Statistical Analysis Plan	
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A phase 3b, multicenter, prospective, randomized, double blind, placebo-controlled study to reduce incidence of pre-dialysis hyperkalemia with Sodium Zirconium Cyclosilicate (DIALIZE)

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Phastar Study Statistician [redacted] [redacted]

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Global Product Statistician [redacted] Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
BMI	Body Mass Index
c-lab	Central laboratory
CRF	Case Report Form
EOS	End of Study
EOT	End of Treatment
ESRD	End Stage Renal Disease
FAS	Full Analysis Set
IDWG	Interdialytic weight gain
LIDI	Long Inter-Dialytic Interval
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
PT	Preferred Term
Qb	Blood flow (dialysis)
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SIDI	Short Inter-Dialytic Interval
S-K	Serum potassium
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).
TFL	Tables, Figures and Listings
URR	Urea Reduction Ratio
WHO	World Health Organization
SZC	Sodium Zirconium Cyclosilicate

AMENDMENT HISTORY

Date	Brief description of change
30May2018	N/A
14Dec2018	In summary, the following aspects of the SAP have been amended: - The definition of study periods has been clarified (Sections 1.2.2 and 1.2.3) - The definition of baseline has been clarified (Section 3.1) - The imputation algorithms for the S-K measurements have been clarified (Section 3.2) - The definition of rescue therapy has been clarified (Section 3.5) - The handling of the vital signs measured in triplicate is clarified (Section 3.6.2) - Actual exposure is added (Section 3.8.4) - Definition of compliance is clarified (Section 3.8.5) - Concomitant medications definition is clarified (Section 4.1) - Updated to SZC throughout document. - Expanded Section 7, Changes of analysis from protocol.

1 STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

To evaluate the efficacy of Sodium Zirconium Cyclosilicate (SZC) in the treatment of hyperkalemia in patients on hemodialysis.

1.1.2 Secondary objectives

To evaluate the need for rescue therapy.
To evaluate the safety of SZC in hemodialysis.

1.1.3 Exploratory objectives

To evaluate if the treatment of hyperkalemia with SZC in hemodialysis patients allows for an increase in the dialysate K concentration prescription.

1.2 Study design

This is a randomized, double-blind, placebo-controlled study to determine the safety and efficacy of Sodium Zirconium Cyclosilicate (SZC) in the treatment of hyperkalemia in patients with End Stage Renal Disease (ESRD) on stable hemodialysis.

Approximately 180 patients with ESRD and persistent pre-dialysis hyperkalemia requiring maintenance hemodialysis treatments 3 times per week will be enrolled in the study across research sites in US, Europe and Japan. Patients must have hemodialysis access consisting of an arteriovenous fistula, AV graft, or tunneled (permanent) catheter which is expected to remain in place for the entire duration of the study.

The study consists of a one-week screening period, an 8 week randomized treatment period, and a two week follow-up period.

1.2.1 Screening period

The screening period will run for one week, beginning on a hemodialysis day following the Long Inter-Dialytic Interval (D -7) until the treatment period starts on study day 1 (D1). Informed consent will be obtained on study day -7 and patients will then be assessed to ensure they meet the eligibility criteria during the screening period.

1.2.2 Treatment period

Patients who meet the eligibility criteria will be enrolled and randomized on study day 1 to receive either SZC or placebo (1:1). SZC or placebo will be administered orally on non-dialysis days for a treatment period of eight weeks.

The treatment period will be divided into two sub-periods, the dose-adjustment period and the evaluation period. During the dose-adjustment period, the initial SZC dose of 5g once daily on non-dialysis days will be titrated during a period of 4 weeks to achieve and maintain a pre-dialysis serum potassium between 4 - 5mmol/L after the Long Inter-dialytic Interval (LIDI). Note that, although the duration of this period is 4 weeks, only 3 dose adjustments are allowed to be made. For details on the titration algorithm, see CSP Section 7.2. This period will start on day 1, the randomization visit, and end on the visit 11 day (planned day 29). During the evaluation period, starting day after visit 11 (planned day 30), the treatment will continue unchanged. The evaluation period will end on the same day as the overall treatment period with a corresponding End of Treatment (EOT) visit. That is, EOT visit is included in the treatment period.

