Clinical Study Report Synopsis	
Drug Substance	Sodium Zirconium Cyclosilicate (SZC)
Study Code	D9485C00001
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A Phase 3b, Multicentre, Prospective, Randomised, Double-Blind, Placebo-Controlled Study to Reduce Incidence of Pre-Dialysis Hyperkalaemia with Sodium Zirconium Cyclosilicate in Chinese Subjects (DIALIZE China)

Study dates: First subject enrolled: 16 November 2020
Last subject last visit: 03 January 2022

Phase of development: Therapeutic confirmatory (3b)

International Co-ordinating Investigator: [redacted]

Sponsor's Responsible Medical Officer: [redacted]

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study Centres

This study was conducted in 37 centres in China.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints/Variable
Primary	
• 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	• Classification of each subject as either a "responder" or a "non-responder", with a responder defined as a subject who, during the evaluation period (last 4 weeks of the treatment period), maintained a pre-dialysis S-K between 4.0 and 5.0 mmol/L (≥ 4.0 mmol/L to ≤ 5.0 mmol/L) on at least 3 out of 4 dialysis treatments following LIDI, and who did not receive rescue therapy.
Secondary	
• To evaluate the efficacy of SZC as compared to placebo in maintaining the pre-dialysis S-K concentration below 5.5 mmol/L	• Pre-dialysis S-K values after SIDI and LIDI during the evaluation period (≤ 5.5 mmol/L)
• To evaluate the efficacy of SZC as compared to placebo in maintaining the pre-dialysis LIDI S-K concentration between 5.5 and 3.5 mmol/L	• Pre-dialysis S-K values after LIDI during the evaluation period (≥3.5 mmol/L to ≤ 5.5 mmol/L)
• 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	• Instances of pre-dialysis after LIDI S-K between 4.0 and 5.0 mmol/L during the evaluation period (≥4.0 mmol/L to ≤ 5.0 mmol/L)
• To evaluate the efficacy of SZC as compared to placebo in reducing the K gradient to below 3.0 mmol/L	• Instances of K gradient of < 3.0 mmol/L after LIDI during the evaluation period
Safety	
• To assess the safety and tolerability of SZC as compared to placebo in subjects on haemodialysis	• Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory, and ECG. Assessments related to AEs include: ◦ Occurrence/frequency

Table S1 Objectives and Endpoints

Objectives	Endpoints/Variable
	◦ Relationship to IP as assessed by investigator ◦ Intensity ◦ Seriousness ◦ Death ◦ AEs leading to discontinuation of IP
• To assess the interdialytic weight gain in subjects on haemodialysis, in subjects on SZC as compared to placebo	• Interdialytic weight gain

Exploratory objectives are not reported in the CSR synopsis, but they are reported in the CSR.

AE, adverse event; CSR, clinical study report; ECG, electrocardiogram; IP, investigational product; LIDI, long inter-dialytic interval; S-K, serum potassium, SIDI, short inter-dialytic interval; SZD, sodium zirconium cyclosilicate.

Study Design

This was a randomised, multicentre, double-blind, placebo-controlled Phase 3b study to evaluate the efficacy and safety of sodium zirconium cyclosilicate (SZC) in the treatment of hyperkalaemia in Chinese subjects with end-stage renal disease (ESRD) on stable haemodialysis. Eligible subjects were randomly assigned to either SZC or placebo (ratio 1:1 [blocked randomisation]) using an interactive voice/web response system (IVRS/IWRS). Individual sachets were enclosed in a carton with a tamper evident seal intended to be broken exclusively by subjects just before taking the investigational product (IP). The study consisted of a 1-week screening period, a 4-week dose adjustment period, a 4-week evaluation period, and a 2-week follow-up period. The dose was titrated to achieve and maintain pre-dialysis serum potassium (S-K) levels between 4.0 and 5.0 mmol/L after the long inter-dialytic interval (LIDI) during the dose-adjustment period. The dose was to remain stable during the evaluation period unless, in the judgment of the principal investigator, there was a compelling medical need to treat an abnormal potassium (K) concentration.

Target Subject Population and Sample Size

The target population consisted of adults (≥ 18 years) with ESRD receiving maintenance haemodialysis (or haemodiafiltration) treatments 3 times per week in China.

