit 1 (Day -7) |
| 101 | 1.5 / Visit 1.5 (Day -7) |
| 2 | 2 / Visit 2 (Day -5) |
| 201 | 2.5 / Visit 2.5 (Day -5) |
| 3 | 3 / Visit 3 (Day -3) |
| 301 | 3.5 / Visit 3.5 (Day -3) |
| 4 | 4 / Visit 4 (day 1) |
| 5 | 5 / Visit 5 (Day 3) |
| … | … |
| X | X / Visit X (Day Y) |
| … | … |
| X.0X | X.0X / Unscheduled X.0X |
| … | … |
| 22 | Visit 22 EOT (Day 57) |
| 2201 | Visit 2201 Unscheduled EOT |
| 23 | Visit 23 EOS (Day 71) |
| 99 | 99 / PSDV 99 |

EOS End of Study; EOT End of Treatment; PSDV Premature Study Discontinuation Visit.

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment are used (regardless of whether the value is recorded at a scheduled or unscheduled visit).

- Listings display all values contributing to a time point for a subject.

For visit-based summaries:

- Only scheduled visits are included, excluding unscheduled visits and the premature study discontinuation visit (PSDV), in tables which summarize data by visit.

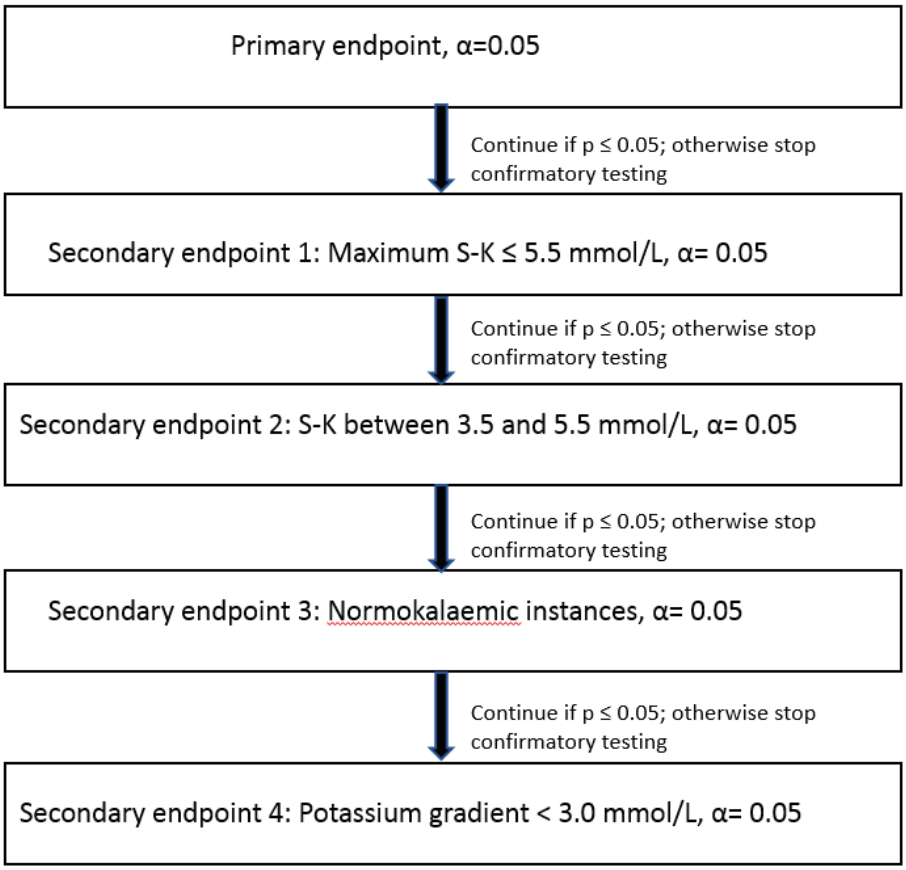
### 3.3.4 Handling of Unscheduled Visits

Unscheduled visits are not included in summary tables which are summarize by visit, however will be considered when finding extreme values. Unscheduled visits will be presented in listings.

### 3.3.5 Multiplicity/Multiple Comparisons

In case of rejection of the null hypothesis corresponding to the primary endpoint, the four secondary efficacy hypotheses will be considered. A multiplicity testing procedure that controls the family-wise Type I error rate will be applied, and statistical significance will be claimed in case of rejection at the family-wise significance level of 0.05. The multiplicity testing procedure will be a fixed sequence procedure, with the hypotheses ordered as in Figure 1.

**Figure 1: Multiple testing procedure**




### 3.3.6 Handling of Protocol Deviations in Study Analysis

For this study, the following general categories are considered important protocol deviations (IPDs) and are either programmatically derived from the electronic case report form (eCRF) data or from review of case notes. These are listed and summarised by randomized treatment group and discussed in the clinical study report (CSR) as appropriate:

- Inclusion criteria deviations.
- Exclusion criteria deviations.
- Discontinuation Criteria for study product met but subject not withdrawn from study treatment.
- Discontinuation Criteria for overall study withdrawal met but subject not withdrawn from study.
- Received the wrong treatment or incorrect dose.

- Received prohibited concomitant medications. Refer to CSP Section 6.5 for those medications that are detailed as being 'excluded' from permitted use during the study.
- Deviations related to study procedures.
- Written informed consent not obtained prior to mandatory study specific procedures, sampling and analyses.
- Site procedure for unblinding the subject is not compliant with CSP.

Important protocol deviations relating to subject-level and subject-visit level events are reviewed by appropriate medical, data management, and statistical members of the study team and are documented prior to database lock.

A full list of subject inclusion and exclusion criteria is provided in the study protocol. A table comprising all important protocol deviations is provided in the Non-Compliance Handling Plan.

# 4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain.

All data collected on the CRFs and contributing to the analysis are provided in listings, except for data collected only for confirmation of study entry criteria and for study management purposes. Data for all participants who are randomized are included in the participant data listings. Data for non-randomized participants are listed where available.