1.2.3 Follow-up period

The post-treatment follow-up period will start on the day following the EOT visit and will last for 2 weeks (14 days +/-3 days) to match the dialysis schedule. The last visit will be scheduled after the LIDI and will be denoted the End of Study (EOS) visit.

1.3 Number of subjects

180 patients at approximately 70 sites across the US, Europe and Japan will be enrolled, yielding 90 patients per treatment group (SZC and placebo).

1.3.1 Sample size justification

For the primary efficacy endpoint, 90 patients per treatment group (180 patients in total) will yield power at least 90%, assuming a placebo proportion of at most 0.3, a difference in proportions (SZC – placebo) of 0.25, using a 2-sided Fisher's exact test at significance level 5%.

2 ANALYSIS SETS

2.1 Definition of analysis sets

Two analysis sets are defined for this study, full analysis set (FAS) and safety analysis set (SAS).

2.1.1 Full analysis set (FAS)

The full analysis set (FAS) includes all randomized patients, regardless of whether they received any trial medication or not. FAS will be the primary analysis set for the efficacy analysis. Patients will be analyzed according to their randomized treatment group.

2.1.2 Safety analysis set (SAS)

The safety analysis set (SAS) will comprise all randomized patients who received at least one dose (SZC or placebo) on study. Safety summaries will be based on the safety analysis set. Patients will be analyzed according to the treatment actually received. Patients who receive more than one treatment will be analyzed according to their randomized treatment.

2.1.3 Disposition of Patients

Patient accounting will be provided for the following:
1. Enrolled patients
2. Randomized patients
3. Non-randomized patients
4. Patients who received treatment
5. Patients who did not receive treatment
6. Randomized patients who completed treatment
7. Randomized patients who discontinued treatment.
8. Randomized patients who completed the study
9. Randomized patients who withdrew from the study.

At screen failure a patient can be re-screened if deemed appropriate by the investigator. A maximum of one re-screening period is allowed (for a total of two screenings). Patients will remain associated with the same enrolment number throughout the entire study, E-codes are not reused, and patients do not receive a new E-code if re-screened.

2.2 Deviations

Important protocol deviations relating to patient-level and patient-visit level events will be reviewed by appropriate medical, clinical, data management, and statistical personnel and will be documented prior to database lock.

A full list of patient inclusion and exclusion criteria is provided in the study protocol. A table comprising all important protocol deviations is provided in the Dialize Protocol Deviation Instructions document.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Baseline

3.1.1 Efficacy baseline

For all efficacy and the presentation of summary statistics, where relevant, the baseline will be defined as measurements obtained at visit 1, which takes place on study day -7.

3.1.2 Safety baseline

For change from baseline tabulations (laboratory measurements, vital signs, ECG, weight and Interdialytic weight gain (IDWG)) the baseline will be defined as follows:

- **Safety lab assessments:** the last value before the start of the treatment period (i.e. the last non-missing measurement taken during the screening period)
- **Vital signs and BP:** the last value before the start of the treatment period (i.e. the last non-missing measurement taken during the screening period)

- **ECG:** the last value before the start of the treatment period (i.e. the last non-missing measurement taken during the screening period)
- **Weight**: Pre-dialysis weight obtained during the screening period on study day -7.
- **IDWG:** The latest IDWG that takes place during the screening period, which occurs immediately prior to Visit 4 (i.e. visit 4 pre-dialysis – visit 3 post-dialysis weight). See Sections 3.7 and 3.8.6 for further details on this parameter.

3.2 Missing data

S-K levels

The S-K levels used for the primary analysis will be based on the c-lab measurements obtained during the evaluation period. For the purpose of the primary analysis, if missing, the S-K values will not be imputed.

For the sensitivity analysis and listings (but not the primary analysis nor the summary tables), if a pre-dialysis c-lab measurement is missing, it will be imputed using the corresponding pre-dialysis i-STAT measurement using the following rule:

1) Calculate the average difference between the LIDI pre-dialysis i-STAT and LIDI pre-dialysis c-lab S-K measurement for the visit when the imputation takes place. All the patients with both LIDI i-STAT and LIDI c-lab measurements available at the relevant time point and visit will be used
2) Impute the missing LIDI c-lab value to be the corresponding LIDI i-STAT value for the patient in question minus the average difference obtained in step 1.

