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Non-inferiority of sodium zirconium cyclosilicate versus potassium-restricted diet in achieving normokalaemia in patients with type 2 diabetes mellitus: protocol for a multicentre, open-label, randomised controlled, two-arm clinical trial (SILVERSTAR study)

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ABSTRACT

Background To effectively manage the progression of diabetic kidney disease, it is essential to address the associated hyperkalaemia while concurrently using renin-angiotensin-aldosterone system inhibitors and mineralocorticoid receptor antagonists. In this study, we aim to evaluate the effects of administering sodium zirconium cyclosilicate (SZC) to patients with type 2 diabetes mellitus (T2DM) complicated by hyperkalaemia.

Methods and analysis A total of 80 patients with type 2 diabetes and hyperkalaemia will be included in the study and randomly stratified into two groups.

After consent, both groups will enter an initiation phase, receiving 10 g of SZC, three times per day for 2 days. SZC administration (5 g once daily) will subsequently commence in group A, while dietary therapy will be initiated in group B by implementing a potassium-restricted diet. The primary endpoint of the study is the proportion of normokalaemic (3.5 mEq/L≤serum potassium (sK)<5.0 mEq/L) participants at visit 7. The secondary endpoints are: (a) the proportion of normokalaemic participants (3.5 mEq/L≤sK<5.0 mEq/L) at visit 4 and (b) serum potassium levels at visit 7.

Ethics and dissemination Written informed consent will be obtained from all participants prior to commencing the study. This study has been approved by the Kyoto Prefectural University of Medicine Clinical Research Review Board. All data obtained from this study will be published in a peer-reviewed journal.

Trial registration number jRCTs051230067.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study aligns with Kidney Disease: Improving Global Outcomes 2024 guidelines by evaluating the non-inferiority of sodium zirconium cyclosilicate (SZC) (a second-line treatment) compared to dietary potassium restriction (first-line treatment) for managing hyperkalaemia.

⇒ The study design prioritises patient safety by incorporating regular monitoring of serum potassium levels and allowing adjustments to the intervention as needed.

⇒ The study design facilitates a clear comparison of the interventions by evaluating the proportion of participants maintaining normokalaemia over a 4-week period.

⇒ Dietary adherence is rigorously assessed through percentage compliance at each visit and detailed nutrient intake analysis using the Brief-type self-administered Diet History Questionnaire.

⇒ The study's evaluation period is limited to 4 weeks, which may not provide insights into the long-term effects and safety of SZC or dietary interventions.

INTRODUCTION

Hyperkalaemia is a critical complication of cardiac and renal failure. A serum potassium level of ≥5.0 mEq/L is associated with a significant increase in the HR for renal composite endpoints (1.22; 95% CI 1.00 to 1.50) and an increase in the mortality rate among

post-myocardial infarction patients.[1] Therefore, the serum potassium levels must be maintained at ≤4.9 mEq/L to achieve optimal renal prognosis and longevity.[2]

The 'Fantastic Four' strategy, a renowned treatment strategy, is recommended for the management of cardiac and renal failure.[3] The regimen for heart failure involves the administration of angiotensin receptor-neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors.[3] The regimen for renal failure involves the administration of renin-angiotensin-aldosterone system (RAAS) inhibitors, SGLT2 inhibitors, MRAs and metformin. RAAS inhibitors, the first-line treatment for the management of blood pressure in patients with diabetes,[4] have renoprotective and hypotensive effects. These drugs slow disease progression and improve the prognosis; however, their use is associated with an increased risk of developing hyperkalaemia.[5] A previous study has shown that more than 25% of chronic kidney disease (CKD) patients with an estimated glomerular filtration rate (eGFR) of 15–29 and diabetes mellitus develop hyperkalaemia.[6]

While RAAS inhibitors and MRAs are effective in treating CKD, previous meta-analyses have indicated a significantly elevated risk of hyperkalaemia when these medications are used alone or in combination (OR for combination therapy compared with placebo: 6.08; 95% CI 2.30 to 16.08).[7]

Effective management of hyperkalaemia is crucial to ensure the continued use of these medications. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines previously recommended the discontinuation of the administration of RAAS inhibitors if the patient develops hyperkalaemia. However, the latest guidelines recommend continuing their administration and advocating for the active management of serum potassium levels.[8] The current approach recommends identifying a differential diagnosis based on the incidence of rapid renal decline, metabolic acidosis or hyperkalaemia owing to the concomitant use of other medications and suggests tailored actions for each scenario.[9] Maintaining the serum potassium level at <5.5 mEq/L while continuing the administration of RAAS inhibitors, in addition to the implementation of a potassium-restricted diet or the administration of cationic medications, is advised if the elevation in the serum potassium levels is caused by excessive potassium intake.[9–16] Medical nutritional therapy prescribed by a registered nutritionist, which facilitates the regulation of serum potassium levels via the implementation of dietary restrictions, is the pillar of this management strategy. The KDIGO 2024 CKD Guidelines recommend a potassium-restricted diet as the first-line treatment for hyperkalaemia, with medications as a second-line option. However, in practical clinical settings, adhering to a potassium-restricted diet may not always be feasible.

