

# BMJ Open Evaluation of safety, effectiveness and treatment patterns of sodium zirconium cyclosilicate in management of hyperkalaemia in China: a real-world study protocol

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## ABSTRACT

**Introduction** Hyperkalaemia (HK) is a potentially life-threatening electrolyte imbalance associated with several adverse clinical outcomes. The efficacy and negative effects of currently existing treatment options have made HK management questionable. Sodium zirconium cyclosilicate (SZC), a novel highly selective potassium binder, is approved for the treatment of HK. The present study will be aimed to assess the safety, effectiveness and treatment patterns of SZC in Chinese patients with HK in a real-world clinical setting as it is required by China's drug review and approval process.

**Methods and analysis** This is a multicentre, prospective cohort study which plans to enrol 1000 patients taking SZC or willing to take SZC from approximately 40 sites in China. Patients  $\geq 18$  years of age at the time of signing the written informed consent and with documented serum potassium levels  $\geq 5.0$  mmol/L within 1 year before study enrolment day will be included. Eligible patients will receive SZC treatment and will be followed up for 6 months from enrolment day. The primary objective will be to evaluate the safety of SZC for the management of HK in Chinese patients in terms of adverse events (AEs), serious AEs as well as discontinuation of SZC. The secondary objectives will include understanding the SZC dosage information in terms of its effectiveness and treatment patterns under real-world clinical practice and assessing effectiveness of SZC during the observational period.

**Ethics and dissemination** This study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University (approval number: YJ-JG-YW-2020). All the participating sites have received the ethics approval. Results will be disseminated through national and international presentations and peer-reviewed publications.

**Trial registration number** NCT05271266.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The present study will be aimed to evaluate the safety, effectiveness and treatment patterns of sodium zirconium cyclosilicate (SZC) in patients with hyperkalaemia (HK) in Chinese population under real-world settings.
- ⇒ It will address the evidence gaps about SZC usage in patients with HK with comorbidities and will further aid in future development of Chinese HK management.
- ⇒ Robust and clinically relevant evidence will be generated for long-term safety and effectiveness by monitoring of patients receiving SZC treatment, including the correction and maintenance phases, dialysis and non-dialysis patients, etc, by virtue of the large sample size anticipated for this study.
- ⇒ This observational study has a limitation that it will not compare the safety and tolerability of patients with HK treated with SZC with non-SZC treatment patients. Moreover, a limited number of patients using a specific treatment option may introduce some extent of bias as it is a single-arm study.

## INTRODUCTION

The distribution of total potassium levels in the human body is controlled by internal homeostasis, whereas external homeostasis regulates renal potassium excretion to balance dietary and supplementary intake, extrarenal loss as well as related deficiencies.<sup>1</sup> Potassium levels within the body are maintained by these two parallel processes. Under normal physiological conditions, most of the potassium is distributed within the

intracellular space (98%), while the rest is distributed within extracellular spaces (2%). The concentration of potassium in the extracellular fluid is a critical determinant of the resting membrane potential of cells and it is important to strictly maintain the extracellular serum potassium (sK) levels (3.5–5.0 mmol/L) for the regulation of physiological functions.<sup>2,3</sup>

The imbalance in the homeostasis of potassium in the extracellular space (>5.0 mmol/L) is referred to as hyperkalaemia (HK).<sup>4</sup> HK can be acute which can be prevented by the cellular uptake of potassium in the liver and muscles along with renal excretion of potassium ions, whereas chronic HK is typically due to a defect in the renal excretion of potassium.<sup>5,6</sup> Different comorbidities like chronic kidney disease (CKD), heart failure (HF), diabetes and use of renin-angiotensin-aldosterone system inhibitors (RAASi) depict high-risk factors involved in the development of chronic HK. Patients with renal dysfunction, CKD, HF, diabetes and arterial hypertension using RAASi for their treatment have a two to three times higher risk of developing HK, thereby leading to serious cardiac dysrhythmias and increased mortality.<sup>7,8</sup> In a Chinese epidemiological study, 3.86% of general outpatients reported incidence of HK, while patients with CKD, HF, diabetes and hypertension had higher rates of HK.<sup>9</sup> Furthermore, the incidence of HK increased by 25% for every 5 mL/min/1.73 m<sup>2</sup> decrease in glomerular filtration rate (eGFR).<sup>10,11</sup>

