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Evaluation of Safety, Effectiveness and Treatment Patterns of Sodium Zirconium Cyclosilicate in Management of Hyperkalemia in China: A Real-World Study Protocol

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Title Page

Title: Evaluation of Safety, Effectiveness and Treatment Patterns of Sodium Zirconium Cyclosilicate in Management of Hyperkalemia in China: A Real-World Study Protocol

Short title: Evaluation of SZC for Hyperkalemia Management in China

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Abstract

Introduction: Hyperkalemia (HK) is a potentially life-threatening electrolyte imbalance associated with several adverse clinical outcomes. The efficacy and negative effects of current existing treatment options has 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 HK patients in a real-world clinical setting as it is required by China's drug review and approval process.

Methods and analysis: This is a multi-centre, prospective, cohort study which plans to enrol 1000 patients taking SZC or willing to take SZC from approximately 40 sites in China. Patients ≥18 years of age at the time of signing the written informed consent and with documented sK levels ≥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/Institutional Review Board (IRB)/Independent Ethics Committee (IEC), (Approval number: YJ-JG-YW-2020). Results will be disseminated through national and international presentations and peer-reviewed publications.

Trial Registration: The trial is registered with the Clinical trials website https://www.clinicaltrials.gov/ (NCT05271266).

Strengths and Limitations

- The present study will be aimed to evaluate the safety, effectiveness and treatment patterns of SZC in HK patients in Chinese population under real world settings.
- It will address the evidence gaps about SZC usage for HK patients 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 monitoring of patients receiving SZC treatment, including the correction

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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 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.

Keywords: Hyperkalemia; serum potassium; sodium zirconium cyclosilicate; potassium binder; real-world study

Introduction

The distribution of total body potassium levels is controlled by internal homeostasis, whereas external homeostasis regulates renal potassium excretion to balance dietary and supplementary intake, extra-renal loss as well as related deficiencies [1]. Potassium levels within the body are maintained by these two parallel processes. Under normal physiological conditions, most of the potassium is distributed intracellular space (98%) 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 [2,3].

The imbalance in the homeostasis of potassium in the extracellular space (>5.0 mmol/L) is referred as hyperkalemia (HK) [4]. 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 and chronic hyperkalemia which is typically due to a defect in the renal excretion of potassium [5,6]. Different co-morbidities 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 2–3 times higher risk of developing HK thereby leading to serious cardiac dysrhythmias and increased mortality [7,8]. In a Chinese epidemiological study, 3.86% of general outpatients reported of having experienced HK, while patients with chronic kidney disease (CKD), heart failure, diabetes, and hypertension had higher rates of HK [9]. Furthermore, the incidence of HK increases by 25% for every 5 mL/min/1.73 m^2 decrease in eGFR [10,11].

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Insulin, β2 stimulants, and sodium bicarbonate are available first treatments that merely encourage potassium's translocation from the extracellular to the intracellular region, offering a transient benefit for 1 to 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 SPS [12]. As per Chinese study, insulin plus glucose is the most common treatment suggested for HK management [13]. 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 adverse events with safety concerns [14,15]. Therefore, there is a need for medications that can effectively manage and safely treat both acute and chronic hyperkalemia. 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 fecal potassium excretion by binding to potassium ions across the GI tract. SZC received approval in China in December 2019 for the management of HK in adults [3]. Regardless of the underlying aetiology of HK, age, sex, race, comorbid disease, or concurrent use of RAAS inhibitors, SZC was found to lower sK and maintained normal sK levels in the phase II/III clinical studies with no severe adverse effects [16–18]. As per the National Medical Products Administration (NMPA) regulations, a new drug's effectiveness and safety profile must be closely evaluated within five years of the first approval date. To date, the real-world safety and effectiveness of SZC in HK patients in China has not been studied. Hence the present study was designed to evaluate safety, effectiveness and treatment patterns of SZC in real-world setting.