We aim to evaluate the efficacy of this conventional dietary approach with that of sodium zirconium cyclosilicate (SZC), a new therapeutic agent that binds potassium in the gastrointestinal tract and promotes its excretion, thereby reducing serum potassium levels. This non-inferiority trial aims to demonstrate that SZC can provide effects comparable or superior to those of standard dietary therapy. The findings of this trial could aid in improving the management of hyperkalaemia in patients with cardiac and renal failure via the Fantastic Four strategy. Furthermore, determining whether the efficacy of SZC is equivalent to or greater than that of the first-line treatment could significantly expand the treatment options, thereby offering new therapeutic options. This protocol meticulously examines these aspects and aims to facilitate the establishment of future treatment strategies.

METHODS AND ANALYSIS

study design

A total of 80 patients with type 2 diabetes mellitus (T2DM) complicated by hyperkalaemia will be randomly stratified into two groups in this multicentre, open-label, randomised controlled trial (RCT) (Non-inferiority of sodium zirconium cyclosilicate versus potassium-restricted diet in achieving normokalaemia in patients with type 2 diabetes mellitus: protocol for a multicentre, open-label, randomised controlled, two-arm clinical trial (SILVERSTAR study)) (figure 1).

Study population

The following inclusion and exclusion criteria were set such that only patients who met the purpose of this study were included in the study while ensuring their safety. Patients who require legal representatives will be excluded to ensure that the efficacy is assessed appropriately. The serum potassium level and ECG results recorded within 3 days before providing and other parameters recorded within 6 weeks before providing consent will be used to determine eligibility.

The study will include only those patients who meet all of the following criteria: (a) patients diagnosed with T2DM according to the treatment guideline for diabetes mellitus released by the Japan Diabetes Society in 2019, (b) patients with a serum potassium level of ≥5.0 mEq/L but ≤6.0 mEq/L at the time of providing consent, (c) patients aged ≥20 years but <90 years at the time of providing consent and (d) patients providing written consent.

Patients who meet any of the following criteria will be excluded: (a) patients who received other conventional pharmacotherapy for the management of hyperkalaemia within 7 days before providing consent; (b) patients diagnosed with acute kidney injury according to the KDIGO criteria; (c) patients with an eGFR of <15 mL/min/1.72 m^2, serum creatinine level of ≥3.5 mg/dL or history of undergoing dialysis; (d) patients with cardiac failure (NYHA classification III or IV), (e) patients whose activities

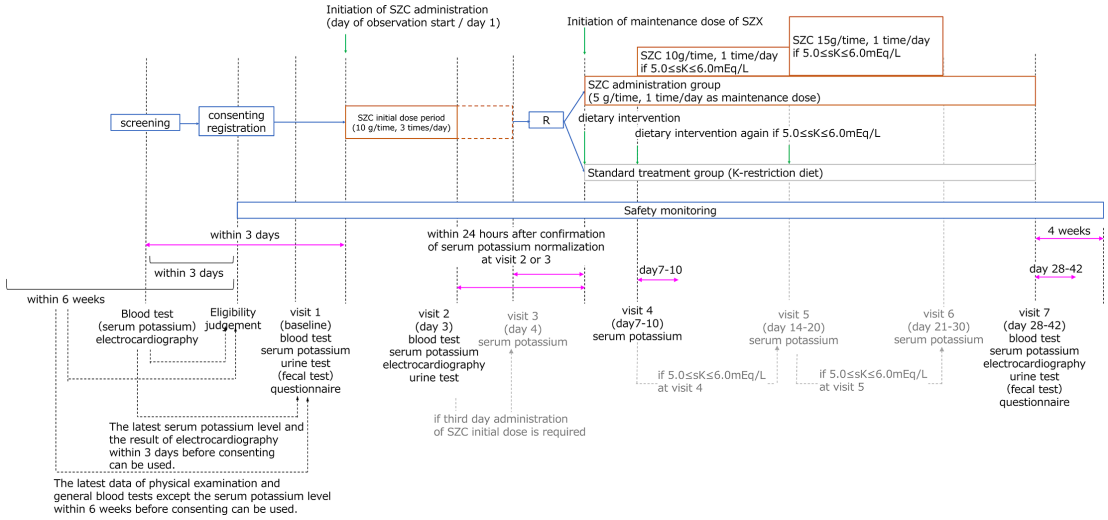

Figure 1 Study design. sK, serum potassium; SZC, sodium zirconium cyclosilicate.

of daily living level is PS2 or higher and aged ≥65 years; (f) patients with a history of QT prolongation induced by other pharmaceutical agents and those with a history of discontinuing pharmacotherapy; (g) patients with congenital long QT syndrome; (h) patients with QTc (f) of >550 ms; (i) patients with a pacemaker; (j) patients with symptomatic or uncontrolled atrial fibrillation despite receiving treatment or patients with asymptomatic sustained ventricular tachycardia (patients with atrial fibrillation well-controlled by pharmacotherapy can be included in this study); (k) pregnant women and those planning to conceive; (l) patients receiving treatment for the management of malignant neoplasms; (m) patients with moderate to severe anaemia (haemoglobin (Hb) level of ≤100 g/L) whose primary disease is other than diabetic nephropathy; (n) patients with hypoalbuminaemia (serum albumin level of ≤3.5 g/dL) whose primary disease is other than diabetic nephropathy; (o) patients with nephrotic syndrome (urine protein and serum albumin levels of ≤3.5 g/day and ≤3.0 g/dL, respectively) whose primary disease is other than diabetic nephropathy; (p) patients with poor adherence, as judged by the attending physician; (q) patients who require a legal representative; and (r) patients with conditions deemed unsuitable for the administration of SZC by the attending physician.