All safety and efficacy parameters are summarized by treatment unless specified otherwise.

## 4.1 Study Population

The domain study population covers subject disposition, analysis sets, IPDs, demographics, baseline characteristics, medical history, prior and concomitant medication, study drug compliance, dialysis history and dialysate K.

### 4.1.1 Subject Disposition and Completion Status

#### 4.1.1.1 Definitions and Derivations

Subject disposition and completion status are comprised of the following:

- Enrolled subjects
- Randomized subjects

- Randomized subjects after re-screening
- Non-randomized subjects
- Subjects who received treatment
- Subjects who do not receive treatment
- Randomized subjects who completed treatment
- Randomized subjects who discontinued treatment
- Randomized subjects who completed the study
- Randomized subjects who withdrew from the study

#### 4.1.1.2 Presentation

A disposition table for all participants will be provided. Subject disposition and completion status as defined by the categories in section 4.1.1.1 are summarized for all enrolled subjects by treatment group.

### 4.1.2 Analysis Sets

#### 4.1.2.1 Definitions and Derivations

Refer to section 3.2 for definition of analysis sets.

#### 4.1.2.2 Presentation

The number of subjects randomized, included in the FAS, SAS and who were randomized but did not receive treatment are summarized by randomized treatment arm (SZC or placebo).

### 4.1.3 Protocol Deviations

#### 4.1.3.1 Definitions and Derivations

Refer to section 3.3.6 for details regarding the definitions and derivations of protocol deviations.

The study Non-compliance Handling Plan (NCHP) outlines the management of Protocol Deviations (PDs) and includes the proposed specific categories of PDs in this trial. Any PDs which are not defined as important will not be reported and discussed in the CSR.

#### 4.1.3.2 Presentation

The number and percentage of participants for each IPD are presented by randomized treatment for FAS population. IPDs are summarized overall and separately by COVID-19 related or not. Subjects with IPDs are also listed.

### 4.1.4 Demographics

#### 4.1.4.1 Definitions and Derivations

Demographics are comprised of: age, age group [<50, ≥50 - <65, ≥65 - <85 and ≥85 years], sex, race and ethnicity.

#### 4.1.4.2 Presentation

Demographics are summarized for all subjects in the FAS by randomized treatment group.

### 4.1.5 Baseline Characteristics

#### 4.1.5.1 Definitions and Derivations

Subject characteristics at baseline are comprised of:
height (cm)
dry-weight (kg)
BMI ($kg/m^2$)
pre-dialysis weight (kg)
IDWG (kg)
SBP/DBP (mmHg)
heart rate ( bpm)
Pre-dialysis S-K (mmol/L)
Pre-dialysis iSTAT K (mmol/L)
Dialysate K (mmol/L)
dialysis prescription (blood flow (ml/min), dialysis flow (ml/hr), ultrafiltration (ml))
dialysis adequacy (spKt/V, URR)

Dry-weight is used in the calculation of BMI.

#### 4.1.5.2 Presentation

Subject characteristics at baseline are summarized for all subjects in the FAS by randomized treatment group.

### 4.1.6 Disease Characteristics

#### 4.1.6.1 Definitions and Derivations

Not Applicable.

#### 4.1.6.2 Presentation

Not Applicable.

### 4.1.7 Medical and Surgical History

#### 4.1.7.1 Definitions and Derivations

Medical and surgical history are collected at Visit 1 and during the study period and is classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA).

#### 4.1.7.2 Presentation

Medical history and surgical history are grouped by MedDRA system organ class and preferred term and are summarized for all subjects in the FAS by randomized treatment group.

### 4.1.8 Pre-treatment, Concomitant and Post-treatment Medications

#### 4.1.8.1 Definitions and Derivations

All medications/treatments are classified according to the latest version of the WHO Drug Dictionary.

Pre-treatment medication is any medication which stopped being taken prior to the first dose of study treatment.
Concomitant medications during study treatment are those with a stop date on or after the first dose date of study treatment or ongoing, with a start date on or before the treatment completion date (and could have started prior to or during treatment).

Post-treatment medication is any medication that was used at any time after the day of treatment completion or treatment discontinuation.

#### 4.1.8.2 Presentation

Pre-treatment, concomitant during study treatment and post-treatment medication data are summarized for the full analysis set. Allowed and disallowed concomitant medications are presented by treatment arm, ATC classification and generic term for the FAS. Subjects with the same concomitant medication multiple times are counted once per medication. A medication that can be classified into more than once chemical and/or therapeutic subgroup are presented in each subgroup.

### 4.1.9 Study Drug Compliance

#### 4.1.9.1 Definitions and Derivations

**Compliance rate**

Compliance rate for each subject is obtained by summing up the number of sachets taken by each subject and dividing it by the number of sachets planned to be administered to the

subject, where the number to be administered is calculated over the subject's actual duration in the trial and not the planned duration. A subject's actual duration takes into account potential dose reductions/interruptions and early treatment stopping.

Subjects are considered compliant if percent compliance is ≥80% and ≤120% for the treatment period.

#### 4.1.9.2 Presentation

Compliance of study treatment (SZC or placebo) is summarized for the overall treatment period, dose adjustment period and evaluation period by treatment group using the FAS. The number and percentage of subjects considered compliant (≥80% and ≤120%) is also reported.

### 4.1.10 Dialysis History

#### 4.1.10.1 Definitions and Derivations

Dialysis history is comprised of time since first dialysis (years) ((randomization date – date of first dialysis +1)/365.25) and dialysis access type.

#### 4.1.10.2 Presentation

Descriptive statistics are calculated for dialysis history and are summarized for all subjects in the FAS by randomized treatment group.

### 4.1.11 Dialysate K

#### 4.1.11.1 Definitions and Derivations

See section 8.1.2 of CSP for details of dialysate K concentration prescription.

