Clinical Study Report	
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A Phase 3 Multicenter, Prospective, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Safety and Efficacy of ZS (Sodium Zirconium Cyclosilicate), in Patients With Hyperkalaemia HARMONIZE Asia

Study dates: First patient enrolled: 06 May 2021
Last patient last visit: 15 September 2022
The analyses presented in this report are based on a clinical data lock date of 08 November 2022

Phase of development: Therapeutic confirmatory (III)

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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2 SYNOPSIS

Study Centre(s)

This study was conducted in 35 centres in China.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints/Variables
Primary	
• To evaluate the efficacy of two different doses (5 and 10 g) of SZC orally administered qd for 28 days in maintaining normokalaemia [S-K between 3.5-5.0 mmol/L (inclusive)] in normokalaemia patients, following treatment in the OLP, for hyperkalaemic patients (two consecutive i-STAT potassium values ≥ 5.1 mmol/L, taken 60 minutes apart) at baseline.	• Comparison between placebo and each SZC treatment group (high to low) with regard to the mean S-K level during the RTP Days 8-29.
Secondary	
<u>Open-Label Initial Phase:</u> • To evaluate the proportion of patients who achieve normokalaemia after the completion of OLP treatment.	<u>Open-Label Initial Phase Efficacy Endpoints:</u> • Proportion of patients who achieve normal S-K (3.5-5.0 mmol/L) at 24 hours during and at the end of the OLP (classification of each screened patient as either a 'responder' or a 'non-responder') • Exponential rate of change in S-K levels during the OLP 24 hours post-dose • The mean change (absolute and percent changes) from baseline in S-K levels at all post-dose time intervals during the OLP • Time to normalization in S-K levels during the OLP
<u>28-Day Randomized Treatment Phase:</u> • To evaluate the efficacy of SZC in patients with hyperkalaemia for the following subgroups as applicable[a]: - CKD - DM - HF - those on RAASi • To evaluate the effect of SZC on S-Aldo and P-Renin levels.	<u>28-Day Randomized Treatment Phase Efficacy Endpoints:</u> • The proportion of patients who remain normokalaemia during and at the end of RTP • The number of days when patients remained normokalaemia during the RTP • The time to reoccurrence of hyperkalaemia (defined as S-K ≥ 5.1 mmol/L) • The mean change (absolute and percent changes) in S-K level at all post-dose time intervals during the RTP • Mean changes from baseline in S-Aldo and P-Renin levels

Objectives	Endpoints/Variables
Safety	
• To evaluate the effect of SZC on other serum electrolytes in both the OLP and the RTP. • To evaluate the safety and tolerability profiles of SZC in both the OLP and the RTP.	• S-Ca, S-Mg, S-Na, S-PO_4, S-HCO_3, and BUN • AEs, SAEs, vital signs, physical examinations • ECG • Clinical laboratory evaluations, including assessment of hypokalaemia

[a] Primary efficacy endpoint and the secondary efficacy endpoint of the proportion of patients who remain normokalaemia [as defined by S-K between 3.5-5.0 mmol/L (inclusive)] at the end of the 28-day randomized treatment phase were evaluated in patients with hyperkalaemia for the subgroups. More details were described in the SAP.

AE = adverse event; BUN = blood urea nitrogen; CKD = chronic kidney disease; DM = diabetes mellitus; ECG = electrocardiogram; HF = heart failure; OLP = open-label initial phase; RTP = 28-day randomized treatment phase; S-Aldo = serum aldosterone; P-Renin = plasma renin; qd = once daily; RAASi = renin-angiotensin-aldosterone system inhibitor; SAE = serious adverse event; SAP = statistical analysis plan; S-Ca = serum calcium; S-HCO_3 = serum bicarbonate; S-K = serum potassium; S-Mg = serum magnesium; S-Na = serum sodium; S-PO_4 = serum phosphate; SZC = sodium zirconium cyclosilicate.