Treatment protocol

Figures 2 and 3 present the flowcharts of the interventions in the SZC and standard treatment groups.

SZC (10 g) will be administered three times per day for 2–3 days to the patients in both groups after obtaining consent. The potassium-restricted diet will be implemented in accordance with the guidelines.[4 9 17] The instructions for the potassium-restricted diet prescribed by registered dietitians are as follows:

1. Continue the restriction of total energy, protein and sodium prescribed before participating in the study.
2. Total energy: 25–35 kcal/kg/day, according to physical activity.
3. Protein: 0.8–1.0 g/kg/day (diabetic nephropathy stage 3); 0.6–0.8 g/kg/day (diabetic nephropathy stage 4).
4. Sodium: <6 g/day if the participant is hypertensive.
5. Implement potassium restriction to achieve a potassium intake level of <1.5 g/day.

In addition, standard diet therapy for the management of diabetes mellitus will continue in both groups. The schedule is outlined below.

Screening

Potential participants will be selected based on the inclusion and exclusion criteria (screening). The most recent serum potassium level and ECG results recorded within 3 days before providing consent, along with other parameters recorded within 6 weeks before consent, will be used to assess eligibility.

Consenting and registration

Written informed consent will be obtained after explaining the study objectives, and the investigators will enter the required information into a specific web system after obtaining consent (registration). Consent form is presented as online supplemental material 1. In principle, the dosage and type of medication must remain the same during the period between obtaining consent and the end of the observation period.

Tests performed at visit 1 (baseline)

Blood (fasting) and urine (spot) tests will be performed at visit 1 (baseline) after registration and within 3 days of the screening test. The study subjects will also complete the Diabetes Diet-Related Quality of Life Revised (DDRQOL-R), Brief-type self-administered Diet History Questionnaire (BDHQ) and Gastrointestinal Symptom Rating Scale (GSRS) questionnaires.[18–20]