#### 4.1.11.2 Presentation

The number and percentage of subjects with "increase from baseline", "no change", "decrease from baseline" is summarized by treatment and visit, including all visits post-randomization.

## 4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses. For each endpoint below, unless otherwise specified, missing data due to dropout or missed visits is not imputed.

Unless otherwise stated all analyses excludes records which are not considered to be "true LIDI". The cut-off identifying true LIDI interval is at least 55 hours between the previous dialysis starting time and the dialysis starting time on the visit after LIDI interval.

Rescue therapy is the only intercurrent event taken into account. The others will follow

treatment policy.

**Table 3: Endpoint Summary**

| Statistical category | Endpoint | Population | Intercurrent event strategy | Population level summary (analysis) | Details in section |
|---|---|---|---|---|---|
| **Primary Objective:** To evaluate the efficacy of SZC as compared to placebo in keeping the S-K concentration between 4.0 and 5.0 mmol/L in subjects on haemodialysis | | | | | |
| Primary | Classification of each randomized subject as either a "responder" or a "non-responder" | FAS | Composite strategy: Intercurrent event (use of rescue therapy) is included as part of a composite endpoint | Fisher's exact test is used to produce odds ratio between SZC and placebo group with the corresponding 95% CI.<br><br>Additionally, risk difference and exact unconditional confidence limits are calculated.<br><br>The measurements from non-true LIDI visits will be excluded from analysis. | 4.2.1 |
| Primary (sensitivity 1) | Classification of each randomized subject as either a "responder" or a "non-responder" | FAS | Composite strategy: Intercurrent event (use of rescue therapy) is included as part of a composite endpoint | Same as primary analysis of primary endpoint, without excluding records which are not true LIDI. | 4.2.1.4 |
| Primary (sensitivity 2) | Classification of each randomized subject as either a "responder" or a "non-responder" | FAS | Composite strategy: Intercurrent event (use of rescue therapy) is included as part of a composite endpoint | Same as primary analysis of primary endpoint, with missing S-K values imputed using multiple imputation before classification as | 4.2.1.4 |

| Statistical category | Endpoint | Population | Intercurrent event strategy | Population level summary (analysis) | Details in section |
|---|---|---|---|---|---|
| | | | | responder or non-responder. | |
| **Secondary Objective 1:** To evaluate the efficacy of SZC as compared to placebo in maintaining the pre-dialysis S-K concentration below or equal to 5.5 mmol/L | | | | | |
| Secondary | Classification of each randomized subject as either a "responder" or a "non-responder" | FAS | Hypothetical strategy: S-K measurements obtained while a subject was receiving rescue therapy are excluded from the analysis | Overall estimate of OR, 95% CI and p-value are obtained after pooling together results of logistic regression from each imputed dataset.<br><br>Additionally, risk difference and 95% CI are obtained from a generalized linear model. | 4.2.2 |
| **Secondary Objective 2:** To evaluate the efficacy of SZC as compared to placebo in maintaining the pre-dialysis LIDI S-K concentration between 3.5 and 5.5 mmol/L | | | | | |
| Secondary | Classification of each randomized subject as either a "responder" or a "non-responder" | FAS | Hypothetical strategy: S-K measurements obtained while a subject was receiving rescue therapy are excluded from the analysis.<br>S-K values. | Overall estimate of OR, 95% CI and p-value are obtained after pooling together results of logistic regression from each imputed dataset.<br><br>Additionally, risk difference and 95% CI are obtained from a generalized linear model. | 4.2.3 |
| **Secondary Objective 3:** To evaluate the efficacy of SZC as compared to placebo with respect to number of pre-dialysis LIDI visits with S-K concentration between 4.0 and 5.0 mmol/L | | | | | |
| Secondary | Instances of pre-dialysis after LIDI S- | FAS | Hypothetical strategy: The S-K measurements | P-value obtained from a test of equality of odds | 4.2.4 |

| Statistical category | Endpoint | Population | Intercurrent event strategy | Population level summary (analysis) | Details in section |
|---|---|---|---|---|---|
| | K between 4.0 and 5.0 mmol/L during the evaluation period | | impacted by rescue therapy are excluded from the analysis. | ratios using a generalized linear mixed model with random intercept and OR between SZC and placebo and 95%CI are presented. | |
| **Secondary Objective 4:** To evaluate the efficacy of SZC as compared to placebo in reducing the potassium gradient to below 3.0 mmol/L | | | | | |
| Secondary | Instances of potassium gradient of < 3.0 mmol/L after LIDI during the evaluation period | FAS | Hypothetical strategy: The S-K measurements impacted by rescue therapy are excluded from the analysis. | P-value obtained from a test of equality of odds ratios using generalized linear mixed model with random intercept and OR between SZC and placebo and 95%CI are presented. | 4.2.5 |
| **Exploratory Objective 1:** [redacted] | | | | | |
| [redacted] | | | | | |
| [redacted] | | | | | |
| [redacted] | | | | | |

| Statistical category | Endpoint | Population | Intercurrent event strategy | Population level summary (analysis) | Details in section |
|---|---|---|---|---|---|
| [redacted] | | | | | |
| **Exploratory Objective 2:** [redacted] | | | | | |
| [redacted] | | | | | |
| **Exploratory Objective 3:** [redacted] | | | | | |
| [redacted] | | | | | |
| **Exploratory Objective 4:** [redacted] | | | | | |
| [redacted] | | | | | |
| **Exploratory Objective 5:** [redacted] | | | | | |
| [redacted] | | | | | |

| Statistical category | Endpoint | Population | Intercurrent event strategy | Population level summary (analysis) | Details in section |
|---|---|---|---|---|---|
| | | | | | |
| **Exploratory Objective 6:** | | | | | |
| | | | | | |
| **Exploratory Objective 7:** | | | | | |
| | | | | | |
| **Exploratory Objective 8:** | | | | | |
| | | | | | |
| **Exploratory Objective 9:** | | | | | |
| | | | | | |

### 4.2.1 Primary Endpoint

The analysis of the primary (and the secondary) endpoints will be conducted according to the intention to treat principle using FAS. Thus, the population under study consists of all subjects that are deemed as suitable for randomization by the investigators.