Methods

Study design

In this multi-centre, 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 reviewing their medical records. Patients are considered eligible if ≥18 years of age at the time of signing the written informed consent; with documented sK levels ≥5.0 mmol/L within 1 year before study enrolment; currently on SZC, or be willing to take SZC with physicians' prescription; with or without hemodialysis

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treatment. Patients that 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. The patients will be divided into 2 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 at 1st, 3rd and 6th month from study enrolment, additionally the new SZC user group is planned to have a follow-up visit at 3rd day for potassium re-testing. Safety and effectiveness data, sK levels, SZC treatment data (if relevant), and additional associated data (if available) will all be recorded during each visit. 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 (ICH-GCP), Guidelines for Good Pharmacoepidemiology Practices (GPP) and the applicable legislation on Non-Interventional Studies and/or Observational Studies. The study will be initiated after obtaining approval from ethics committee/Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Informed consent will be obtained from all the included patients before study initiation. The trial 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 (eCRF). The study will collect 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 angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), mineralocorticoid receptor antagonist (MRA) and angiotensin receptor neprilysin inhibitor (ARNi) during the study from enrolment (Day 1 to Month 6 if data available) will be collected. Serum electrolyte levels, serum creatinine, serum blood urea nitrogen (BUN), serum

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albumin, serum bicarbonate, serum aspartate aminotransferase (AST), and serum alanine aminotransferase (ALT) values will be assessed according to standard clinical practice.

Treatment regimens

The treating physician will have control over the dose 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 3 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 one 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 adverse events (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 hypokalemia. All SAEs and non-serious AEs 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, musculo-skeletal including spine and extremities, neurological systems), ECG and biochemistry evaluations.

Patient and public involvement

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

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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 no formal testing of the hypotheses will be done. The analyses will include estimates (probabilities, rates, averages) with the corresponding 95% confidence intervals (CIs), as well as supportive descriptive statistics like mean, standard deviation (SD), median, minimum, maximum, and quartiles. The duration of SZC treatment will be estimated using a Kaplan-Meier method. SZC treatment discontinuation with the corresponding CIs, will be analyzed by landmark analysis for new and ongoing users. All statistical analyses will be performed using SAS 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 enrollment and new users who took at least one dose of SZC post the completion of the initial period (FAS-P2). Additional analyses will also be performed where applicable in patients on hemodialysis (FAS-H) at study enrollment.

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% to 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 [17]. 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/pre-defined 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 one month of follow-up (Visit 3). This interim analysis will include safety, effectiveness and

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treatment patterns of SZC and patients' characteristics at enrolment, while other variables might also be analyzed as applicable.

Discussion

The prevalence of hyperkalemia, a clinical condition that can be fatal, is significant, especially in patients with comorbid conditions. Up to 10% of hospitalized patients have been documented to have hyperkalemia [19]. According to a recent epidemiological study, the prevalence of HK climbed to 22.89% in CKD patients and to 3.86% among Chinese outpatients [9]. Renin-angiotensin-aldosterone system inhibitors (RAASi) are associated with hyperkalemia in patients with cardiorenal disorders [20–22].

Different approaches traditionally have been employed for lowering of potassium levels in patients with acute hyperkalemia which include agents such as β2-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 [23,24]. Redistribution of extracellular potassium to the intracellular space with the help of a β2-adrenergic receptor agonist, sodium bicarbonate or glucose and insulin is temporary and not highly preferred because of their short duration of action. Use of emergency dialysis and diuretics help 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 [14, 25–27]. Therefore, newer and reliable approaches are still required for HK management with promising effectiveness as well as minimal adverse events.

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 to placebo group was reported after the administration of first dose of 10g SZC [14]. Previous studies have shown safety and efficacy on SZC globally.[10,14,16,28] However, 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.

A phase 1 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

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by high K^+/low Na^+ diet compared to placebo while no significant change in urinary excretion of sodium. The study also reported mild treatment-emergent AEs and none related to SZC [29]. Similar results reported in a study on Chinese adult healthy participants [30]. A phase 2 z002 clinical study carried out on patients with CKD and hyperkalemia demonstrated significant reduction in sK levels in patients administered with 3g and 10g SZC in a dose dependant manner as compared to placebo. Even after administration of 10g SZC, lower sK levels were observed for additional 3.5 days as compared to 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 no clinically relevant. The safety profile of SZC showed mild to moderate AEs with no SAEs with SZC 10 g compared to placebo [16]. 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 well tolerated with mild AEs and no SAEs.