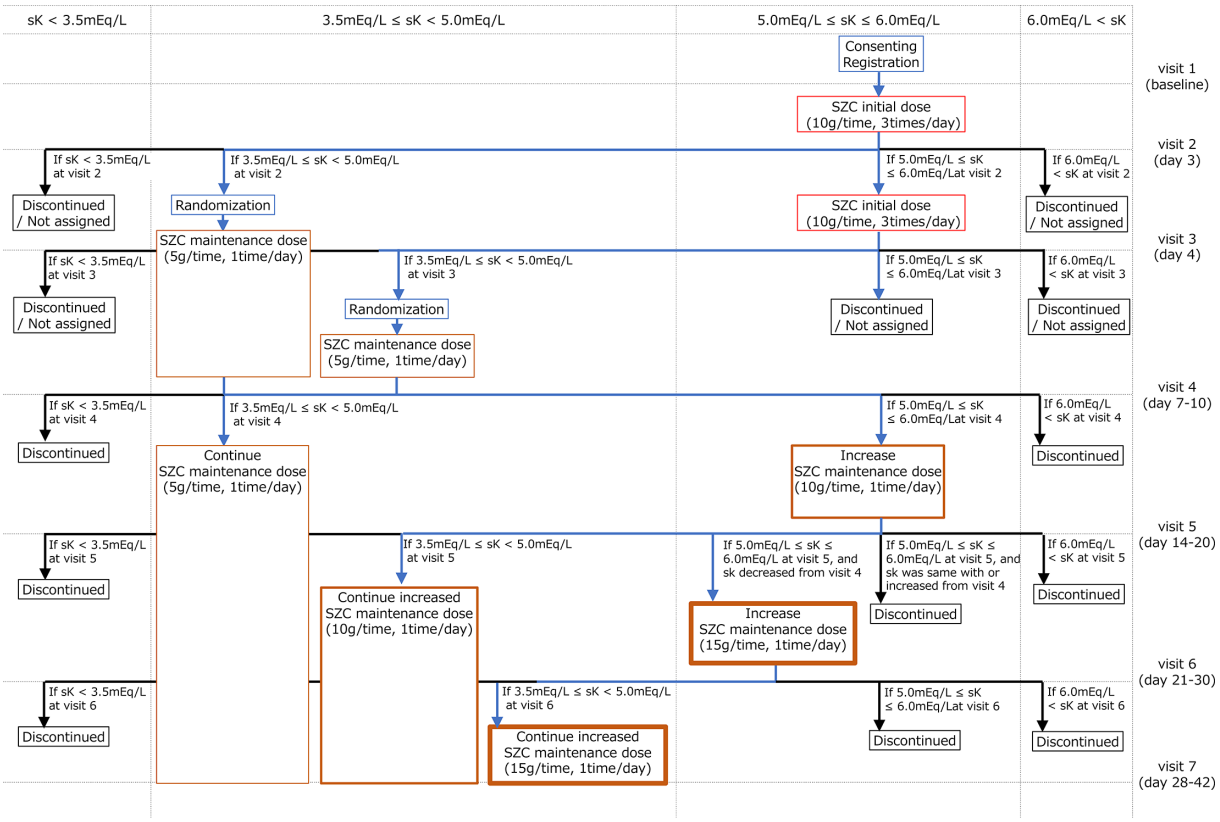

Figure 2 Flowchart of the interventions in the SZC group. sK, serum potassium; SZC, sodium zirconium cyclosilicate.

Administration of the initial dose of SZC (reference date/day 1)

The initial dose of SZC (10 g of SZC administered three times per day) will be administered after completing the tests to be performed at visit 1 (baseline) and within 3 days of the screening test. The administration

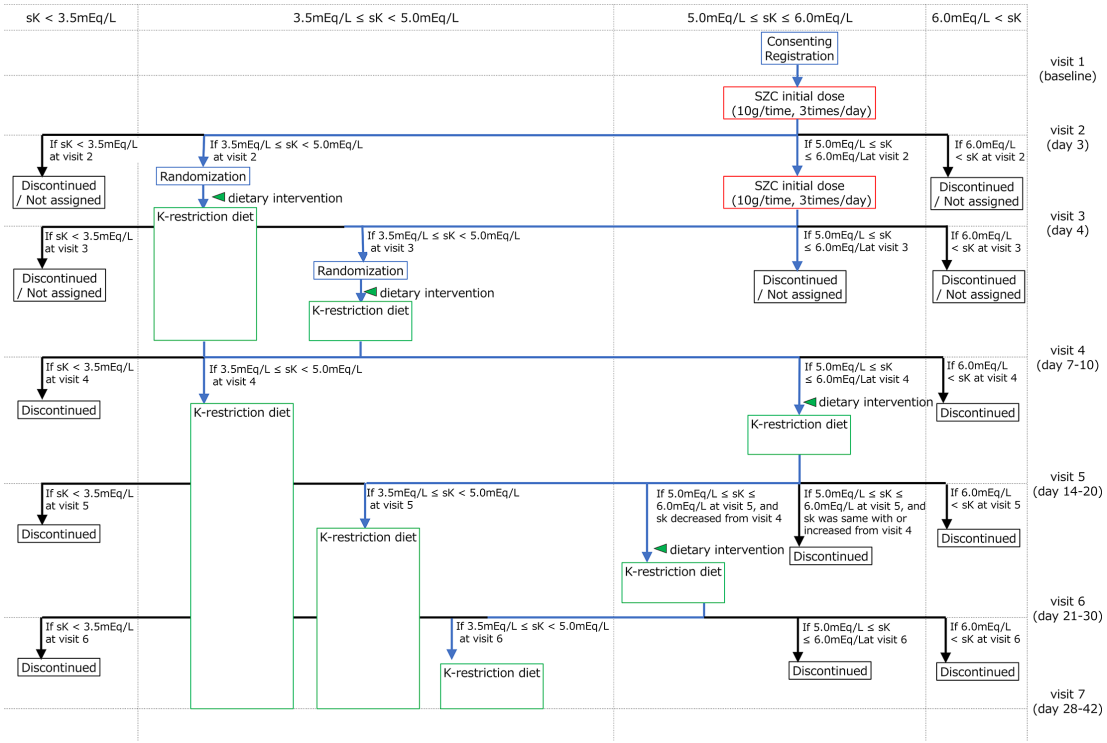

Figure 3 Flowchart of the interventions implemented in the standard treatment group. sK, serum potassium; SZC, sodium zirconium cyclosilicate.

period will be 2–3 days. The day of administering the initial dose of SZC will be considered the start of the observation (reference date/day 1).

Tests performed at visit 2 (day 3)

Blood tests (fasting), urine tests and an ECG will be performed at visit 2, that is, day 3 after the reference day. Adherence to the study intervention will be determined through interviews. Assignment will be conducted within 24 hours after completing the tests performed at visit 2 (day 3) if the serum potassium level is ≥3.5 mEq/L but <5.0 mEq/L at that visit. SZC will be administered on the 3rd day, and visit 3 (day 4) will be scheduled on the day after visit 2 (day 3) if the serum potassium level is ≥5.0 mEq/L but ≤6.0 mEq/L at visit 2 (day 3). Visit 3 (day 4) and assignment will not be conducted, and the measures for hyperkalaemia or hypokalaemia described in the criteria for discontinuing the study intervention will be commenced if the serum potassium level is >6.0 mEq/L or <3.5 mEq/L at visit 2 (day 3).