#### 4.2.1.1 Definition

The primary efficacy endpoint is the proportion of subjects with maintained pre-dialysis S-K between 4.0 – 5.0mmol/L on at least 3 out of 4 dialysis treatments following the long interdialytic interval (LIDI) during the evaluation period (last 4 weeks of the treatment period) and who did not receive rescue therapy during the evaluation period.

Each randomized subject is classified into a responder or a non-responder category (i.e. a 0-1 type of response), with a subject being a responder if they meet both conditions a and b below:

a. Have pre-dialysis S-K between 4.0 and 5.0 mmol/L on at least 3 out of 4 LIDI visits that occur during the evaluation period
b. Do not receive any rescue therapy during the evaluation period

Rescue therapy is defined as any therapeutic intervention considered necessary in accordance to local practice patterns to reduce S-K in the setting of severe hyperkalemia (> 6 mmol/L). This may include an introduction of a rescue treatment, additional dialysis or a reduction of the dialysate K concentration. Refer to section 6.5 of CSP for further details.

The evaluation period will be used to define responders and non-responders. It runs over the last 4 weeks of the treatment period, starting after visit 14 and ending on visit 22, thus it comprises post-LIDI Visits 16, 18, 20 and 22.

One intercurrent event of concern has been identified in this setting, namely the use of rescue therapy. For the primary analysis, rescue therapy use is included as part of a composite endpoint, hence the addition of b) in the primary endpoint definition (this is referred to as a “Composite strategy” in ICH E9 (R1) 2017 p. 17).

The primary analysis excludes records which are not considered to be “true LIDI”. The cut-off identifying true LIDI interval is at least 55 hours between the previous dialysis starting time and the dialysis starting time on the visit after LIDI interval.

#### 4.2.1.2 Primary Analysis of Primary Endpoint

The primary endpoint is analyzed using Fisher's exact test applied to the contingency table of counts of responders and non-responders in a particular treatment group with the rejection / non-rejection of the null hypothesis based on the resulting p-value. In addition to the Fisher’s exact test, the odds ratio (OR) between SZC and placebo group, with the

corresponding 95% Confidence Interval (CI), are presented. The CI is obtained using the approach for calculation of the exact confidence limits for odds ratio implemented in SAS PROC FREQ. For illustrative purposes, proportions of responders in the respective treatment groups are presented.

In addition, a table is provided detailing the number of subjects defined as responders and non-responders for the primary endpoint including a breakdown of the reason(s) subjects were assigned to the non-responder category.

Finally, a table is presented detailing the risk difference between SZC and Placebo as well at the exact unconditional 95% CI for the risk difference.

#### 4.2.1.3 Handling of Dropouts and Missing Data

Missing data due to dropout or missed visits is handled via its effect on the classification of a subject into a responder or a non-responder, whereby if a subject has 2 or more missing S-K values during the evaluation period then they are classified as a non-responder, as per the definition outlined above in section 4.2.1.1.

The impact of missing S-K data on classification of responder versus non-responder is assessed in sensitivity analysis 2 as outlined below in section 4.2.1.4.

#### 4.2.1.4 Sensitivity Analyses of the Primary Endpoint

The impact of being classed as a non-responder due to missing S-K data on the primary endpoint is assessed through two sensitivity analyses outlined below.

**Sensitivity Analyses 1: Including non-true LIDI records**

The first sensitivity analysis entails the primary analysis described in section 4.2.1.2 (i.e. Fisher's exact test, p-value, odds ratio and the corresponding 95% CI.) being repeated without excluding records which are not true LIDI.

**Sensitivity Analyses 2: Multiple imputation**

The second sensitivity analysis consists of repeating the primary analyses described in section 4.2.1.2 (i.e. Fisher's exact test, p-value, odds ratio and the corresponding 95% CI) using a data set where the missing S-K values have been imputed using multiple imputation.

Multiple imputation is implemented using Markov Chain Monte Carlo (MCMC) to generate the imputed values.

Fisher's exact test is applied to the contingency table of counts of responders and non-responders in a particular treatment group for each imputed dataset. In addition to the Fisher's exact test, the odds ratio (OR) between SZC and placebo group, with the

corresponding 95% Confidence Interval (CI), are obtained for each imputed dataset. The MIANALYZE procedure combines the results of the analyses of imputations by reading ORs and associated confidence intervals and generates valid statistical inferences. A final estimate OR (95%CI) and p value are presented which are computed by the MIANALYZE procedure.

The above can be broken down into a three-step process (imputation phase, followed by analysis phase, followed by pooling phase), where the imputation phase can be further broken down into S-K imputation and classification after imputation.

1) **Imputation phase**:
    a. ***S-K imputation***: pre-dialysis S-K data is imputed using PROC MI in SAS separately for LIDI evaluation visits, where missing data is assumed to be missing at random (MAR). It is also assumed that the pattern of missingness is arbitrary (non-monotone), thus making appropriate a two-step imputation where the first step entails using the MCMC to partially impute the data filling in only those missing values that create a non-monotone pattern, whilst the second step entails imputing the remaining data using monotone regression [O'Kelly and Ratitch, 2014]. The MCMC process is initiated using the Expectation Maximization (EM) algorithm, where M=100 imputed datasets are generated, sampling from multiple (100) MCMC chains. For each chain there are 500 iterations between imputations and 1000 burn-in iterations, where the seed used to start pseudo-random number generation is 22438. The imputation model includes treatment and baseline pre-dialysis S-K as predictors.
    b. ***Classification***: once data is complete after multiple imputation, each subject is then classified as a success (1) or failure (2) as defined above, for each of the M=100 imputed datasets. Thus, in effect, resulting in M=100 analysis-ready datasets containing a response variable which assigns a 1 or 0 for each subject.
2) **Analysis phase**: each of the M=100 imputed datasets are analyzed using Fisher's exact test. The odds ratio (OR) between SZC and placebo group, with the corresponding 95% Confidence Interval (CI), are obtained for each imputed contingency table.
3) **Pooling phase**: an overall set of pooled results is generated using PROC MIANALYZE in SAS which combines the analysis results from step 2 above. Since the estimates of the odds ratio follow a log-normal distribution, a log-transformation can be applied to normalize these estimates in order that Rubin's combination rules can be applied [Ratitch et al. 2013]. Finally, the overall set of pooled results present overall OR, associated 95% CI, and p-value from the hypothesis test of the pooled log-OR being equal to 0.