Study Design

This was a prospective, randomized, double-blind, placebo-controlled phase III study to investigate the safety and efficacy of sodium zirconium cyclosilicate (SZC, formerly abbreviated as ZS) in patients with hyperkalaemia. Patients qualified for the study who achieved normokalaemia [based on serum potassium (S-K) measured by a portable blood analyser (i-STAT)] by the morning of Day 2 or 3 in open-label initial phase (OLP) were eligible to enter the 28-day randomized treatment phase (RTP). Eligible patients were randomly assigned (ratio 2:2:1) to receive SZC 5 g qd (once daily), SZC 10 g qd, or placebo qd in RTP. This study consisted of the optional pre-screening period, the screening period (1 day), the OLP (24 or 48 hours), the RTP and end of study (EOS) visit which was 7 ± 1 days after the last administration of investigational product.

Target Population and Sample Size

The target patient population included male and female patients aged ≥ 18 to ≤ 90 years with hyperkalaemia, defined as two consecutive i-STAT potassium values measured 60-minutes apart, both ≥ 5.1mmol/L within 1 day of the first SZC dose.

The sample size was determined to detect a clinically meaningful difference in the primary endpoint. Assuming an inter-patient standard deviation of 0.50, approximately 250 patients (100 patients per SZC dose group and 50 patients for placebo control group) could provide > 90% power to detect a mean difference of 0.30 in mean S-K between groups during Study Days 8-29 when comparing each SZC dose group (high to low) vs placebo control group using a two-sided t-test at a significance level of 5%. Assuming 90% of patients were normokalaemia after treatment in the OLP, approximately 280 patients were needed to enter the OLP.

The assumptions used in the above sample size estimations were taken from the ZS-004 study (A phase III multicentre, multi-phase, multi-dose, prospective, randomized, double-blind, placebo-controlled maintenance study to investigate the safety and efficacy of ZS, an oral sorbent, in patients with hyperkalaemia).

Investigational Product and Comparator(s): Dosage & Mode of Administration

During the OLP, all patients received an oral powder of SZC at a dose of 10 g tid (three times a day) for a maximum of 6 doses.

During the RTP, patients received SZC 5 g qd, SZC 10 g qd or placebo qd for 28 days. Both SZC and placebo were provided as oral powder. Sachets of SZC 5 g, SZC 10 g, and placebo were provided by AstraZeneca.

Duration of Treatment

This study consisted of the optional pre-screening period, the screening period (1 day), the OLP (24 or 48 hours), the RTP (28 days) and EOS visit which was 7 ± 1 days after the last administration of investigational product.

Statistical Methods

All efficacy analyses were performed separately for the OLP and the RTP based on their respective full analysis sets. Safety data was separately summarized in a descriptive manner based on the safety analysis sets for the OLP and the RTP, respectively.

Efficacy and safety data were listed by patient. Descriptive statistics consisted of the number of non-missing patients (n), mean, standard deviation, median, minimum, and maximum. For categorical variables, they consisted of the number of observations in the respective category, as well as the corresponding percentages.

Results of all statistical analyses were presented with descriptive statistics, 95% confidence interval (CI) or two-sided probability (p) value, unless otherwise stated.

Intercurrent events of interest in the study included use of disallowed medications, change in treatment (including treatment discontinuation), and death.

The primary endpoint of this study was the model-based least squares mean of all S-K values from Days 8 to 29 during RTP. In consideration of lognormal distribution of S-K seen from previous data, the S-K values were logarithmically transformed for variance stabilizing. Subsequently, mixed-effects models were used to estimate least-squares means from Days 8 to 29 by comparing each active drug dose group (high to low dose) with placebo group during the 28-day RTP. For the primary analysis of the primary endpoint, a treatment policy that ignored the effect of intercurrent events was used.

The treatment policy that ignored the effect of intercurrent events was used for all the secondary endpoints in the OLP except for some specific supplementary analysis. Primary Analysis of Secondary Endpoints for OLP:

1 The proportions of patients achieving normokalaemia at 24 hours (OLP Day 2) and end of OLP, provided with observed values and 95% two-sided Clopper-Pearson exact CIs.
2 The exponential rate of change in S-K levels at 24 hours post-dose during OLP was derived from a mixed-effects model of log-transformed S-K levels during OLP.
3 For absolute changes and percent changes from baseline in S-K levels at 24 hours (OLP Day 2) and end of OLP, one sample, two-sided t-test was applied to test the null hypotheses that the means were equal to zero.
4 The time to normalization in S-K levels was summarized using Kaplan-Meier life table curves.