Insulin,  $\beta_2$  stimulants and sodium bicarbonate are the first treatments currently available that merely encourage potassium's translocation from the extracellular to the intracellular region, thereby offering a transient benefit for 1–4 hours. As per a US report, the frequently used therapeutics for acute management of HK include calcium gluconate, insulin plus glucose/dextrose, albuterol, furosemide and Sodium Polystyrene Sulfonate (SPS).<sup>12</sup> As per Chinese study, insulin plus glucose is the most common treatment suggested for HK management.<sup>13</sup> Dialysis, diuretics and exchange resins are all used to remove potassium from the body. The use of non-specific polymeric exchange resins is the current standard procedure for the acute elimination of potassium (sodium or calcium polystyrene sulfonate). But the efficacy of using these conventional polymer resins in HK management is questionable and is linked to significant gastrointestinal (GI) adverse events (AE) with safety concerns.<sup>14,15</sup> Therefore, there is a need for medications that can effectively manage and safely treat both acute and chronic HK. One such recently developed potassium-binding agent is the non-absorbed, non-polymer material, sodium zirconium cyclosilicate (SZC), which is available as an inorganic powder for oral suspension (in water). It has a consistent micropore structure and preferentially entraps potassium ions in exchange for hydrogen and sodium cations. It helps in lowering sK levels and increase faecal potassium excretion by binding to potassium ions across the GI tract (GIT). SZC has received approval in China in December 2019 for the management of HK in adults.<sup>3</sup> Regardless of

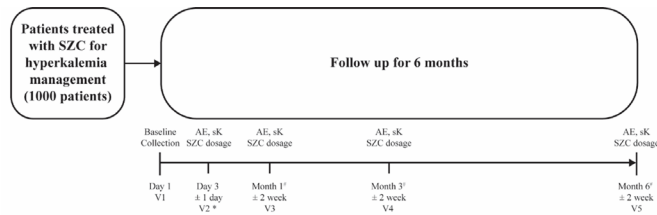
the underlying aetiology of HK, age, sex, race, comorbid disease or concurrent use of RAASi, SZC was found to lower sK levels and maintain normal sK levels in the phase II/III clinical studies with no severe adverse effects.<sup>16–18</sup> As per the National Medical Products Administration regulations, a new drug's effectiveness and safety profile must be closely evaluated within 5 years of the first approval date. Even though the phase II/III clinical studies conducted previously confirm the effectiveness and safety of SZC in treating HK, the enrolled population does not include Chinese patients. Besides, conducting postmarket real-world studies can provide a better perspective regarding the product safety profile in a broader population and closer to the clinical practice. According to Guidelines of Drug Intensive Monitoring of Manufacturers, observational studies are recommended designs for drug intensive monitoring. To date, the real-world safety and effectiveness of SZC in patients with HK in China has not been studied. Hence, this is the first study which has been designed to evaluate safety, effectiveness and treatment patterns of SZC in real-world settings. This study is expected to enhance and supplement currently available SZC safety and tolerability data from the premarket phase II/III clinical studies with expansion to broader Chinese population.

## METHODS

### Study design

In this multicentre, prospective cohort study, 1000 patients taking SZC or willing to take SZC will be enrolled from approximately 40 sites in China. Physicians from the study sites will identify eligible study patients by assessing the patients or reviewing their medical records. Patients are considered to be eligible if they are  $\geq 18$  years of age at the time of signing the written informed consent; have documented sK levels  $\geq 5.0$  mmol/L within 1 year before study enrolment; are currently on SZC, or willing to take SZC with physicians' prescription; and with or without haemodialysis treatment. As the present study requires that the enrolled patients are undergoing SZC treatment and there is a strict indication management system in China due to which SZC cannot be administered to patients without HK, this setting is more in line with the clinical practice of China's real-world studies. Patients who do not comply with the guidelines of the study protocol and those who have previously participated in the present study or any other interventional study at study enrolment day or within the last 3 months will be excluded. The study design has been represented in [figure 1](#). Patients will be divided into two groups: new SZC user group (without SZC treatment within 7 days before study enrolment) and ongoing SZC user group (with SZC treatment within 7 days before study enrolment).