### 4.2.2 Secondary Endpoint 1: Maximum S-K less than or equal to 5.5 mmol/L (Yes/No)

#### 4.2.2.1 Definition

For this endpoint, each randomized subject is classified into a success or a failure category (i.e. a 0-1 type), with success being if a subject's maximum pre-dialysis S-K value during the evaluation period is below or equal to 5.5 mmol/L.

#### 4.2.2.2 Primary Analysis of Secondary Endpoint 1

Before imputation, any pre-dialysis S-K measurements impacted by rescue therapy are excluded i.e. the next pre-dialysis S-K from the next dialysis after rescue therapy or the pre-dialysis S-K measurements during period of the rescue therapy is set to missing. This reflects a hypothetical scenario where rescue therapy is not available to subjects (i.e. a "hypothetical strategy" type of approach, see ICH E9 (R1) 2017 p. 18).

In addition, any records which are not considered to be "true LIDI" are set to missing and S-K values for these records also imputed. The cut-off identifying true LIDI interval is at least 55 hours between the previous dialysis starting time and the dialysis starting time on the visit after LIDI interval.

In order to mitigate the possible impact of missing potassium values during the evaluation period, multiple imputation is implemented using Markov Chain Monte Carlo (MCMC) to generate the imputed values. This imputation process is implemented separately for LIDI and SIDI potassium measurements, before the imputed LIDI and SIDI data are then recombined in order that a subject can be classified as a success or failure based on the complete data and analysis undertaken on this binary outcome using logistic regression.

A generalized linear model is used. Details are provided in the Analysis Phase section below. The MIANALYZE procedure combines the results of the analyses of imputations by reading log ORs and associated standard errors and generates valid statistical inferences. A final estimate OR (95%CI) and p value are presented which are computed by the MIANALYZE procedure.

The above can be broken down into a three-step process (imputation phase, followed by analysis phase, followed by pooling phase), where the imputation phase can be further broken down into S-K imputation and classification after imputation. The proportion of patients whose maximum S-K less than or equal to 5.5 mmol/L in each treatment group will be presented by visit and overall.

1) **Imputation phase**:

a. ***S-K imputation***: pre-dialysis S-K data is imputed using PROC MI in SAS separately for LIDI visits and SIDI visits, where missing data is assumed to be missing at random (MAR). It is also assumed that the pattern of missingness is arbitrary (non-monotone), thus making appropriate a two-step imputation where the first step entails using the MCMC to partially impute the data filling in only those missing values that create a non-monotone pattern, whilst the second step entails imputing the remaining data using monotone regression [O'Kelly and Ratitch, 2014]. The MCMC process is initiated using the Expectation Maximization (EM) algorithm, where M=100 imputed datasets are generated, sampling from multiple (100) MCMC chains. For each chain there are 500 iterations between imputations and 1000 burn-in iterations, where the seed used to start pseudo-random number generation is 22438. The imputation model includes treatment and baseline pre-dialysis S-K as predictors.
b. ***Classification***: once data is complete after multiple imputation, each subject is then classified as a success (1) or failure (2) as defined above, for each of the M=100 imputed datasets. Thus, in effect, resulting in M=100 analysis-ready datasets containing a response variable which assigns a 1 or 0 for each subject alongside the covariates necessary for analysis.

2) **Analysis phase**:
- each of the M=100 imputed datasets are analyzed using PROC GENMOD. A generalized linear model is used to model the binary response variable, using treatment and baseline as covariates with logit link. The statistics of interest from the results of this analysis are the odds ratio (OR) (with OR>1 favoring SZC over Placebo) and its associated 95% CI. Additionally, a generalised linear model with identity link function is used to obtain the risk difference (with risk difference > 0 favoring SZC over Placebo) and probability in each treatment group.
If the results show that the model fit may not be valid (for example if the probability estimate is outside [0,1]), then alternative methods of obtaining probability estimates, such as fitting a model without baseline as a covariate will be investigated.

3) **Pooling phase**: an overall set of pooled results is generated using PROC MIANALYZE in SAS which combines the analysis results from step 2 above. Since the estimates of the odds ratio follow a log-normal distribution, a log-transformation can be applied to normalize these estimates in order that Rubin's combination rules can be applied [Ratitch et al. 2013]. Finally, the overall set of pooled results present overall probability in each treatment group, risk difference and its 95% CI, overall OR, associated 95% CI, and p-value from the hypothesis test of the pooled log-OR being equal to 0.

### 4.2.3 Secondary Endpoint 2: Maximum S-K between 3.5 and 5.5 mmol/L (Yes/No)

#### 4.2.3.1 Definition

For this endpoint, each randomized subject is classified into a success or a failure category (i.e. a 0-1 type), with success being if a subject's maximum pre-dialysis S-K value at the planned LIDI visits only during the evaluation period is below or equal to 5.5 mmol/L and their minimum pre-dialysis S-K value during the evaluation period is greater than or equal to 3.5 mmol/L. Therefore, subjects where not all of their S-K values lie between 3.5 and 5.5 mmol/L are classified as a failure.

As with secondary endpoint 1, the pre-dialysis S-K measurements impacted by subject receiving rescue therapy are excluded from the analysis – i.e. overwritten as missing – reflecting a hypothetical scenario where rescue therapy is not available to subjects (i.e. a "hypothetical strategy" type of approach, see ICH E9 (R1) 2017 p. 18). In addition, any records which are not considered to be "true LIDI" are set to missing and S-K values for these records also imputed.