The treatment policy that ignored the effect of intercurrent events was used for all the secondary endpoints in the RTP except for some supplementary analysis. Primary Analysis of Secondary Endpoints for RTP:

1 The likelihood of maintaining normokalaemia at the end of RTP was compared using a logistic regression model.
2 The likelihood of being normokalaemia during the RTP was analyzed using generalized linear mixed model which included a random intercept and logit link.
3 The number of days maintaining normokalaemia was analyzed using linear regression model.
4 The time to re-occurrence of hyperkalaemia (days) was summarized using Kaplan-Meier life table curves.
5 Serum aldosterone (S-Aldo) and plasma renin (P-Renin) levels were analyzed using a mixed-effects model separately.

Study population

This study was conducted in 35 centres in China. The study population was patients with hyperkalemia (two consecutive i-STAT-measured serum potassium values ≥ 5.1 mmol/L, taken 60 minutes apart). All patients were Chinese. A total of 270 patients received SZC treatment during the OLP of the study. 256 patients completed OLP, including 253 patients completed OLP with the i-STAT potassium value within the normal range [3.5-5.0 mmol/L (inclusive)]. Of these, 250 patients were eligible for the randomization and randomized to receive RTP treatment, and 3 patients were not randomized due to other reasons (e.g., ECG did not meet the inclusion/exclusion criteria).

94.8% of patients completed the OLP treatment, and 77.2% of the patients completed the 28-day treatment in RTP. Completion was balanced across treatment groups. The demographics, baseline characteristics and use of concomitant medications were generally balanced across treatment groups.

During OLP, 103 (38.1%) patients were female and 167 (61.9%) patients were male. The median age of patients was 56.4 years (range: 20-85 years), and 33.3% of patients were > 64 years. The mean body weight was 64.7 kg (range: 41-119 kg), the mean BMI was 23.8 kg/m^2(range: 15.8-40.1 kg/m^2), the mean estimated glomerular filtration rate (eGFR) was 17.9 $mL/(min \cdot 1.73m^2)$ [range: 4.0-83.3 $mL/(min \cdot 1.73m^2)$], and the mean serum potassium was 5.85 mmol/L (range: 4.8-7.3 mmol/L). In terms of medical history, 251 patients (93.0%) had chronic kidney disease (CKD), most of whom were at CKD stage 4 or stage 5 ; 111 patients (41.1%) had diabetes mellitus (DM), and 29 patients (10.7%) had heart failure (HF). In addition, 40 (14.8%) patient were using renin-angiotensin-aldosterone system inhibitors (RAASi).

The baseline demographic and patient characteristics, comorbid conditions, as well as the medical, surgical, and prior medication histories, were similar between the OLP and RTP, as most patients were included in both study phases. In terms of medical history, RTP was similar to OLP; 232 patients (92.8%) had CKD, most of whom were at CKD stage 4 or stage 5. During RTP, baseline characteristics of patients were similar across treatment groups.

There were 16.3% and 16.0% of patients experienced important protocol deviations during OLP and RTP, respectively, and no patients were excluded from the analysis due to protocol deviations. Important protocol deviations did not significantly affect the interpretation of study results.

Summary of efficacy results

The results of the primary endpoint showed that both SZC 10 g and SZC 5 g reduced the mean S-K level during Days 8 to 29 of RTP in patients compared with placebo, and the difference was clinically significant and statistically significant, and the mean S-K decreased in a dose-dependent manner. The exponentially transformed values of the log S-K geometric mean were 4.859 mmol/L (95% CI: 4.709, 5.014), 4.440 mmol/L (95% CI: 4.304, 4.580), and 5.225 mmol/L (95% CI: 5.055, 5.400) for SZC 5 g, SZC 10 g, and placebo groups, respectively; the mean difference between the SZC 5 g group and placebo group was 0.930 (back-transformed) (95% CI: 0.902, 0.959; $p < 0.001$), S-K level decreased by 7.0% in the SZC 5 g group compared with the placebo group; the difference between the SZC 10 g group and the placebo group was 0.850 (back-transformed) (95% CI: 0.825, 0.876; $p < 0.001$), and S-K level decreased by 15.0% in the SZC 10 g group compared with the placebo group. Results from sensitivity and supplementary analyses were consistent with the primary analysis, supporting the robustness of the result of primary efficacy analysis.