A sample size of 67 randomised subjects per treatment group (134 randomised subjects overall) was required to achieve an approximate power of 90% for the primary variable analysis.

Investigational Product and Comparator: Dosage, Mode of Administration and Batch Numbers

SZC 5 g or placebo, powder for oral suspension in a sachet. A single dose contained 1 to 3 sachets that were suspended in 45 mL of water by the subject and administered on non-dialysis days.

Batch numbers: One batch of each IP was used in this study (SZC: [redacted]; placebo: [redacted]).

Duration of Treatment

This study consisted of a 4-week dose-adjustment period and a 4-week evaluation period during which the dose was to remain stable (unless there was a compelling medical need to adjust the dose).

Statistical Methods

The primary endpoint was analysed using a Fisher's exact test. The secondary endpoints concerning S-K profile over time were analysed using the probability estimation with a multiple imputation-based approach combined with a generalized linear model. The secondary objectives concerning the number of visits with S-K within normal limits and the K gradient, were addressed through the application of a generalised linear mixed model (logit link) with a corresponding test of equality of odds ratios. All tests were 2-sided and performed using a Type I error rate of 0.05. A multiplicity correcting procedure (fixed sequence) was applied. All efficacy analyses were performed in accordance with intention to treat principle (ie, using the full analysis set).

Study Population

In total, 281 subjects were enrolled by 37 centres across China and 134 subjects were randomised (67 in each treatment group). All randomised subjects were included in the full analysis set. One subject in the SZC group did not receive treatment and was excluded from the safety analysis set. Most subjects completed study treatment: 62 (92.5%) subjects in the SZC group and 64 (95.5%) subjects in the placebo group. Study completion rates were also high: 63 (94.0%) subjects in the SZC group and 64 (95.5%) subjects in the placebo group.

The treatment groups were generally balanced with respect to demographic and subject characteristics, dialysis history, baseline dialysis parameters (adequacy, prescription variables, and duration), medical history, and prior and concomitant mediations. Overall, 49.3% of subjects were male and the mean (standard deviation [SD]) age was 54.7 (11.30) years. Most subjects were ≥ 50 to <65 years old (49.3%) or <50 years (31.3%). The mean dry weight was 59.88 kg and the mean body mass index was 21.95 kg/m^2. All subjects were Chinese and living in China. The overall mean and median values of dialysis history were 6.061 and 5.388 years, respectively.

Important protocol deviations, which occurred in 18.7% of the study population, were balanced between the SZC and placebo groups and are not expected to have affected the analyses.

Summary of Efficacy Results

For the primary endpoint, a "responder" was defined as a subject who, during the evaluation period (last 4 weeks of the treatment period), maintained a pre-dialysis S-K between 4.0 to 5.0 mmol/L (normokalaemia) on at least 3 out of 4 dialysis treatments following LIDI, and who did not receive rescue therapy. There was a significantly higher proportion of responders in the SZC group (37.3%) compared with the placebo group (10.4%); the estimated odds ratio (95% CI) was 5.10 (1.90, 15.12), $p < 0.001$.

Results from the secondary endpoint analyses were consistent with the primary analysis:

- The probability of maintaining pre-dialysis S-K values ≤ 5.5 mmol/L at LIDI and short inter-dialytic interval (SIDI) visits during the evaluation period was statistically significantly higher for subjects in the SZC group (0.54) compared with subjects in the placebo group (0.15); the estimated odds ratio (95% CI) was 6.41 (2.64, 15.55), $p < 0.001$.

- The probability of maintaining pre-dialysis S-K values between ≥ 3.5 and ≤ 5.5 mmol/L at LIDI visits during the evaluation period was statistically significantly higher for subjects in the SZC group (0.58) compared with subjects in the placebo group (0.17); the estimated odds ratio (95% CI) was 6.41 (2.71, 15.12), $p < 0.001$.