All patients will be followed up for 6 months with visits planned during the 1st, 3rd and 6th months from study enrolment day, additionally the new SZC user group is planned to have a follow-up visit at the third day for



\* For patients in ongoing user group, there will not be a visit on Day 3.  
 # For patients in ongoing user group, the Month 1, Month 3 and Month 6 visits are planned from Day 1.  
 † For patients in new user group, the follow-up visits are planned from Day 3.

**Figure 1** Study design. AE, adverse event; sK, serum potassium; SZC, sodium zirconium cyclosilicate.

potassium retesting. Safety and effectiveness data, sK levels, SZC treatment data (if relevant) and additional associated data (if available) will be recorded during each visit (day 1 to month 6 if data are available). In addition to study-specified visits, investigators may perform monthly or any additional sK tests as needed to intensify sK monitoring according to clinical practice.

### Ethics and dissemination

The study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, the International Conference on Harmonization’s Good Clinical Practice, Guidelines for Good Pharmacoepidemiology Practices and the applicable legislation on non-interventional studies and/or observational studies. This study was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University (approval number: YJ-JG-YW-2020), and all the participating sites have received the ethics approval. Informed consent will be obtained from all the included patients before study initiation. The present study is registered with the clinical trials website: <https://www.clinicaltrials.gov/> (NCT05271266).

### Data collection

All the necessary data will be collected and recorded in electronic case report form. The study will collect

**Table 1** Study plan and time points of key assessments

	Day 1 V1	Day 3±1 day V2*	Month 1±2 weeks V3†	Month 3±2 weeks V4†	Month 6±2 weeks V5†
Screening patients based on inclusion and exclusion criteria	X				
Informed consent‡	X				
Demographics	X				
Medical history	X				
Physical examination	X				
Vital signs	X				
eGFR§	X	X	X	X	X
NYHA class	X				
ECG§	X	X	X	X	X
sK test¶	X	X	X	X	X
Biochemistry values**	X	X	X	X	X
AEs	X	X	X	X	X
SZC dosage information††	X	X	X	X	X
Concomitant treatment‡‡	X	X	X	X	X

\*On-site visit at V2 for new SZC users only.  
 †All visits carried out during this study will be conducted on-site. If an on-site visit is not feasible because of COVID-19, an investigator will call the patient for evaluation of parameters.  
 ‡Informed consent form should be signed by the patients between day 0 and day 7.  
 §Physicians will record eGFR and ECG from the enrolment day according to the availability as per standard clinical practice.  
 ¶sK values will be collected at each visit and the follow-up period, along with the blood potassium test results for dialysis patients and predialysis sK measurements which will be collected as per clinical practice on patient visit.  
 \*\*Other biochemistry values including serum electrolyte values, serum creatinine, serum BUN, serum albumin, serum bicarbonate, serum AST and serum ALT will be collected if available as per clinical practice.  
 ††SZC dosage information includes current daily dose and frequency, dose adjustment, interruption/discontinuation and reason for dose change.  
 ‡‡Concomitant treatment especially on the use of RAASi collected in the CRF as per availability of information in the electronic medical record including drug/treatment name, usage, dosage, administration duration and indication.  
 AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRF, case report form; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; RAASi, renin-angiotensin-aldosterone system inhibitor; sK, serum potassium; SZC, sodium zirconium cyclosilicate.