Results for the secondary endpoints of the study were as follows:

During OLP, S-K level declined after patients were treated with SZC 10 g tid:

- 69.0% and 87.4% of patients achieved normokalaemia at 24 hours after treatment with SZC 10 g tid and at the end of OLP (at 24 or 48 hours after the first dose), respectively.
- The exponential rate of change in the S-K level was -0.0051 (95% CI: -0.0056, -0.0045; $p < 0.001$) at 24 hours of treatment with SZC 10 g tid.
- There was a statistically significant difference for S-K levels from baseline at 24 hours of treatment with SZC 10 g tid and at the end of OLP. The mean change in serum potassium at 24 hours was -0.936 mmol/L (95% CI: -0.982, -0.890; $p < 0.001$) with a percent change of -15.880% (95% CI: -16.609%, -15.152%; $p < 0.001$), and the mean serum potassium level change at the end of OLP was -1.107 mmol/L (95% CI: -1.163, -1.050; $p < 0.001$) with a percent change of -18.588% (95% CI: -19.405%, -17.772%; $p < 0.001$).
- The time to normalization in S-K levels during OLP was presented based on Kaplan-Meier curves in this study.

During the RTP, all confirmatory S-K analyses showed that SZC 5 g and SZC 10 g were more effective than placebo and a dose-dependent manner was observed. The detailed results are as follows:

- The proportions of patients who remained normokalaemia during RTP and at the end of RTP were higher in both SZC 5 g group and SZC 10 g group than in the placebo group. At the end of RTP, the proportion of patients who remained normokalaemia was 58.8% in the SZC 5 g group, 76.5% in the SZC 10 g group, and 36.8% in the placebo group. A statistically significantly higher likelihood of maintaining normokalaemia was observed in SZC 5 g and SZC 10 g groups compared with the placebo group. At the end of RTP, the odds ratio was 2.54 (95% CI: 1.07, 6.05; $p = 0.035$) for SZC 5 g group versus placebo group, and 6.25 (95% CI: 2.56, 15.27; $p < 0.001$) for SZC 10 g group versus placebo group.
- Compared with the placebo group, the mean number of days for maintaining normokalaemia in patients in the SZC 10 g group and the SZC 5 g group was significantly higher (both $p < 0.001$), which were 14.54 days in the SZC 10 g group (95% CI: 11.79, 17.29), 9.11 days in the SZC 5 g group (95% CI: 6.33, 11.90), 3.40 days in the placebo group (95% CI: 0.49, 6.30), respectively.
- Compared with placebo, there was a statistically significant reduction in the risk of recurrent hyperkalemia in the SZC 10 g and SZC 5 g groups with the hazard ratio decreased in a dose-dependent manner. The hazard ratio was 0.39 (95% CI: 0.27, 0.57; $p < 0.001$) for SZC 5 g group versus placebo group and 0.16 (95% CI: 0.10, 0.25; $p < 0.001$) for SZC 10 g group versus placebo group.

Other results for the secondary endpoints during RTP: the curves of S-K level changes over time showed a dose-dependent separation of mean S-K levels across treatment groups after randomization. Compared with the placebo group, the SZC 10 g and the SZC 5 g groups showed a statistically significant decrease in mean S-Aldo from baseline, while the mean change in P-Renin from baseline was not statistically significant.

Summary of safety results

During OLP, all patients (100.0%) received IP dosing for at least 1 day, with a mean exposure duration of 1.3 days, and 14 patients (5.2%) discontinued treatment in OLP. During RTP, all patients (100.0%) received IP dosing for at least 1 day, with an overall mean duration of exposure of 24.7 days. The total duration of exposure to IP was similar across treatment groups with a mean between 24.1 and 25.2 days in each treatment group. Overall, 77 (77.0%), 80 (80.0%), and 36 (72.0%) patients in the SZC 5 g, SZC 10 g, and placebo groups, respectively, had exposures to investigational product of ≥ 28 days.