#### 4.2.3.2 Primary Analysis of Secondary Endpoint 2

The analysis of this endpoint is conducted in the same manner as that of secondary endpoint 1 above - see section 4.2.2.2.

### 4.2.4 Secondary Endpoint 3: Number of normokalaemic (4.0 - 5.0 mmol/L) instances

#### 4.2.4.1 Definition

The number of normokalaemic instances is defined as instances of pre-dialysis after LIDI S-K between 4.0 and 5.0 mmol/L during the evaluation period.

The endpoint in this analysis is the 0-1 indicator of whether S-K is between 4.0 and 5.0 mmol/L for each LIDI visit in the evaluation period. The intercurrent event of rescue therapy is, again, incorporated through omission of observations that coincide with rescue therapy use from the analysis. Non-"true LIDI" values are also excluded from the analysis.

#### 4.2.4.2 Primary Analysis of Secondary Endpoint 3

This endpoint is analyzed through application of a generalized linear mixed model which includes a random intercept and logit link. Treatment, baseline, visit and visit by treatment interaction are specified as fixed effects. Visit is specified as a repeated measures factor within a subject with an underlying assumption of an unstructured covariance matrix. SAS PROC GLIMMIX is used.

P-value of a test of no difference, estimates of the expected number of normokalaemic instances in the respective treatment groups, the difference between the two groups and the

corresponding CI are presented. This CI is calculated using bootstrap using 10,000 resamples with replacement. The presented p-value is obtained from the test of equality of odds ratios using the generalized linear mixed model. The p-value for treatment-by-visit interaction will be presented.

Note that the rejection of this null hypothesis implies the rejection of the null hypothesis of no difference between the expected number of visits with S-K between 4.0 and 5.0 mmol/L, as equivalence of odds ratios (OR) implies equivalence of probabilities (of S-K between 4.0 and 5.0 mmol/L in the respective treatment groups at a particular visit) which, in turn, implies equivalence of expected number of normokalaemic visits. Similar logic applies to the test of the secondary endpoint described in section 4.2.5 below.

The number (%) of subjects with at least 1, at least 2, at least 3 and at least 4 normokalaemic (4.0-5.0 mmol/L) occasions during the evaluation period are summarized by treatment group.

The number (%) of subjects with at least 1, at least 2, at least 3 and at least 4 normokalaemic (3.5-5.5. mmol/L) occasions during the evaluation period are summarized by treatment group.

### 4.2.5 Secondary Endpoint 4: Potassium gradient

#### 4.2.5.1 Definition

Instances of potassium gradient of < 3.0 mmol/L after LIDI during the evaluation period will be compared between treatment arms.
The K gradient is defined as the difference between the S-K level and dialysate K concentration and is derived as follows;

K gradient = (pre-dialysis S-K measurement) – (dialysate K concentration)

The endpoint in this analysis is the 0-1 indicator of whether potassium gradient, defined as the difference between pre-dialysis S-K and dialysate K concentration, is below 3.0 mmol/L for each “true” LIDI visit in the evaluation period. That is, similarly to the secondary endpoint 3, multiple measurements for each subject are considered. Again, the intercurrent event of rescue therapy is incorporated through omission of observations that coincide with rescue therapy use from the analysis, resulting in the hypothetical scenario of no rescue therapy being available.

#### 4.2.5.2 Primary Analysis of Secondary Endpoint 4

For this objective, the probability that the potassium gradient for a particular LIDI visit is below 3.0 mmol/L is of interest. This probability is estimated for each treatment group

through application of generalized linear mixed model with random intercept and logit link. Treatment, baseline, visit and visit by treatment interaction are specified as the fixed effects. Visit is specified as a repeated measures factor within a subject with an underlying assumption of an unstructured covariance matrix.

The p-value from a test of no difference between treatment groups, CI and the corresponding OR, estimates of probability of observing a gradient below 3.0 mmol/L in each treatment group and the difference between the two groups, are presented. The presented p-value is obtained from the test of equality of odds ratios using the aforementioned generalized linear mixed model. SAS PROC GLIMMIX is used to obtain the above estimates, CI and p-value.

### 4.2.6 Exploratory Endpoint 1: [redacted]

[redacted]

produced for the treatment difference.

[redacted]

[redacted]

### 4.2.7 Exploratory Endpoint 2: [redacted]

[redacted]

[redacted]

### 4.2.8 Exploratory Endpoint 3: [redacted]

[redacted]

[redacted]

[redacted]

### 4.2.9 Exploratory Endpoint 4: [redacted]

[redacted]

### 4.2.10 Exploratory Endpoint 5: [redacted]

[redacted]

### 4.2.11 Exploratory Endpoint 6: [redacted]

[redacted]

### 4.2.12 Exploratory Endpoint 7: [redacted]

[redacted].

[redacted]

### 4.2.13 Exploratory Endpoint 8: [redacted]

[redacted]

### 4.2.14 Exploratory Endpoint 9: [redacted]

[redacted]

[redacted]

## 4.3 Pharmacodynamic Endpoint (Not Applicable)

## 4.4 Pharmacokinetics (Not Applicable)

## 4.5 Immunogenicity (Not Applicable)

## 4.6 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, ECG and other safety assessments including IDWG.

Safety and tolerability data are presented by treatment arm using the SAS. Safety summaries will be descriptive only. No formal statistical analyses are performed on the safety variables. Tables and listings are provided.

### 4.6.1 Exposure

#### 4.6.1.1 Definitions and Derivations

**Exposure**

Duration of exposure is defined as the number of days between the first and the last dose of SZC or placebo + 1 day.

**Actual exposure**

Actual exposure for each subject is obtained by summing up the days for which at least one dose of the study drug (SZC or placebo) was taken.