This imputation will take place only if at least 50% of the patients in the population have both i-STAT and c-lab measurements available at the time-point.

For the sensitivity analysis of the primary endpoint, an additional “last value carried forward” imputation method will be utilized as a second step to further impute missing values of pre-dialysis S-K during the evaluation period. This technique will replace missing c-lab S-K values with the last available non-missing pre-dialysis LIDI observation recorded for that patient (and this could be a c-lab value or an imputed c-lab value)

The last value carried forward imputation will be performed after the i-STAT imputation has been performed as described above. As the SIDI and the LIDI measurements are not comparable and neither are the pre- and post-dialysis measurements, only the pre-dialysis LIDI measurements will be used in this imputation.

The earliest values that can be carried forward will be the value obtained at the randomization visit. Thus, a patient that has no c-lab values during the treatment period, and for which i-STAT imputation could not be performed, will be excluded from this analysis.

Dialysate K

For the purpose of the exploratory analysis, missing values for dialysate K concentrations will be imputed using the "last value carried forward" approach as described above. Patients with a missing visit 4 dialysate K concentration will be excluded from this analysis. Note that this imputation will not be done for the K-gradient tabulations or any dialysate K related listings.

Other measurements

No other imputation of missing data will be conducted.

3.3 Primary variable

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

Patients who have at least 3 pre-dialysis S-K measurements within 4.0-5.0mmol/L and who did not receive rescue therapy during the evaluation period will be defined as responders. All other patients will be defined as non-responders, i.e. if a patient has more than one missing S-K measurement and/or if they received rescue therapy they will be classified as a non-responder.

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 11 and ending on visit 15, thus it comprises post-LIDI Visits 12, 13, 14 and 15.

All randomized patients will be classified as either a responder or a non-responder regardless of premature discontinuation of IP, premature discontinuation of study or receiving treatments other than rescue therapy.

Additionally, a sensitivity analysis for the primary efficacy endpoint will be carried out to account for patients being classified as non-responders due to missing S-K data, additional details are provided in Section 4.2.1.2.

3.4 Secondary variable

The secondary outcome measure is the frequency and proportion of patients requiring any urgent intervention (i.e. rescue therapy) consistent with local practice patterns to reduce S-K.

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 or a reduction of the dialysate K

concentration. In practice, instances of rescue will be identified as AEs of hyperkalemia requiring rescue as judged by the investigator.

Treatments considered rescue include the potassium binders: sodium polystyrene sulfonate (SPS, Kayexalate, Resonium), calcium polystyrene sulfonate (CPS, Resonium calcium) and patiromer (Veltassa), as well as beta-adrenergic agonists, sodium bicarbonate, insulin/glucose and any additional dialysis or other forms of renal replacement treatments when used specifically for the treatment of severe hyperkalemia. In addition, any reduction in the dialysate K concentration that is prescribed for the treatment of severe hyperkalemia during the study is also considered rescue therapy.

3.5 Exploratory variables

The exploratory efficacy outcome measure is the proportion of patients who are able to increase dialysate K concentration at the end of treatment (visit 15) compared to baseline.

3.6 Safety variables

Safety variables will include adverse events (AEs), serious AEs (SAEs), vital signs, ECGs, laboratory parameters and physical examinations.

3.6.1 Adverse events

Adverse Events will be collected from time of randomization throughout the treatment period and the follow-up period (until visit 16 or the last patient visit in the study). Adverse events based on both signs and symptoms as reported by the patient or care provider, revealed by observation, or through examinations, laboratory tests or vital signs will be recorded.

Serious Adverse Events (SAEs) will be 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-patient 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 patient or may require medical intervention to prevent one of the outcomes listed above.

Note: Any AEs that are unresolved at the patient's last visit in the study will be followed up by the Investigator for as long as medically indicated, but not recorded on the CRF.

3.6.2 Vital Signs

Vital signs include systolic and diastolic blood pressure, heart rate, height (only recorded at visit 1) and weight. Vital signs will be assessed at predetermined visits during the study. Heart

rate and blood pressure will be measured in triplicate, with the average over the triplicate used for vital signs tabulations. All abnormal values will be displayed in listings. Blood pressure will be measured prior to the initiation of each hemodialysis procedure.