Tests performed at visit 3 (day 4)

Fasting blood test will be conducted on the day after visit 2 (day 3) and the administration of SZC will be continued if the serum potassium level at visit 2 (day 3) is ≥5.0 mEq/L but ≤6.0 mEq/L. Adherence to the study intervention will be determined by conducting interviews. Assignment will be conducted within 24 hours after completing the tests to be performed at visit 3 (day 4) if the serum potassium level is ≥3.5 mEq/L but <5.0 mEq/L at visit 2 (day 3). Assignment will not be conducted and the measures for hyperkalaemia or hypokalaemia described in the criteria for discontinuing the study intervention will be implemented if the serum potassium level is >5.0 mEq/L or <3.5 mEq/L at visit 2 (day 3).

Assignment

The investigators will enter the required information into the specific web system (DC Entry Maker) for assignment within 24 hours after completing the tests conducted at visit 2 (day 3) or visit 3 (day 4) if the serum potassium level of the participant is ≥3.5 mEq/L but <5.0 mEq/L at either visit. Random assignment to the SZC or standard treatment (potassium-restricted diet) group will be performed at a ratio of approximately 1:1 using a computer-based dynamic allocation method with a minimisation procedure to balance two allocation factors (eGFR (<30 mL/min/1.73 m^2 and ≥30 mL/min/1.73 m^2) at the time of providing consent and the serum potassium level (<4.3 mEq/L and ≥4.3 mEq/L) at visit 2 (day 3)). Assignment will not be conducted, the study intervention will be discontinued, and the measures for hyperkalaemia or hypokalaemia described in the criteria for discontinuation of the study intervention will be implemented if the serum potassium level is ≥5.0 mEq/L or <3.5 mEq/L at visit 2 (day 3) or visit 3 (day 4).

Commencement of the administration of the SZC maintenance dose and implementation of the potassium-restricted diet prescribed by a registered dietitian

Participants in the SZC group will receive a maintenance dose of the study agent (5 g of SZC administered once daily) within 24 hours after completing the tests conducted at visit 2 (day 3) or visit 3 (day 4). The potassium-restricted diet prescribed by a registered dietitian will be implemented in the standard treatment group within 24 hours after completing the tests conducted at visit 2 (day 3) or visit 3 (day 4). The administration of the maintenance dose of the study agent or the implementation of the potassium-restricted diet prescribed by a registered dietitian should commence after completing the tests conducted at visit 2 (day 3) and assignment.

Tests performed at visit 4 (days 7–10)

Blood tests (fasting) will be conducted 7–10 days after the reference day. Adherence to the study intervention or the potassium-restricted diet will be determined by conducting interviews. The administration of SZC (5 g administered once daily) will continue if the serum potassium level is ≥3.5 mEq/L but <5.0 mEq/L at visit 4 (days 7–10). Visits 5 (days 14–20) and 6 (days 21–30) will be omitted, and the administration of SZC (5 g administered once daily) will be continued till visit 7 (days 28–42). Implementation of the potassium-restricted diet will continue without providing the instructions for the potassium-restricted diet prescribed by a registered dietitian in the standard treatment group. Visits 5 (days 14–20) and 6 (days 21–30) will be omitted, and the potassium-restricted diet will be continued until visit 7 (days 28–42).

SZC (10 g) will be SZC administered once daily in the SZC group and visit 5 (days 14–20) will be conducted if the serum potassium level is ≥5.0 mEq/L but ≤6.0 mEq/L at visit 4 (days 7–10). The potassium-restricted diet prescribed by a registered dietitian will be implemented again in the standard treatment group and visit 5 (days 14–20) will be conducted.

The study intervention will be discontinued and the treatment for hyperkalaemia or hypokalaemia as described in the criteria for the discontinuation of the study intervention will be commenced in both groups if the serum potassium level is >6.0 mEq/L or <3.5 mEq/L at visit 4 (days 7–10).

Tests performed at visit 5 (days 14–20)

Blood tests (fasting) will be conducted 7–10 days after visit 4 if the serum potassium level (day 3) is ≥5.0 mEq/L but ≤6.0 mEq/L at visit 4. Adherence to the study intervention or the potassium-restricted diet will be determined by conducting interviews.

The administration of SZC (10 g) will continue once daily in the SZC group if the serum potassium level of the participant is ≥3.5 mEq/L but <5.0 mEq/L at visit 5 (days 14–20). Visit 6 (days 21–30) will be omitted, and the administration of SZC (10 g) will be continued once daily until visit 7 (days 28–42). The instructions for

implementing the potassium-restricted diet prescribed by a registered dietitian will not be provided in the standard treatment group, but the implementation of the potassium-restricted diet will continue. Visit 6 (days 21–30) will be skipped and the potassium-restricted diet will continue to be implemented until visit 7 (days 28–42).

The administration of SZC (15 g) will continue once daily in the SZC group, and visit 6 (days 21–30) will be conducted if the serum potassium level is ≥5.0 mEq/L but ≤6.0 mEq/L at visit 5 (days 14–20) and if the serum potassium level decreases from visit 4 (days 7–10). The registered dietitians will provide instructions on how to implement the potassium-restricted diet again, and visit 6 (days 21–30) will be conducted in the standard treatment group.