- The estimated mean number of normokalaemic (pre-dialysis S-K ≥ 4.0 and ≤ 5.0 mmol/L) LIDI visits was 1.91 for subjects in the SZC group and 0.70 for subjects in the placebo group, with a corresponding difference of 1.20 (95% CI 0.77, 1.64). The probability of maintaining normokalaemia at each LIDI visit during the evaluation period was statistically significantly higher for subjects in the SZC group compared with subjects in the placebo group. Averaged over all visits, the probability for success was 0.48 in the SZC group and 0.17 in the placebo group; the estimated odds ratio (95% CI) was 4.41 (2.53, 7.67), $p < 0.001$ (formal test of difference between the groups for this endpoint).

- The probability of maintaining a potassium gradient < 3.0 mmol/L at each LIDI visit during the evaluation period was statistically significantly higher for subjects in the SZC group compared with subjects in the placebo group. Averaged over all visits, the probability for success was 0.52 in the SZC group and 0.16 in the placebo group; the estimated odds ratio was 5.82 (3.15, 10.73), $p < 0.001$ (formal test of difference between the groups for this endpoint).

Summary of Safety Results

The total intended duration of exposure to treatment during the overall treatment period was high (53.3 days) and balanced between treatment groups.

The proportion of subjects with adverse events (AEs) and the types of AEs were generally well balanced between treatment groups. Overall, 63.6% of subjects in the SZC group and 65.7% of subjects in the placebo group had an AE during the study. The proportion of subjects who had serious adverse events (SAEs) was balanced between the treatment groups (6 subjects [9.1%] in the SZC group and 8 subjects [11.9%] in the placebo group) and the SAEs were distributed amongst MedDRA System Organ Classes (SOCs) and preferred terms (PTs). Few subjects discontinued the study due to an AE (2 subjects [3.0%] in each treatment group) or had interruption of IP due to an AE (2 subjects [3.0%] in each treatment group). In the SZC group, 10 subjects [15.2%]) had AEs that were considered possibly related to IP by the Investigator compared with 7 subjects (10.4%) in the placebo group. There was one death during the study in a subject randomised to the placebo group.

The most commonly reported AE, by PT, was hypokalaemia which was reported by 7 subjects (10.6%) in the SZC group and 6 subjects (9.0%) in the placebo group. The hypokalaemia AEs occurred pre-dialysis in one subject in each treatment group and post-dialysis in the remaining 11 subjects. The second most common AE was constipation which was reported by 6 subjects (9.1%) in the SZC group and 2 subjects (3.0%) in the placebo group. All constipation AEs were mild to moderate in intensity and none were reported as serious.

Except for pre-dialysis hypokalaemia, changes in clinical laboratory variables over time were generally balanced across treatment groups with no clinically important differences observed. Seven (10.6%) subjects in the SZC group and 1 subject (1.5%) in the placebo group had pre-dialysis hypokalaemia (S-K < 3.5 mmol/L as measured by the central lab) while on treatment.

Mean changes in weight, systolic/diastolic blood pressure and heart rate were generally balanced across treatment groups and not clinically meaningful.

ECG changes on treatment showed a higher rate of QTcF prolongation (QT interval corrected for heart rate using Fridericia's formula) in the SZC group compared with the placebo group. In the SZC group, 26 subjects (39.4%) had QTcF values above 450 ms (compared with 8 subjects [11.9%] on placebo) and 20 subjects (30.3%) had a QTcF increase of > 30 ms (compared with 1 subject [1.5%] on placebo). The QTcF lengthening during the study was consistent with the potassium lowering effect of SZC and not considered clinically meaningful. There were no AEs of cardiac arrhythmia, torsades de pointes, or sudden cardiac death reported in the SZC group. In the placebo group, 2 subjects had AEs of cardiac arrhythmia during the study (supraventricular tachycardia, arrhythmia).

There were no clinically meaningful differences in any of the dialysis prescription and adequacy variables over time or in the interdialytic weight gain over time between the SZC group and placebo group.

Conclusions

- In subjects in China on chronic haemodialysis, SZC 5 g, 10 g or 15 g administered as a single dose on non-dialysis days (titrated weekly during a 4-week dose-adjustment period) effectively maintained pre-dialysis S-K between 4.0 and 5.0 mmol/L without receiving rescue therapy during the evaluation period, as shown by a statistically significant higher proportion of responders compared with placebo.
- Treatment with SZC raised no new safety concerns.