3.6.3 Physical examinations

A complete physical examination will be performed on study days -7, 1 and EOS, and targeted physical examinations will be conducted on study days 8, 15, 22 and 50.

Physical examinations include the following assessments; general appearance including skin, height (study day -7 only) and weight, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular including assessment of signs of heart failure, lungs, abdomen, and neurological systems.

No separate analyses for Physical Examinations will be provided since any new or aggravated clinically relevant abnormal medical findings at a physical examination as compared with the baseline assessment will be reported as an AE.

3.6.4 Electrocardiogram

A 12-lead ECG will be conducted during screening (day -7), at study days 8, 29 and again during follow-up at EOS. ECGs can be classified as normal, borderline, abnormal-not clinically significant and abnormal-clinically significant.

Visit number, ECG date, heart rate (HR), P Wave and QRS durations and PR and QT intervals (if available), overall interpretation and relevant comments will be recorded.

3.6.5 Laboratory parameters

Blood samples will be taken for the determination of clinical chemistry and hematology; a full list of the laboratory parameters for this study is provided in Section 9.3.

3.7 Other assessments

Dialysis prescription parameters including blood flow (Qb, ml/min) and duration of dialysis (minutes) will be recorded, as well as dialysis adequacy indices including Single-Pool Kt/V (spKt/V) and/or urea reduction ratio (URR). Note: Sites should continuously use either spKt/V or URR in determining dialysis adequacy, a combination of both is not acceptable. Investigators should record the most recent values, but these should be no more than 5 weeks old.

Interdialytic weight gain (IDWG) will be used to assess fluid volume retention during pre-determined long-term interdialytic intervals. It will be recorded during the screening period (days -7, -5 and -3) and on three occasions during the treatment period (days 1, 29 and 57).

K shift during dialysis sessions (pre-dialysis minus post-dialysis S-K concentrations) will be calculated to evaluate the magnitude of the serum potassium reduction caused by

hemodialysis. In addition, K gradient (pre-dialysis S-K minus dialysate K concentrations) will be calculated. The potassium shift and gradient will be investigated with respect to differences between treatment groups.

A full schedule of assessments taken during the study is provided in Sections 9.1 and 9.2.

3.8 Derived variables

3.8.1 K shift

To analyze the difference in pre- and post-dialysis S-K levels descriptive statistics for K shift will be presented where K shift is defined as;

K shift = (pre-dialysis S-K measurement) – (post-dialysis S-K measurement)

3.8.2 K gradient

The K gradient, defined as the difference between the S-K level and dialysate K concentration, will be derived as follows;

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

3.8.3 Exposure

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

3.8.4 Actual exposure

Actual exposure for each patient will be obtained by summing up the days for which at least one dose of the drug was taken.

3.8.5 Compliance rate

Compliance rate for each patient will be obtained by summing up the number of sachets taken by each patient and dividing it by the number of sachets planned to be administered to the patient, where the number to be administered is calculated over the patient's actual duration in the trial and not the planned duration. A patient's actual duration takes into account potential dose reductions/interruptions and early treatment stopping.

3.8.6 Interdialytic weight gain

IDWG is calculated as the difference between current pre-dialysis weight minus post-dialysis weight (measured at immediate dialysis session prior to the visit) in kilograms. For example, IDWG at visit 4 would be 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 ANALYSIS METHODS

4.1 General principles

Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category.

Unless otherwise stated, percentages will be calculated out of the population total and for each treatment group.

For continuous data, the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data. In instances when 1st and 3rd quartiles are presented these will be rounded to 1 additional decimal place than the original data. For safety laboratory parameters the number of decimal places has been pre-specified by laboratory test type.

For categorical data, percentages will be rounded to 1 decimal place.

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

SAS® version 9.4 will be used for all analyses.

Demographic and patient characteristics obtained during screening, namely age, gender, race, ethnicity, height, dry weight and BMI will be summarized for the FAS.

Concomitant medication data will be summarized for the full analysis set. Medications will be classified according to the latest version of the WHO Drug Dictionary. Concomitant medications include medications that started prior to, but continued after, the randomization day, or medications started on or after the randomization day.