The study intervention will be discontinued, and the treatment measures for hyperkalaemia, as described in the criteria for the discontinuation of the study intervention, will be implemented in both groups if the serum potassium level is >6.0 mEq/L or <3.5 mEq/L at visit 5 (days 14–20) or if the serum potassium level is ≥5.0 mEq/L but ≤6.0 mEq/L visit 5 (days 14–20) and the serum potassium level does not decrease from visit 4 (days 7–10).

Tests performed at visit 6 (days 21–30)

Blood tests (fasting) will be conducted 7–10 days after visit 5 (days 14–20) if the serum potassium level is >6.0 mEq/L or <3.5 mEq/L at visit 5 (days 14–20). Adherence to the study intervention or the potassium-restricted diet will be determined by conducting interviews.

Visit 6 (days 21–30) will be skipped if visit 7 (days 28–42) is conducted 7–10 days after visit 5 (days 14–20).

The administration of SZC (15 g) will be continued once daily in the SZC group if the serum potassium level is ≥3.5 mEq/L but <5.0 mEq/L at visit 6 (days 21–30). The instructions for implementing the potassium-restricted diet will not be provided to the registered dietitians in the standard treatment group and the potassium-restricted diet will continue to be implemented.

The study intervention will be discontinued and treatment for hyperkalaemia or hypokalaemia will be commenced in both groups if the serum potassium level is >5.0 mEq/L or <3.5 mEq/L at visit 6 (days 21–30).

Tests performed at visit 7 (days 28–42)

Blood tests (fasting), urine tests and an ECG will be conducted 28–42 days after the reference day. The participants assigned to the SZC group will receive the study agent until the morning of visit 7 and will undergo the tests to be performed at visit 7 at the earliest. Adherence to the study intervention or the potassium-restricted diet will be determined by conducting interviews.

The study subjects will be instructed to complete the DDRQOL-R, BDHQ and GSRS questionnaires. The participants at medical institutions where faecal tests can be conducted will also be instructed to provide samples of their faeces using a specific vessel on a day as close to visit 7 (days 28–42) as possible. The samples will be sent to the Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine by post.

Safety monitoring (throughout the observation period)

The investigators monitored the safety information of the study subjects throughout the observation period (from registration to the end of the tests at visit 7 (days 28–42)), including the occurrence of any adverse events or diseases. In addition, the investigators monitored the safety information of the study subjects 4 weeks after the tests at visit 7 (days 28–42) by asking them to contact the attending physician as soon as possible if any adverse events occurred.

Observation schedule

Online supplemental material 2 provides an overview of the observation schedule.

Treatment/intervention

Prohibited concomitant drugs/treatment

The implementation of pharmacotherapies for the management of hyperkalaemia, other than the SZC regimen, will be prohibited in both groups during the administration period of the initial dose of SZC.

The implementation of any pharmacotherapy for the management of hyperkalaemia, other than the SZC regimen, will be prohibited in the SZC group after completing the tests performed at visit 2 (day 3). The implementation of all pharmacotherapies for the management of hyperkalaemia, including the administration of SZC, will be prohibited in the standard treatment group.

Instructions for the implementation of the potassium-restricted diet prescribed by a registered dietitian will be prohibited in the SZC group.

Restricted concomitant drugs/treatment

In principle, the addition, discontinuation, switching or dose changes of RAAS inhibitors and diuretic agents will not be permitted during the observation period. Follow-up monitoring to assess safety will be conducted via interviews or telephone calls approximately 1 week later if the addition, discontinuation, switching or dose changes of RAAS inhibitors and diuretic agents are required.

The implementation of other pharmacotherapies will not be restricted in this study; however, in principle, the addition, discontinuation, switching or dose changes of any medication will not be permitted.

Criteria for discontinuing the study intervention

Necessary measures, such as discontinuing the administration of SZC or the implementation of the potassium-restricted diet, will be taken if the responsible investigator or sub-investigator judges that the study intervention is difficult to continue for any of the following reasons. The data of these participants will be considered as the data of a ‘study intervention discontinuation case’. The date, time point, reason for discontinuation and course of the disease will be entered into the card and case report form (CRF).

All necessary tests will also be performed on discontinuation of the study intervention. The efficacy and safety of the treatment will be evaluated at this point. Observation will continue until visit 7 (days 28–42) if the study intervention is discontinued due to criteria 2–5 (hyperkalaemia or hypokalaemia). Moreover, the items to be evaluated will be followed up to assess safety even if the study intervention is discontinued owing to other criteria. The participant will be considered a 'dropout case' if consent is withdrawn. The responsible investigator or sub-investigator will use the consent withdrawal form to confirm whether the data that has already been collected can be used.