#### 4.6.1.2 Presentation

Planned and actual duration of exposure are summarized for the SAS overall and by treatment group, as well as by treatment sub-periods (dose adjustment period and evaluation period).

### 4.6.2 Adverse Events

#### 4.6.2.1 Definitions and Derivations

An AE is the development of any untoward medical occurrence in a subject or clinical study subject 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 (e.g., 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.

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 screening period, even if no study treatment has been administered.

AEs are collected from randomization throughout the treatment period and the follow-up period, up to end of study or premature study discontinuation visit.

SAEs are recorded from the time of signing of informed consent form until end of study or premature study discontinuation visit.

The medical dictionary for regulatory activities (MedDRA) [using the latest or current MedDRA version] is used to code AEs apart from hypokalemia. The identified risk of hypokalaemia is defined by laboratory values and not by specific MedDRA terms.

#### 4.6.2.2 Presentation

The number and percentage of subjects experiencing an AE sorted on international order of System Organ Class (SOC) and descending order of Preferred Term (PT) by SZC arm, are tabulated by treatment group (SZC and placebo) for:

- All AEs
- Most common AEs
- AEs with outcome of death
- All SAEs
- AEs leading to discontinuation of study treatment
- AEs possibly related to study drug
- AEs leading to interruption of study treatment

An overall summary of the number and percentage of subjects in each category is presented as well as the number of total AEs and SAEs recorded by SOC and PT. For the truncated AE table of most common AEs, all events that occur in at least 2 subjects in one of the treatment arms are summarized by preferred term, by decreasing frequency sorted by SZC treatment arm.

Subjects with AEs are tabulated by treatment and causality (related or not related as assessed by the Investigator) and by intensity (mild, moderate, or severe; missing determinations will be assumed to be severe). In the latter tabulation a subject's most severe event within each PT is counted.

Key subject information is provided in 3 separate listings for all SAEs, AEs with an outcome of death and all AEs leading to treatment discontinuation. The following duration variables are presented in the listings, where applicable;

- Time from start of treatment to onset of AE (days)
- Time from last dose to death (days)
- Time from first dose to death (days)
- Time from previous dose prior to AE start date (days) - Calculated for AEs starting after the discontinuation of the study treatment.
- Time from start of treatment to AE becoming serious (days)
- Time from start of treatment to discontinuation of investigational product (due to adverse event) (days)

The derivations for these parameters are the difference between the two dates stated above + 1 day.

Only AEs with onset occurring during the treatment or follow-up periods are included in the AE summaries noted above. Additional listings presenting all AEs by study period and treatment group (including AEs with an onset before study treatment) are also provided.

SAEs however are recorded from the time of informed consent. SAEs fulfil one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-subject hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.

- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

An overview of oedema-related AEs (includes fluid overload, fluid retention, generalised oedema, hypervolemia, Localised oedema, Oedema, Oedema peripheral, Peripheral swelling) and instances of pre-dialysis S-K < 3.5 is presented. Additionally, a listing is provided for any subjects who experience an AE of hypokalemia.

The number of subjects who had dialysate K adjustment due to AE and percentage is summarized.

AEs for subjects who were enrolled but not randomized and for subjects who were not exposed to treatment are also listed.

### 4.6.3 Clinical Laboratory, Blood Sample

#### 4.6.3.1 Definitions and Derivations

Laboratory data is collected throughout the study as described in Tables 1 and 2 of the CSP. Blood and serum samples for determination of clinical chemistry and hematology are collected as described in Section 8.2.1 of the CSP.

For the derivation of baseline and post baseline visit values, the rules described in Section 3.3.1 of this document considering definition of baseline, visit windows and how to handle multiple records are used.

Absolute values are compared to the project reference range and classified as low (below range), normal (within range or limits of range) and high (above range).

Project reference ranges are used throughout for reporting purposes. If the project range is unavailable for a test, local ranges are used.

**Table 4: Laboratory Safety Variables**

| Haematology/Haemostasis (whole blood) | Clinical Chemistry (serum) |
|---|---|
| B-Erythrocyte count (RBC) | S-Creatinine |
| B-Haemoglobin (Hb) | S-Bilirubin, total |
| B-Leukocyte count | S-Alkaline phosphatise (ALP) |
| B-Leukocyte differential count (absolute count and %) | S-Aspartate transaminase (AST) |
| B-Platelet count | S-Alanine transaminase (ALT) |
| | S-Gamma-glutamyl transferase (GGT) |
| | S-Albumin |

S-Potassium

S-Calcium, total

S-Sodium

S-Chloride

S-Creatine kinase (CK)

S-Bicarbonate

S-Phosphorus

S-Glucose

S-Blood urea nitrogen

S-Magnesium

S-Lactate dehydrogenase

S-Total protein

S Pregnancy test (serum hCG)

#### 4.6.3.2 Presentations

Summary statistics for hematology and clinical chemistry laboratory variables are calculated for absolute values and change from baseline to each subsequent planned visit where applicable. Pre-dialysis S-K and Bicarbonate are presented separately from the other hematology and clinical chemistry laboratory variables.

Separate shift tables are provided for select tests as described below:

- shift from baseline to the minimum value during treatment
- shift from baseline to the maximum value during treatment
- shift from baseline to each post visit with the value (low, normal, high) during treatment (also provided separately for Pre-dialysis S-K and Bicarbonate)

Treatment emergent laboratory changes are also reported for subjects with post-baseline value higher or lower than standard reference limit for the subset of laboratory assessments expected to be within the standard normal ranges at baseline for the population under study. A treatment emergent change is defined as a change that occurs during the treatment period or follow-up period. The number and percentage of subjects with treatment emergent laboratory changes is summarized. Additionally, a separate listing is provided for individuals with abnormal serum laboratory values.

All the above tables are displayed separately for the following laboratory values and units:

- Haemoglobin (g/dL)
- Calcium (mg/dL)
- Magnesium (mg/dL)

Summary table for pre-dialysis bicarbonate by visit and change from baseline at each visit during evaluation period is presented.