AEs and Medical/Surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA).

4.2 Analysis methods

4.2.1 Efficacy Analyses

Efficacy analyses will be undertaken on the full analysis set unless otherwise stated.

4.2.1.1 Analyses of the primary objective

The primary efficacy endpoint will be analyzed using a test of independence between the being a responder and treatment assignment (SZC / placebo), namely a 2-sided Fisher's exact test at 5% significance level. Responders are defined as patients who maintained a pre-dialysis S-K between 4.0-5.0mmol/L on 3 out of 4 dialysis treatments and did not receive rescue therapy during the evaluation period – see Section 3.3 for full responder allocation details.

In addition to the Fisher's exact test, the odds ratio between SZC and placebo group, with the corresponding 95% CI, will be presented. The CI will be obtained using the approach for calculation of the exact confidence limits for odds ratio implemented in SAS PROC FREQ[1]. The Fisher's exact p-value will be used for determination of whether the null hypothesis can be rejected.

The frequency and percentage of responders will be presented by treatment group with the p-value of the difference of the two proportions.

All potassium measurements (i-STAT, c-lab and imputed c-lab) will be listed.

4.2.1.2 Sensitivity analysis of the primary objective (if applicable)

The impact of being classed as a non-responder due to missing S-K data on the primary endpoint will be assessed through a sensitivity analysis. This analysis will consist of repeating the analyses described in section 4.2.1.1 (i.e. 2-sided 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 the available i-STAT measurements and last value carried forward method, as described in Section 3.2.

4.2.1.3 Analyses of the secondary objective

The frequency and proportion of patients who required any urgent intervention in the case of hyperkalemia with clinical manifestations to reduce S-K during the study will be reported.

Overall frequency counts and a breakdown of rescue therapies by treatment group and study period will be provided for the FAS.

4.2.1.4 Analysis of the exploratory objective

The potential effect of treatment on the dialysate K concentration will be analyzed and presented using methods as described in Section 4.2.1.1. The comparison will analyze patients who have been able to increase their dialysate K concentration at the end of treatment (visit

15, day 57) as compared to baseline (visit 1, day -7) versus those who have not been able to increase their dialysate K concentration (i.e., no change or decrease in dialysate K concentration). The analysis will be performed using a data set where missing values have been imputed as described in Section 3.2.

There will be no adjustments for multiplicity and hence the p-value from the analysis is descriptive.

4.2.2 Safety Analyses

The safety analysis will be undertaken on the safety analysis set. Safety data will be summarized by treatment and listed unless otherwise stated.

4.2.2.1 Adverse events

Adverse events will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). All adverse events will be summarized by SOC and PT.

The number and percentage of patients experiencing an AE, as well as the number of events recorded, classified by System Organ Class (SOC) and Preferred Term (PT), will be tabulated by treatment group (SZC and placebo).

Patients with AEs in the following categories will be similarly tabulated: serious, with an outcome of death and leading to study treatment discontinuation. Patients with AEs will also be 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 patient's most severe event within each PT will be counted.

The following duration variables will be 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 last 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 will be the difference between the two dates stated above + 1 day.

Key subject information will be provided for all SAEs, AEs with an outcome of death, all AEs leading to treatment discontinuation.

Only AEs with onset occurring during the treatment or follow-up periods will be 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) will also be provided. Only SAEs are reported during the screening period.

A listing will be provided for any patients who experience an AE of hypokalemia.

4.2.2.2 Vital signs

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

Any vital signs which are reported as abnormal will be listed for the safety analysis set by treatment group.

4.2.2.3 Physical examinations

As stated in Section 3.6.3, no separate analyses for Physical Examinations will be provided since any new or aggravated clinically relevant abnormal medical findings at a physical examination as compared with the baseline assessment will be reported as an AE.

4.2.2.4 Electrocardiogram

ECGs will be presented in a shift table showing baseline (screening) classification against follow-up (EOS) classification.

ECG variables; ECG mean heart rate, P wave duration, PR interval aggregate, QRS duration aggregate and QT interval aggregate will be descriptively summarized by treatment and visit to include change from baseline to each subsequent visit.

A listing over patients with overall ECG evaluation reported as abnormal or borderline abnormal will be provided.