1. Participant voluntarily wishes to discontinue participation in the study or withdraw consent.
2. The serum potassium level is ≥5.0 mEq/L at visit 3 (day 3) or visit 6 (days 21–30).
3. The serum potassium level is >6.0 mEq/L at visit 2 (day 3), visit 4 (days 7–10), or visit 5 (days 14–20).
4. The serum potassium level is ≥5.0 mEq/L but ≤6.0 mEq/L at visit 5 (days 14–20) and the serum potassium level does not decrease from visit 4 (days 7–10) to visit 5 (days 14–20).
5. Incidence of hypokalaemia (serum potassium level of <3.5 mEq/L).
6. QTc (f) is>550 ms.
7. QTc (f) is >500 ms and the serum potassium level within 1 hour after ECG meets criteria 2–5.
8. Continuing the administration of SZC or the implementation of the potassium-restricted diet is deemed inappropriate owing to the worsening of the primary disease or complications.
9. Necessity of discontinuing the administration of SZC or the implementation of the potassium-restricted diet owing to the incidence of adverse events or diseases.
10. Remarkably poor adherence (medication rate or adherence to the potassium-restricted diet is <75% or ≥120% than the planned number).
11. Major deviation from the study protocol that severely affects the study results.
12. Discontinuation of the study intervention considered appropriate by the investigators owing to other reasons.

The following treatments will be administered if criteria 2–4 (hyperkalaemia) are met:

1. Treatment for the management of hyperkalaemia, including the administration of sodium polystyrene sulfonate, calcium polystyrene sulfonate, sodium bicarbonate, calcium gluconate or glucose-insulin therapy, will be commenced by the attending physician.
2. The administration of SZC will be discontinued if any potassium binders are administered.
3. Haemodialysis or renal replacement therapy will be considered if severe hyperkalaemia occurs.

The following treatments will be administered if criterion 5 (hypokalaemia) is met:

1. The administration of SZC will be discontinued in the SZC group, whereas the implementation of the potassium-restricted diet will be discontinued in the standard treatment group.
2. The treatment for the management of hypokalaemia will be determined at the discretion of the attending physician.

Criteria for discontinuing the whole study

The principal investigator will determine whether the patient's participation in the study should be continued if it is difficult to continue the study for any of the following reasons. The principal investigator shall inform the decision to discontinue the study to the responsible investigators of all collaborating institutions, along with the underlying reasons, and information on how to implement necessary measures if continued participation is deemed inappropriate. The principal investigators will report the discontinuation of the study to a certified review board via written documentation.

1. On obtaining critical information about the quality, safety and efficacy of the study agent.
2. If recruiting participants is difficult or if enrolling the planned number of participants is determined to be difficult.
3. If protocol modification is required but cannot be implemented.

The responsible investigators will promptly discontinue the study and report the findings to the head of their institution in the form of a written document if the study is discontinued. The investigators will also notify participants of the discontinuation of the study and take appropriate action.

Outcome

The primary endpoint of this study is the proportion of normokalaemic (3.5 mEq/L≤serum potassium (sK)<5.0 mEq/L) participants at visit 7.

The secondary endpoints of this study are as follows: (a) the proportion of normokalaemic (3.5 mEq/L≤sK<5.0 mEq/L) participants at visit 4 and (b) the serum potassium level at visit 7. The exploratory endpoints are as follows: (a) the serum potassium levels at visit 1, 2, 3, 4, 5 and 6; (b) the changes in the serum potassium levels recorded at each visit; (c) the score of DDRQOL-R in each domain at visits 1 and 7; (d) the amount of changes in the DDRQOL-R scores in each domain from visit 1 to visit 7; (e) the total BDHQ score and the score of each component at visits 1 and 7; (f) the changes in the BDHQ scores (total and those of individual components) from visit 1 to visit 7; (g) the total GSRS and the score of each component at visits 1 and 7; (h) the changes in the GSRS scores (total and those of individual components) from visit 1 to visit 7; (i) the biomarker levels in the blood at each visit and the changes in the levels from visit 1 to visit 7 (red blood cell count, white blood cell count, haemoglobin, haematocrit, blood platelet count, hepatic enzymes (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, γ-glutamyltranspeptidase), uric acid, total cholesterol

high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, blood urea nitrogen, creatinine, eGFR, brain natriuretic peptide, serum sodium, serum chloride, HbA1c (or glycoalbumin), plasma glucose, serum albumin, C-peptide and C-peptide index); (j) the biomarker levels in the urine at each visit and the changes in the levels from visit 1 to visit 7 (specific gravity, pH, protein, glucose, ketone bodies, occult blood, urobilinogen, bilirubin, albumin-to-creatinine ratio, urine sodium/urine creatinine, urine potassium/urine creatinine, urine chloride/urine creatinine); (k) the incidence of adverse event and disease; (l) the proportion of normokalaemic (3.5 mEq/L≤sK<5.0 mEq/L) participants at visit 7 stratified according to the use of RAAS inhibitors; (m) the correlation between adherence to the potassium-restricted diet at visit 7 and the changes in the DDRQOL-R score, serum potassium levels or estimated mean potassium intake in the standard treatment group; (n) the changes in serum metabolome; (o) the changes in urine metabolome; and (p) the changes in faecal metagenome.