See Table 4: Laboratory Safety Variables in section 4.6.3.1 for list of laboratory parameters for this study.

### 4.6.4 Clinical Laboratory, Urinalysis (Not Applicable)

### 4.6.5 Other Laboratory Evaluations (Not Applicable)

### 4.6.6 Vital Signs

#### 4.6.6.1 Definitions and Derivations

The following vital signs are measured as described in Section 8.2.3 of the CSP: systolic and diastolic blood pressure (BP) and heart rate. Body weight (dry-weight, pre-dialysis weight and post-dialysis weight) is also recorded at each visit along with vital signs and height is recorded at visit 1 only.

Heart rate and blood pressure is measured in triplicate, with the average over the triplicate used for vital signs tabulations. All abnormal values are displayed in listings. Measurements are taken prior to the initiation of each hemodialysis procedure.

#### 4.6.6.2 Presentations

Summary statistics for vital signs are calculated for absolute values and change from baseline to each subsequent planned visit where applicable. An additional table is produced to summarize clinically significant results.

All vital signs readings are listed for the safety analysis set by treatment group. Abnormal readings will be flagged as either Low or High.

### 4.6.7 Electrocardiogram

#### 4.6.7.1 Definitions and Derivations

Resting 12-lead ECGs are conducted at screening (day -7), at study days 8, 29 and again during follow-up at EOS and described in Section 8.2.4 of the CSP. ECGs can be classified as normal, borderline, abnormal – not clinically significant and abnormal – clinically significant.

The following ECG variables are collected: ECG heart rate, P wave and QRS duration, PR, RR, QT, QTc(b) and QTc(f) intervals, and overall ECG evaluation.

#### 4.6.7.2 Presentations

ECGs are presented in a shift table showing baseline (screening) classification against follow-up (EOS) classification. All ECG variables collected on the CRF (ECG Mean Heart Rate; P Wave Duration; PR Interval, Aggregate; QRS Duration, Aggregate; QT Interval, Aggregate; QTcF Interval, Aggregate; RR Interval, Aggregate) are descriptively summarized by treatment and visit to include change from baseline to each subsequent visit.

The number (%) of participants fulfilling the criteria below for QTcF will also be included:

Absolute QTcF interval at any time during treatment:

- QTcF interval > 450 milliseconds
- QTcF interval > 480 milliseconds
- QTcF interval > 500 milliseconds

Change from baseline in QTcF interval at any time during treatment:

- QTcF interval increases from baseline > 30 milliseconds
- QTcF interval increases from baseline > 60 milliseconds
- QTcF interval increases from baseline > 90 milliseconds

Absolute QTcF interval and change from baseline in QTcF interval at any time during treatment:

- QTcF interval > 450 milliseconds and QTcF interval increases from baseline > 30 milliseconds
- QTcF interval > 500 milliseconds and QTcF interval increases from baseline > 60 milliseconds

A listing for subjects with overall ECG evaluation reported as abnormal or borderline is provided.

## 4.6.8 Other Safety Assessments: Dialysis prescription

### 4.6.8.1 Definitions and Derivations

Dialysis prescription parameters including blood flow (Qb, ml/min), time on dialysis (minutes), prescribed ultrafiltration rate (ml) and dialysate flow (Qd, ml/hr) are recorded at the times specified in Table 1 and Table 2 of CSP.

### 4.6.8.2 Presentations

The Dialysis prescription parameters listed above are summarized over time by visit (including visit 4, visit 14, visit 22 and PSDV) and treatment arm.

## 4.6.9 Other Safety Assessments: Dialysis adequacy

### 4.6.9.1 Definitions and Derivations

Dialysis adequacy indices including spKt/V and/or urea reduction ratio (URR) are recorded at the times specified in Table 1 and Table 2 of CSP. Investigators should record the most recent values, but these should be no older than 5 weeks. If no values within 5 weeks are available, a new assessment of spKt/V or URR should be performed on the next weekly visit. Sites should consistently use either spKt/V or URR in determining dialysis adequacy. A combination of both is not acceptable.

“Adequacy” constitutes either of the following conditions being satisfied: SpKT/V>=1.2 or URR>=63. Otherwise, "non-adequacy" constitutes neither condition being satisfied.

### 4.6.9.2 Presentations

The number of subjects and percentage for adequacy status is analyzed by visit and treatment arm. Meanwhile, descriptive statistics for continuous variables spKt/V or URR are summarized by visit and treatment arm.

## 4.6.10 Other Safety Assessments: Interdialytic weight gain

### 4.6.10.1 Definitions and Derivations

Interdialytic weight gain (IDWG) is 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 is performed as part of the analysis at each study visit. For example, IDWG at visit 4 is calculated as;

Visit 4 IDWG = (Visit 4 pre-dialysis weight) – (Visit 3 post-dialysis weight)

If current pre-dialysis weight or previous post-dialysis weight is missing IDWG cannot be calculated. Note: Post-dialysis weight from the previous visit is denoted as “Post-Dialysis (LAST)” on the CRF.

#### 4.6.10.2 Presentations

Absolute values and change from baseline for IDWG are summarised and presented by visit and treatment group using the SAS.

# 5 INTERIM ANALYSIS

No interim analyses are planned for this study.

## 5.1 Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee (IDMC) is utilized for this study.

The IDMC is the external advisory group for the study which, on a regular basis, reviews accumulating study efficacy and safety data, to determine whether the overall integrity and conduct of the study remain acceptable and makes recommendations to the Sponsor. The IDMC functions independently of all other individuals associated with the conduct of the studies, including AstraZeneca. The committee operates in accordance with an Independent Data Monitoring Committee Charter.

The details of the IDMC analysis would be specified in a separate interim SAP and in the DMC Charter.

# 6 REFERENCES

**ICH E9 (R1) 2017**
ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials.
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# 7 APPENDIX (NOT APPLICABLE)

# SIGNATURE PAGE

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