4.2.2.5 Laboratory parameters

Summary statistics for continuous-scaled analytes will be calculated at baseline and follow-up time points as well as change from baseline.

Any laboratory data reported as abnormal according to reference values will be listed for the safety analysis set by treatment group for the subset of laboratory assessments expected to be within the standard normal ranges at baseline for the population under study. Additionally, individuals with abnormal serum laboratory values will also be summarized and listed.

See Section 9.3 for list of laboratory parameters for this study.

4.2.3 Other Analyses

Patients with important protocol deviations will be listed and summarized by treatment using FAS. Tables summarizing patients with allowed and disallowed concomitant medications will also be produced using the FAS.

Patients defined as responders and non-responders with regards to the primary endpoint will be summarized by treatment group using the FAS. This table will include a breakdown of the reason(s) patients were assigned to the non-responders category.

S-K, K shift and K gradient will be summarized by treatment group and visit for the FAS. Figures displaying mean S-K values by visit will also be produced.

During the study the SZC dose will be titrated on an individual patient level, the number of patients receiving each dose will be summarized at visit 4 (initial dose visit) and subsequent dose adjustment visits (7, 9 and 10) by treatment group using the SAS.

Duration of exposure will be summarized for the SAS overall and by treatment group, as well as by treatment sub-period. Compliance will be summarized overall and by treatment group and treatment sub-period using the FAS.

Dialysis adequacy (spKt/V and/or URR) and dialysis prescription will be summarized by visit and treatment for the SAS.

IDWG will be summarized alongside change from baseline and presented by visit and treatment group using the SAS.

Patients with potential Hy's Law will be displayed in a table using the SAS. Figures displaying maximum post baseline total bilirubin against maximum post baseline ALT and AST will also be produced. Further information on Hy's Law is provided in Appendix C of the SZC-Dialize Protocol.

5 SUBGROUP ANALYSIS (FOR JAPAN)

All tables and figures will be output for the Japan subgroup, no listings are required.

6 INTERIM ANALYSIS

No interim analysis is planned.

7 CHANGES OF ANALYSIS FROM PROTOCOL

The exploratory analysis to assess the proportion of patients who are able to increase their dialysate K concentration over the course of the study was defined in the protocol as the end of the study (EOS, visit 16, D71) dialysate K measurement compared to the baseline dialysate K measurement. However, this has been re-defined in the SAP as the dialysate K

measurement at the end of treatment (EOT, visit 15, D57) compared to the baseline dialysate K measurement.

As an alternative to summarizing abnormal vital signs as outlined in the protocol, it was decided summarizing clinically significant vital signs would be more relevant. However, abnormal vital signs will be listed.

No separate summaries or listings were provided for patients with an "abnormal" physical examination, since such occurrences were collected as AEs (Change from CSP section 8.5).

Tabulation of AE by causality and intensity will be done by PT only, as opposed to SOC and PT, as was specified originally (CSP section 8.5.3).

Additional analysis of the primary variable will be included which will also be adopted for the sensitivity and exploratory analysis. These extra analyses include the addition of an odds ratio and the corresponding 95% confidence interval.

8 REFERENCES

This Statistical Analysis Plan (SAP) is based on SZC-Dialize Protocol Version 4, dated 05 February 2018.

[1] SAS/STAT® 9.3 User's Guide. The FREQ Procedure: Odds Ratio and Relative Risks for 2 x 2 Tables, viewed Jan 2019, https://support.sas.com/documentation/cdl/en/statug/63962/HTML/default/viewer.htm#statug_freq_a0000000565.htm

9 APPENDIX

9.1 Screening period - Schedule of assessments

Table 1 Schedule of assessments - screening

Visit	1	2	3
Day	-7	-5	-3
Day of the week	M/T	W/Th	F/S
Informed consent	X		
Inclusion /exclusion criteria	X	X	X
Demographics	X		
Medical/surgical history	X		
Physical examination	X		
Vital signs and BP[a]	X		
Weight[b]	X	X	X
Height	X		
Safety lab assessments	X		
Serum hCG pregnancy test[c]	X		
12-lead ECG	X		
Serum K[d]	X	X	X
Concomitant medication	X	X	X
Dialysate K prescription	X	X	X
Dialysis prescription[e]	X		
Dialysis adequacy[f]	X		
Interdialytic weight gain[g]	X	X	X
AE review	X	X	X