Both the z003 and z004 clinical studies reported significant reduction in mean sK levels in patients administered with SZC as compared to the placebo during the first 48 hours in a dose dependent manner [14,28]. The z003 clinical study reported constipation to be one of the most commonly occurring AEs along with only 1 SAE from the placebo group [14]. z004 clinical study reported higher incidence of generalized and peripheral edema with mild severity which could be managed without any treatment modifications in patients receiving 15 g SZC compared to placebo. This may be due to inclusion of participants with eGFRs of 15 to <30 (33%) or <15 ml/min/1.73 m2 (6%) and HF (15%). However, these AEs could be managed without any treatment modifications.[28] Another phase 3 z005 clinical study compared SZC efficacy and safety in HK patients with stages 4 and 5 CKD and those having CKD between stages 1-3 with corresponding baseline eGFR levels of <30 or 30mL/min/1.73$m^{2,}$ respectively for a duration of 52 weeks. SZC treatment was continued until they reached normokalemia (3.5–5.0 mmol/L) and was further given maintenance dose to maintain normokalemia. There was evident reduction in sK levels as well as its successful maintenance in HK patients with CKD irrespective of stage. Both the groups (stages 4 and 5 CKD; stage 1-3 CKD) showed constipation (4%, 3%), nausea (2%, 2%) and peripheral edema (2%, 2%) as the most commonly occurring AEs. Higher incidence of overall AEs, serious AEs and AEs leading to discontinuation was observed in HE patients with stage 4/5 CKD as compared to those with CKD between stages 1-3 which may be due to higher proportion of comorbidities, other

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medications or degree of renal impairment since inability to excrete salt and water progresses with CKD stage [10]. No difference in interdialytic weight gain between the SZC and placebo groups was reported in a clinical trial involving patients on chronic hemodialysis, the majority of whom got SZC doses of 5 g–10 g on days when they weren't receiving dialysis.[31] A phase 3 study carried out on Japanese hyperkalemia patients 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 [16,28,32,33]. The most common AEs reported in this study were constipation (6.7%), peripheral edema (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 previous reported studies [10,28]. The present study will be aimed to evaluate the incidence of AEs and their severity along with analyzing the effectiveness and treatment patterns of SZC effective in lowering of sK in HK patients 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, the 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 HK patients 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 HK patients in patients with comorbidities.

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Competing interests: The authors declare no competing interests.

Compliance with Ethics Guidelines: This 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 (ICH-GCP), Guidelines for Good Pharmacoepidemiology Practices (GPP) and the applicable legislation on Non-Interventional Studies and/or Observational Studies.

Data availability statement: The dataset generated during the study will be available from the corresponding author on prior request.

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Tables

Table 1: Study plan and timepoints of key assessments

	Day 1 V1	Day 3 ± 1 day V2[a]	Month 1 ± 2 weeks V3[b]	Month 3 ± 2 weeks V4[b]	Month 6 ± 2 weeks V5[b]
Screening patients based on inclusion and exclusion criteria	X				
Informed consent[c]	X				
Demographics	X				
Medical history	X				
Physical examination	X				
Vital signs	X				
eGFR[d]	X	X	X	X	X
NYHA Class	X				
ECG[d]	X	X	X	X	X
sK Test[e]	X	X	X	X	X
Biochemistry values[f]	X	X	X	X	X
AEs	X	X	X	X	X
SZC dosage information[f]	X	X	X	X	X
Concomitant treatment[g]	X	X	X	X	X

AEs, adverse events; ECG, electrocardiogram; NYHA, New York Heart Association; SZC, Sodium zirconium cyclosilicate

[a]Onsite visit at V2 for new SZC users only.

[b]All visits carried out during this study will be conducted onsite. If an onsite visit is not feasible because of COVID-19, an investigator will call the patient for evaluation of parameters.

[c]Informed consent form should be signed by the patients between day 0 and day 7.

[d] Physicians will record eGFR and ECG from the enrolment day according to the availability as per standard clinical practice.

[e]sK values will be collected at each visit and the follow-up period, along with the blood potassium test results for dialysis patients and pre-dialysis sK measurements which will be collected as per clinical practice upon patient visit.

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[f]Other biochemistry values including serum electrolytes values, serum creatinine, serum BUN, serum albumin, serum bicarbonate, serum AST, serum ALT will be collected if available as per clinical practice.

[g]SZC dosage information includes current daily dose and frequency, dose adjustment, interruption/discontinuation, reason for dose change.

[h]Concomitant treatment especially on the use of RAASi collected in the CRF as per availability of information in the electric medical record including drug/treatment name, usage, dosage, administration duration and indication.

Figure captions

Figure 1: Study design

AE, adverse events; sK, serum potassium; SZC, Sodium Zirconium Cyclosilicate.