data from medical records (such as electronic or paper medical records), local laboratory testing records and investigator's evaluation on patients (table 1). Patient demographics (age, gender, ethnicity) will be collected at the enrolment day. Comorbidities, medical history and COVID-19 vaccination history up to 12 months before the enrolment day will be recorded. Information regarding treatment received especially on the use of RAASi including ACE inhibitor, angiotensin receptor blocker, mineralocorticoid receptor antagonist and angiotensin receptor neprilysin inhibitor will be collected during the study from enrolment (day 1 to month 6 if data are available). Serum electrolyte levels, serum creatinine, serum blood urea nitrogen, serum albumin, serum bicarbonate, serum aspartate aminotransferase and serum alanine aminotransferase values will be assessed according to standard clinical practice.

### Treatment regimens

The treating physician will have control over the dosage and duration of SZC treatment. A break of 7 days or more will be considered as discontinuation of SZC treatment. Patients will be followed up and documented even after discontinuation from the study. The recommended starting dose of 10 g of SZC will be given orally as a suspension in water three times/day for up to 48 hours. Once normokalaemia is achieved, the maintenance regimen should be followed. The recommended starting dose in maintenance regimen is 5 g once daily. The recommended dose ranges from 5 g every other day to 10 g once daily during the maintenance regimen while for patients on dialysis, dose could be adjusted at intervals of 1 week in increments of 5 g up to 15 g once daily on non-dialysis days.

### Study objectives and endpoints

The primary objective will be to evaluate the safety of SZC in terms of AEs, serious adverse events (SAEs) as well as discontinuations of SZC as a result of AEs (DAEs) in addition to specific AEs such as oedema and hypokalaemia. All SAEs and non-SAEs will be monitored until they stabilise, disappear or the patient is lost to follow-up.

The secondary objective will be: understanding the SZC dosage information under real-world clinical practice in terms of effectiveness, average daily dose, frequency at which different SZC doses have been administered, duration of SZC treatment, dose adjustment, interruption/discontinuation and reason for dose change; assessing sK levels in patients administered with SZC during the observational period; and occurrence of AEs, SAEs and DAEs, judged by the investigators to be causally related to SZC. Other endpoints include measurement of vital signs (blood pressure, heart rate/pulse), physical examination (height, body weight, general appearance, respiratory, cardiovascular, abdomen, skin, musculoskeletal including spine and extremities, neurological systems), ECG and biochemical evaluations.

### Patient and public involvement

All aspects of this study (development of the research question, study design and conduction of the present study, interpretation of results and editing of the final manuscript for publication) are taking place independent of patient and public involvement. The results will be disseminated to participants by their physicians.

### Statistical analysis

All enrolled eligible patients will be included in the full analysis set (FAS). As this study is primarily descriptive in nature, there will be no formal testing of the hypotheses. The analyses will include estimates (probabilities, rates, averages) with the corresponding 95% CIs, as well as supportive descriptive statistics like mean, SD, median, minimum, maximum and quartiles. The duration of SZC treatment will be estimated using a Kaplan-Meier method. Discontinuation of SZC treatment along with the corresponding CIs will be analysed by landmark analysis for new and ongoing users. All statistical analyses will be performed using SAS V.9.4 or later.

The analyses will be divided into two periods, the first period roughly covering the first 1–3 days of treatment, or the time between the first and second visits following the start of SZC (considered for new users only), and the second period will start after the first treatment period (potentially available for both new and ongoing users). Subgroup analysis will be done based on time periods involving all new users who took at least one dose of SZC during the first period of 1–3 days following SZC initiation (FAS-P1) and on all patients in the ongoing user group who took at least one dose of SZC after enrolment, and new users who took at least one dose of SZC after the completion of the initial period (FAS-P2). Additional analyses will also be performed wherever applicable in patients on haemodialysis (FAS-H) at study enrolment.