A total of 39 patients (14.4%) had an adverse event (AE) during the OLP. One patient (0.4%) experienced an SAE and there were no AEs with an outcome of death. Five patients (1.9%) experienced an AE leading to discontinuation of IP. Ten patients (3.7%) experienced an AE considered possibly related to IP by the investigator.

The proportion of patients who reported an AE during the RTP was higher in the SZC treatment groups than the placebo group [50 patients (50.0%) in the SZC 5 g group, 44 patients (44.0%) in the SZC 10 g group, and 18 patients (36.0%) in the placebo group], which was mainly attributable to more edema- and constipation-related AEs reported in the SZC treatment groups.

The most frequent AEs were edema-related AEs [9 patients (9.0%) in SZC 5 g group, 15 patients (15.0%) in SZC 10 g group, 0 in placebo group] and constipation [7 patients (7.0%) in SZC 5 g group, 5 patients (5.0%) in SZC 10 g group, 0 in placebo group]. Most of the edema-related AEs were mild to moderate, with one peripheral edema in the SZC 5 g group assessed as a severe AE. One patient (1.0%) (peripheral edema) in SZC 5 g group and 3 patients (3.0%) (1 edema and 2 peripheral edema) in SZC 10 g group had edema-related AEs leading to discontinuation of IP, respectively. There was 1 edema-related SAE each in SZC 5 g group and SZC 10 g group, both of which were judged as not related to IP by the investigator. All AEs of constipation were mild to moderate and none of them led to discontinuation of IP.

During RTP, more SAEs were reported in the SZC 5 g group, i.e. 6 patients (6.0%) in the SZC 5 g group, 3 patients (3.0%) in the SZC 10 g group, and 1 patient (2.0%) in the placebo group. The proportions of patients who had AEs leading to discontinuation of IP were similar across the treatment groups. No AEs with an outcome of death occurred during RTP, and 1 patient in the SZC 5 g group had an AE (renal anemia worsening) after the last dose in RTP and died after the EOS visit. The number of patients with AEs that were considered possibly related to IP by

the investigator was 11 (11.0%) in the SZC 5 g group, 16 (16.0%) in the SZC 10 g group and 3 (6.0%) in the placebo group, respectively.

During OLP, no clinically meaningful trend of changes from baseline were observed in hematology and urinalysis results. For the results of clinical chemistry, the changes of S-K levels have been described in the efficacy results section, which showed a significant decrease after treatment of SZC 10 g tid, and the mean changes of other clinical chemistry results were minor, with no clinically significant changes observed. There were no significant changes from baseline in vital signs and electrocardiogram (ECG) parameters, except an expected small prolongation of the QTcF interval.

During RTP, no clinically meaningful trend of changes from baseline were observed in hematology and urinalysis results. For the results of clinical chemistry, the changes of S-K level, S-Aldo and P-Renin have been described in the efficacy results section, which showed that SZC can effectively maintain the normal S-K level compared with the placebo group; in addition, compared with the placebo group, the SZC 10 g group and the SZC 5 g group showed a decrease in mean S-Aldo from baseline, and the difference was statistically significant but not considered to be of additional clinical significance; the mean changes of other clinical chemistry results were small, with no clinically significant changes observed and no significant difference observed across treatment groups. In terms of hypokalemia, no patient developed hypokalemia during OLP; more patients in the SZC 10 g group reported hypokalemia during RTP; 7 patients (7.0%) in the SZC 10 g group, 1 patient (2.0%) in the placebo group and no patient in the SZC 5 g group developed hypokalemia. The serum potassium ranged from 3.0 to 3.5 mmol/L across all patients with hypokalemia. There were no significant changes from baseline in vital signs and ECG parameters, except an expected small prolongation of the QTcF interval in SZC treatment groups.

Conclusion(s)

SZC 10 g tid treatment can effectively reduce the serum potassium level in patients within 24-48 hours. Both SZC 5 g and 10 g qd were effective in maintaining normokalaemia, and both SZC treatment groups were statistically superior to placebo group according to the results of the primary analysis and all confirmatory secondary analyses. In this study, a dose-dependent mannerof SZC was observed, and SZC 10 g showed a greater effect.

The safety profile of SZC in this study was generally consistent with its overall profile observed during previous clinical development.