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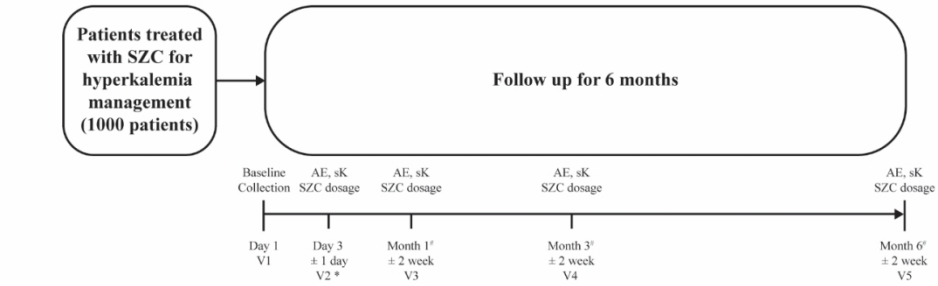

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Evaluation of Safety, Effectiveness and Treatment Patterns of Sodium Zirconium Cyclosilicate in Management of Hyperkalemia in China: A Real-World Study Protocol

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Title Page

Title: Evaluation of Safety, Effectiveness and Treatment Patterns of Sodium Zirconium Cyclosilicate in Management of Hyperkalemia in China: A Real-World Study Protocol

Short title: Evaluation of SZC for Hyperkalemia Management in China

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Abstract

Introduction: Hyperkalemia (HK) is a potentially life-threatening electrolyte imbalance associated with several adverse clinical outcomes. The efficacy and negative effects of currently existing treatment options has 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 HK patients in a real-world clinical setting as it is required by China's drug review and approval process.

Methods and analysis: This is a multi-centre, prospective, cohort study which plans to enroll 1000 patients taking SZC or willing to take SZC from approximately 40 sites in China. Patients ≥18 years of age at the time of signing the written informed consent and with documented sK levels ≥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: The present study is registered with the Clinical trials website https://www.clinicaltrials.gov/ (NCT05271266).

Strengths and Limitations

- The present study will be aimed to evaluate the safety, effectiveness and treatment patterns of SZC in HK patients in Chinese population under real world settings.
- It will address the evidence gaps about SZC usage in HK patients 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

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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 HK patients treated with SZC with non-SZC treatment patients. Moreover, a limited number of patients using a specific treatment options may introduce some extent of bias as it is a single arm study.

Keywords: Hyperkalemia; serum potassium; sodium zirconium cyclosilicate; potassium binder; real-world 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, extra-renal loss as well as related deficiencies [1]. 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 [2,3].

The imbalance in the homeostasis of potassium in the extracellular space (>5.0 mmol/L) is referred as hyperkalemia (HK) [4]. 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 hyperkalemia is typically due to a defect in the renal excretion of potassium [5,6]. Different co-morbidities 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 2–3 times higher risk of developing HK thereby leading to serious cardiac dysrhythmias and increased mortality [7,8]. In a Chinese epidemiological study, 3.86% of general outpatients reported incidence of HK, while patients with chronic kidney disease (CKD), heart failure, diabetes, and hypertension had higher rates of HK [9]. Furthermore, the incidence of HK increased by 25% for every 5 mL/min/1.73 m^2 decrease in eGFR [10,11].

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Insulin, β2 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 to 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 SPS [12]. As per Chinese study, insulin plus glucose is the most common treatment suggested for HK management [13]. 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 adverse events with safety concerns [14,15]. Therefore, there is a need for medications that can effectively manage and safely treat both acute and chronic hyperkalemia. 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 fecal potassium excretion by binding to potassium ions across the GI tract. SZC has received approval in China in December 2019 for the management of HK in adults [3]. Regardless of the underlying aetiology of HK, age, sex, race, comorbid disease, or concurrent use of RAAS inhibitors, SZC was found to lower sK levels and maintain normal sK levels in the phase II/III clinical studies with no severe adverse effects [16–18]. As per the National Medical Products Administration (NMPA) regulations, a new drug's effectiveness and safety profile must be closely evaluated within five 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, however, the enrolled population does not include Chinese patients. Besides, conducting post-market 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 HK patients 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

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safety and tolerability data from the pre-market phase II/III clinical studies with expansion to broader Chinese population.