a: BP should be measured prior to the hemodialysis procedure. HR and BP should be measured in triplicate after being comfortably at rest in either supine or seated position quietly for at least 5 min
b: Dry weight and pre-dialysis weight on Visit 1; pre-dialysis weight on all other visits
c: Collect from female patients of childbearing potential only
d: Serum K sampling: pre-dialysis c-Lab during screening
e: Blood flow (Qb, ml/min), time on dialysis (minutes)
f: spKt/V and/or urea reduction ratio (URR); record the most recent value but this should be no older than 5 weeks
g: Interdialytic weight gain: current pre-dialysis weight minus previous post-dialysis weight in Kg

9.2 Treatment and Follow-up - Schedule of assessments

Table 2 Schedule of assessments – treatment and follow-up phase

Visit description	Randomization																		EOT	EOS
Visit	4	5	6	7	7.5	8	9	9.5	10	10.5	11	11.5	12	12.5	13	13.5	14	14.5	15	16
Day	1	3	5	8	10	12	15	17	22	24	29	31	36	38	43	45	50	52	57	71
Day of the week	M/T	W/Th	F/S	M/T	W/Th	F/S	M/T	W/Th	M/T	W/Th	M/T	W/Th	M/T	W/Th	M/T	W/Th	M/T	W/Th	M/T	+/- 3
Physical exam	X			X[i]			X[i]		X[i]								X[i]			X
Vital signs and BP[a]	X			X			X		X		X		X		X		X			X
Weight[b]	X			X			X		X		X		X		X		X			X
Safety lab assessments	X			X			X		X								X		X	X
Serum hCG pregnancy test[c]	X										X						X			
12-lead ECG				X							X									X
Serum K[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion criteria	X																			
Randomization	X																			
Dialysate K prescription	X	X	X	X		X	X		X		X		X		X		X		X	X
Dialysis prescription[e]	X										X								X	
Dialysis adequacy[f]											X								X	
Interdialytic weight gain[g]	X										X								X	
Drug dispensation/Drug accountability	X[j]			X			X		X		X		X		X		X		X[k]	
Dose adjustment review[h]				X			X		X											
Concomitant medication	X	X	X	X		X	X		X		X		X		X		X		X	X
AE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a: BP should be measured prior to the hemodialysis procedure. HR and BP should be measured in triplicate after being comfortably at rest in either supine or seated position quietly for at least 5 min
b: Dry weight and pre-dialysis weight on Visit 1; pre-dialysis weight on all other visits
c: Collect from female patients of childbearing potential only
d: Serum K sampling: pre- and post-dialysis c-Lab is measured after LIDI (M/T) throughout the study; pre-dialysis i-STAT is measured during treatment phase after LIDI (M/T) on V4 and subsequent dose review visits; only pre-dialysis c-Lab is measured after SIDI (W/Th or F/S) throughout the study on visits as indicated in the table
e: Blood flow (Qb, ml/min), time on dialysis (minutes)
f: spKt/V and/or urea reduction ratio (URR); record the most recent value but this should be no older than 5 weeks
g: Interdialytic weight gain: current pre-dialysis weight minus previous post-dialysis weight (measured at immediate dialysis session prior to the study visit) in Kg
h: Dose adjustment review will be done weekly during the first 4 weeks of the treatment period based on the pre-dialysis iStat serum K level measured following the long interdialytic interval
i: Targeted physical examination only
j: Drug accountability will not be assessed on Visit 4, only dispensation will take place
k: No drug dispensation will take place on the End of Treatment Visit, only drug accountability will be assessed

9.3 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
	S/P-Alanine transaminase (ALT)
	S/P-Gamma-glutamyl transferase (GGT)
	S/P-Albumin
	S/P-Potassium
	S/P-Calcium, total
	S/P-Sodium
	S/P-Chloride
	S/P-Creatine kinase (CK)
	S/P-Bicarbonate
	S/P-Phosphorus
	S/P-Glucose
	S/P-Blood urea nitrogen
	S/P-Magnesium
	S/P-Lactate dehydrogenase
	S/P-Total protein
	S/P Pregnancy test (serum hCG)