### Sample size

The overall sample size planned is 1000 with an estimated 500 patients in the new user group and the remaining patients will be in the ongoing user group. Using the large sample normal approximation method, a sample size of 500 patients in the new user group could provide a 95% CI estimation interval as (7.4%, 12.6%) for the FAS-P1 based on previously published data that indicated 1%–10% of subjects had DAEs, SAEs and overall AEs. A longitudinal mixed model will be used for 95% CI estimation as reported in the previous studies.<sup>17</sup> The corresponding CIs will be determined using normal approximation with a log transformation of the hazard rate as per exponential distribution, with assumption of hazard rate being constant and same fixed/predefined follow-up duration for all patients. The follow-up period is assumed to be between 0.5 and 1.5 months.



### Interim analysis

An interim analysis will be performed on all the enrolled patients who have completed 1 month of follow-up (visit 3). This interim analysis will include safety, effectiveness and treatment patterns of SZC and patients' characteristics at enrolment, while other variables might also be analysed as applicable.

### DISCUSSION

The prevalence of HK, a clinical condition that can be fatal, is significant, especially in patients with comorbid conditions. Up to 10% of hospitalised patients have been documented to have HK.<sup>19</sup> According to a recent epidemiological study, the prevalence of HK climbed to 22.89% in patients with CKD and to 3.86% among Chinese outpatients.<sup>9</sup> RAASi is associated with HK in patients with cardiorenal disorders.<sup>20–22</sup>

Different approaches have been employed traditionally for lowering the potassium levels in patients with acute HK which include agents such as  $\beta$ 2-adrenergic receptor agonist, sodium bicarbonate, glucose and insulin, diuretics, non-specific ion-exchange resins (calcium polystyrene sulfonate, sodium polystyrene sulfonate) as well as emergency dialysis.<sup>23 24</sup> Redistribution of extracellular potassium to the intracellular space with the help of a  $\beta$ 2-adrenergic receptor agonist, sodium bicarbonate or glucose and insulin is temporary and is not highly preferred because of its short duration of action. Use of emergency dialysis and diuretics helps in eliminating potassium ions from the blood. However, emergency dialysis is not widely used due to its invasive nature, high cost as well as logistical challenges. While potassium-binding agents and non-specific ion-exchange resins are suitable to be used in HK management, their efficacy and safety profiles have shown mixed results when used on outpatient population.<sup>14 25–27</sup> Therefore, newer and reliable approaches are still required for HK management with promising effectiveness as well as minimal AEs.

SZC is a potent  $K^+$ -binding agent, and it is highly advantageous due to its selective entrapping of potassium ions in GIT, thereby correcting HK within 48 hours. A significant lowering of sK levels within 1 hour as compared with placebo group was reported after the administration of first dose of 10 g of SZC.<sup>14</sup> Previous studies have shown safety and efficacy on SZC globally.<sup>10 14 16 28</sup> However, there are no previously reported phase II/III clinical studies which have reported safety and efficacy on SZC in Chinese population. Also, there is lack of safety and effectiveness data of SZC in Chinese populations in real-world settings in the management of HK. Therefore, the present study is designed to evaluate the real-world safety, effectiveness and treatment patterns of SZC in management of HK. This study is expected to reflect the efficacy and safety after using SZC on a large number of patients with HK in China through the real-world study, thereby bridging current gaps from the previous phase

II/III clinical studies with expansion to broader Chinese population.

A phase I clinical trial conducted on healthy participants reported a significant decrease in urinary excretion of potassium from baseline and sK concentrations with 10 g of SZC followed by high  $K^+$ /low  $Na^+$  diet compared with placebo while no significant change in urinary excretion of sodium has been reported. The study also reported mild treatment-emergent AEs and none related to SZC.<sup>29</sup> Similar results were reported in a study on Chinese adult healthy participants.<sup>30</sup> A phase II ZS002 clinical study carried out on patients with CKD and HK demonstrated significant reduction in sK levels in patients administered with 3 and 10 g of SZC in a dose-dependent manner as compared with placebo. Even after administration of 10 g of SZC, lower sK levels were observed for additional 3.5 days as compared with the placebo group, thereby underlining its effectiveness in HK management. SZC treatment showed no significant difference in urinary sodium excretion. The changes observed in serum calcium, magnesium and sodium levels as well as other kidney function parameters in both the groups were also not clinically relevant. The safety profile of SZC showed mild to moderate AEs with no SAEs with 10 g of SZC compared with placebo.<sup>16</sup> All these studies indicate that SZC is not linked to a significant release and systemic absorption of  $Na^+$  and specifically targets potassium ions in GIT and is well tolerated with mild AEs and no SAEs.