Methods

Study design

In this multi-centre, 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 ≥18 years of age at the time of signing the written informed consent; have documented sK levels ≥5.0 mmol/L within 1 year before study enrolment; are currently on SZC, or willing to take SZC with physicians' prescription; with or without hemodialysis 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 non-hyperkalemia patients, this setting is more in line with the clinical practice of China's real-world studies. Patients that 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. The patients will be divided into 2 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 month from study enrolment day, additionally the new SZC user group is planned to have a follow-up visit at 3rd day for potassium re-testing. 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 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 (ICH-GCP), Guidelines for Good Pharmacoepidemiology Practices (GPP) 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

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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 (eCRF). The study will collect 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 angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), mineralocorticoid receptor antagonist (MRA) and angiotensin receptor neprilysin inhibitor (ARNi) will be collected during the study from enrolment (Day 1 to Month 6 if data available). Serum electrolyte levels, serum creatinine, serum blood urea nitrogen (BUN), serum albumin, serum bicarbonate, serum aspartate aminotransferase (AST), and serum alanine aminotransferase (ALT) 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 3 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 one 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 adverse events (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 hypokalemia. All SAEs and non-serious AEs will be monitored until they stabilise, disappear, or the patient is lost to follow-up.

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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, musculo-skeletal 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 independently of patients 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% confidence intervals (CIs), as well as supportive descriptive statistics like mean, standard deviation (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 analyzed by landmark analysis for new and ongoing users. All statistical analyses will be performed using SAS 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 enrollment and new users who took at least one dose of SZC post the completion of the initial period (FAS-P2). Additional analyses will also be performed wherever applicable in patients on hemodialysis (FAS-H) at study enrollment.

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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% to 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 [17]. 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/pre-defined 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 one 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 analyzed as applicable.

Discussion

The prevalence of hyperkalemia, a clinical condition that can be fatal, is significant, especially in patients with comorbid conditions. Up to 10% of hospitalized patients have been documented to have hyperkalemia [19]. According to a recent epidemiological study, the prevalence of HK climbed to 22.89% in CKD patients and to 3.86% among Chinese outpatients [9]. Renin-angiotensin-aldosterone system inhibitors (RAASi) are associated with hyperkalemia in patients with cardiorenal disorders [20–22].

Different approaches have been employed traditionally for lowering the potassium levels in patients with acute hyperkalemia which include agents such as β2-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 [23,24]. Redistribution of extracellular potassium to the intracellular space with the help of a β2-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 help 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-

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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 [14,25–27]. Therefore, newer and reliable approaches are still required for HK management with promising effectiveness as well as minimal adverse events.

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 to placebo group was reported after the administration of first dose of 10g SZC [14]. Previous studies have shown safety and efficacy on SZC globally[10,14,16,28]. However, there are no previously reported 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 HK patients 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 1 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 to 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 [29]. Similar results were reported in a study on Chinese adult healthy participants [30]. A phase 2 z002 clinical study carried out on patients with CKD and hyperkalemia demonstrated significant reduction in sK levels in patients administered with 3g and 10g SZC in a dose dependant manner as compared to placebo. Even after administration of 10g SZC, lower sK levels were observed for additional 3.5 days as compared to 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 SZC 10 g compared to placebo [16]. 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.

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Both the z003 and z004 clinical studies reported significant reduction in mean sK levels in patients administered with SZC as compared to the placebo group during the first 48 hours in a dose dependent manner [14,28]. The z003 clinical study reported constipation to be one of the most commonly occurring AEs along with only 1 SAE from the placebo group [14]. z004 clinical study reported higher incidence of generalized and peripheral edema with mild severity which could be managed without any treatment modifications in patients receiving 15g SZC compared to placebo. This may be due to inclusion of participants with eGFRs of 15 to <30 (33%) or <15 ml/min/1.73 m^2 (6%) and HF (15%). However, these AEs could be managed without any treatment modifications [28]. Another phase 3 z005 clinical study compared SZC efficacy and safety in HK patients with stages 4 and 5 CKD and those having CKD between stages 1-3 with corresponding baseline eGFR levels of <30 or 30mL/min/1.73m^2, respectively for a duration of 52 weeks. SZC treatment was continued until they reached normokalemia (3.5–5.0 mmol/L) and was further given maintenance dose to maintain normokalemia. There was evident reduction in sK levels as well as its successful maintenance in HK patients with CKD irrespective of stage. Both the groups (stages 4 and 5 CKD; stage 1-3 CKD) showed constipation (4%, 3%), nausea (2%, 2%) and peripheral edema (2%, 2%) as the most commonly occurring AEs. Higher incidence of overall AEs, serious AEs and AEs leading to discontinuation was observed in HK patients with stage 4/5 CKD as compared to 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 [10]. No difference in interdialytic weight gain between the SZC and placebo groups was reported in a clinical trial involving patients on chronic hemodialysis, the majority of whom got SZC doses of 5 g–10 g on days when they weren't receiving dialysis [31]. A phase 3 study carried out on Japanese hyperkalemia patients 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 [16,28,32,33]. The most common AEs reported in this study were constipation (6.7%), peripheral edema (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 [10,28]. The present study will be aimed to evaluate the incidence of AEs and their severity along with analyzing the effectiveness and treatment patterns of SZC effective in lowering of sK in HK patients in Chinese real-world settings.

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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, the 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 HK patients 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 HK patients in patients with comorbidities.

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Contributorship statement: HL was involved in investigation and conception. Manuscript writing, editing and revision was done by NS. QM, LZ, QZ, CS, XC, HX, JY, XL, JW, JY, XW, ST, LZ, YW, YL, XY, QL, XL, ZS, JZ, GL, CL, YC, JZ, NW, CX, XJ, HW, YH, LL, ZW, JH, JC, FW, CM, XY, ZL and HW were involved in acquisition of data. All the authors approved the final version of the manuscript.

Competing interests: The authors declare no competing interests.

Compliance with Ethics Guidelines: This 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 (ICH-GCP), Guidelines for Good

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Pharmacoepidemiology Practices (GPP) and the applicable legislation on Non-Interventional Studies and/or Observational Studies.

Data availability statement: The dataset generated during the study will be available from the corresponding author on prior request.

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Tables

Table 1: Study plan and timepoints of key assessments

	Day 1 V1	Day 3 ± 1 day V2[a]	Month 1 ± 2 weeks V3[b]	Month 3 ± 2 weeks V4[b]	Month 6 ± 2 weeks V5[b]

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Screening patients based on inclusion and exclusion criteria	X				
Informed consent[c]	X				
Demographics	X				
Medical history	X				
Physical examination	X				
Vital signs	X				
eGFR[d]	X	X	X	X	X
NYHA Class	X				
ECG[d]	X	X	X	X	X
sK Test[e]	X	X	X	X	X
Biochemistry values[f]	X	X	X	X	X
AEs	X	X	X	X	X
SZC dosage information[f]	X	X	X	X	X
Concomitant treatment[g]	X	X	X	X	X

AEs, adverse events; ECG, electrocardiogram; NYHA, New York Heart Association; SZC, Sodium zirconium cyclosilicate

[a]Onsite visit at V2 for new SZC users only.

[b]All visits carried out during this study will be conducted onsite. If an onsite visit is not feasible because of COVID-19, an investigator will call the patient for evaluation of parameters.

[c]Informed consent form should be signed by the patients between day 0 and day 7.

[d] Physicians will record eGFR and ECG from the enrolment day according to the availability as per standard clinical practice.

[e]sK values will be collected at each visit and the follow-up period, along with the blood potassium test results for dialysis patients and pre-dialysis sK measurements which will be collected as per clinical practice upon patient visit.

[f]Other biochemistry values including serum electrolytes values, serum creatinine, serum BUN, serum albumin, serum bicarbonate, serum AST, serum ALT will be collected if available as per clinical practice.

[g]SZC dosage information includes current daily dose and frequency, dose adjustment, interruption/discontinuation, reason for dose change.

[h]Concomitant treatment especially on the use of RAASi collected in the CRF as per availability of information in the electric medical record including drug/treatment name, usage, dosage, administration duration and indication.

Figure captions

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Figure 1: Study design

AE, adverse events; sK, serum potassium; SZC, Sodium Zirconium Cyclosilicate.

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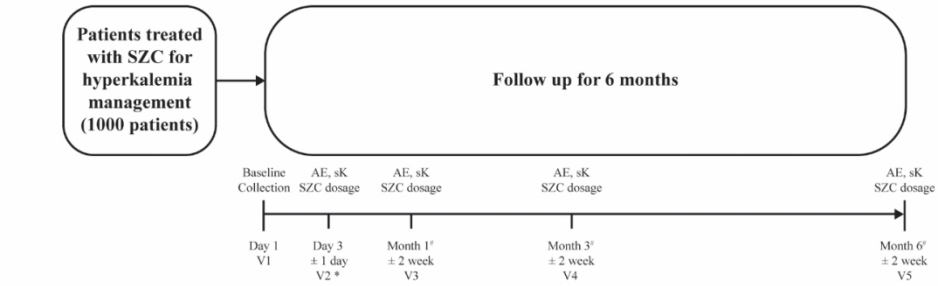

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