Both the ZS003 and ZS004 clinical studies reported significant reduction in mean sK levels in patients administered with SZC as compared with the placebo group during the first 48 hours in a dose-dependent manner.<sup>14 28</sup> The ZS003 clinical study reported constipation to be one of the most commonly occurring AEs along with only one SAE from the placebo group.<sup>14</sup> ZS004 clinical study reported higher incidence of generalised and peripheral oedema with mild severity which could be managed without any treatment modifications in patients receiving 15 g of SZC compared with placebo. This may be due to inclusion of participants with eGFRs of 15 to <30 (33%) or <15 mL/min/1.73 m<sup>2</sup> (6%) and HF (15%). However, these AEs could be managed without any treatment modifications.<sup>28</sup> Another phase III ZS005 clinical study compared SZC efficacy and safety in patients with HK with stage 4 and 5 CKD and those having CKD between stages 1–3 with corresponding baseline eGFR levels of <30 or 30 mL/min/1.73 m<sup>2</sup>, respectively, for a duration of 52 weeks. SZC treatment was continued until they reached normokalaemia (3.5–5.0 mmol/L) and was further given maintenance dose to maintain normokalaemia. There was evident reduction in sK levels as well as its successful maintenance in patients with HK with CKD irrespective of stage. Both the groups (stage 4 and 5 CKD; stage 1–3 CKD) showed constipation (4%, 3%), nausea (2%, 2%) and peripheral oedema (2%, 2%) as the most commonly occurring AEs. Higher incidence of overall AEs, SAEs and AEs leading to discontinuation was observed in patients with HK with stage 4/5 CKD as compared with

those with CKD between stages 1–3 which may be due to higher proportion of comorbidities, other medications or degree of renal impairment since inability to excrete salt and water progresses with CKD stage.<sup>10</sup> No difference in interdialytic weight gain between the SZC and placebo groups was reported in a clinical trial involving patients on chronic haemodialysis, the majority of whom got SZC doses of 5–10 g on days when they were not receiving dialysis.<sup>31</sup> A phase III study carried out on Japanese patients with HK evaluated the long-term safety, tolerability and efficacy of SZC after 1 year of administration. SZC treatment was well tolerated with controlled sK levels and a positive safety profile which was consistent with previous studies carried out in Japan and other Asian countries as well as throughout the world.<sup>16 28 32 33</sup> The most common AEs reported in this study were constipation (6.7%), peripheral oedema (4.0%) and hypertension (2.7%). Majority of the AEs were mild or moderate in severity and could be managed without treatment modification which was similar to the previously reported studies.<sup>10 28</sup> The present study will be aimed to evaluate the incidence of AEs and their severity along with analysing the effectiveness and treatment patterns of SZC effective in lowering of sK in patients with HK in Chinese real-world settings.

This study has certain limitations, as it is a real-world study, the effectiveness and safety will not be compared with non-SZC treatment or placebo. Moreover, a limited number of patients in a specific treatment option may introduce some extent of bias as it is a single-arm study. Selection bias can arise since sites that are already listed or have access to SZC may be more likely to participate in this study. In order to reduce selection bias, patients who are qualified and willing to take part in the study will be enrolled sequentially, in accordance with the protocol and without the investigators' personal preference. Additionally, it has been proposed that the study locations encompass various parts of China.

## CONCLUSION

Overall, this study will assess the real-world safety, effectiveness and treatment patterns of SZC in patients with HK in China. This study is expected to enhance and supplement the currently available safety and effectiveness data of SCZ and provide evidence to support the benefits of SZC usage for Chinese patients with HK.

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