Sample size calculation

Patients with T2DM whose serum potassium level is ≥5.0 mEq/L will receive 10 g of SZC three times per day as the initial dose for 2 days. Thereafter, 5 g of SZC will be administered once daily as the maintenance dose. The proportion of normokalaemic participants in the SZC group will be compared with that in the standard treatment group (potassium-restricted diet) after 28 days.

Kosiborod *et al*[21] conducted a clinical trial of individuals with abnormal serum potassium levels (≥5.1 mEq/L) and reported that the proportion of participants with normalised serum potassium levels in the SZC group and the placebo group was 85.2% and 47.6%, respectively. The HARMONIZE Global study,[22] a national regulatory review, reported that 58.6% of the participants who received 5 g of SZC daily and 24.0% of the participants who received placebo had normalised serum potassium levels. These findings indicate that the proportion of normokalaemic participants in the SZC group at visit 7 (days 28–42) in this study can be assumed to be 58.6%, which is similar to that observed in the HARMONIZE Global study.

No previous study has investigated the proportion of participants whose serum potassium levels were normalised through the implementation of a potassium-restricted diet prescribed by dietitians. The mean serum potassium level on day 29 in the placebo group in the HARMOIZE-Global study[22] was estimated as 5.45 mEq/L (SD=0.565) by counting the number of patients within each serum potassium level subgroup from the distribution graph of the serum potassium level in the HARMONIZE-Global study. The implementation of a potassium-restricted diet can reduce the serum potassium level by 0.22 mEq/L.[23 24] The mean serum potassium level in the standard treatment group can be assumed to be 5.23 mEq/L (SD=0.565) in this study, calculated by subtracting 0.22 mEq/L from the mean serum potassium level at day 29 in the placebo group in the HARMONIZE Global study. Under this assumption, the expected probability of serum potassium normalisation is 34%.

The non-inferiority margin is set at 0.1. Statistical non-inferiority will be tested with a power of 85.5% in each of the 36 cases under α=0.025 using a one-sided Farrington-Manning test. A dropout rate of 10% is assumed for the study period, resulting in a target of 40 cases in each group.

Thus, a randomised, non-inferiority comparison study between the SZC and standard treatment groups with 40 cases in each group can demonstrate that treatment with SZC is as effective as the implementation of a potassium-restricted diet in achieving normokalaemia.

Among the 1763 patients included in the diabetes cohort of the Kyoto Prefectural University of Medicine (the KAMOGAWA-DM cohort), 205 patients (11.6%) were eligible for inclusion. Other collaborative research institutions generally receive approximately 8000 patients with diabetes; consequently, approximately 800 patients were estimated to be eligible for inclusion in this study. The target number of participants to be included in this study (80) is 10% of the potential eligible candidates, and it would be feasible to obtain consent and conduct the study within the planned timeframe.

Statistical analysis

The full analysis set (FAS) and per-protocol set (PPS) will be analysed for the primary and secondary endpoints. The analysis of non-inferiority and superiority will be performed using a one-sided test with a significance level of 2.5%. The other analyses will be performed using a two-sided test with a significance level of 5%. A biomedical statistical expert will create a statistical analysis plan (SAP) separately and specify the details of the statistical methods, including data handling. The SAP will be prepared prior to the database lock. The statistical expert will amend the SAP with version history and records of the content of the amendment if an amendment of the SAP is required.

1. Full analysis set

The FAS will comprise the participants enrolled (after providing consent and screening) in this study who will receive the initial dose of SZC and the treatment defined in this protocol completely or partially. However, participants exhibiting a significant violation of the study protocol (such as participation without written consent) will be excluded.

2. Per protocol set

The PPS data set will exclude the participants with any of the significant protocol violations listed below:

- Violation of the inclusion criteria.
- Violation of the exclusion criteria.
- Use of prohibited concomitant drugs.
- Patients with poor adherence to the study agent (<60%) and the potassium-restricted diet (<60%) in the SZC and standard treatment groups, respectively.

(3) Safety analysis set

The safety analysis set will comprise the participants who receive the initial dose of SZC and the treatment defined in this protocol completely or partially.

Summary statistics will be calculated for the background information of the participants by group. The frequencies and percentages of the categories will be calculated for the nominal variables. Summary statistics (number of cases, mean, SD, and the minimum, median and maximum values) will be calculated for continuous variables. The χ^2 test was used to compare nominal variables between the groups. Fisher's exact test will be used if the proportion of cells with an expected frequency of <5 is ≥20%. A two-sample t-test or Wilcoxon rank-sum test will be used to compare continuous variables between the groups.

Further details regarding the statistical methods are included in the SAP (online supplemental file 3).

Analysis of the primary endpoint

The proportion of normokalaemic (3.5 mEq/L≤sK<5.0 mEq/L) participants at visit 7 and its 95% CI will be calculated based on the number of participants in each group. The Farrington-Manning test (one-tailed test) will be used to assess the non-inferiority of SZC to potassium-restricted diet in achieving normokalaemia (3.5 mEq/L≤sK<5.0 mEq/L). The non-inferiority margin is set at 0.1. The null hypothesis 'the proportion of participants with normal serum potassium levels at visit 7 in the SZC group is at least 10% lower than that in the standard treatment group' will be tested. The alternative hypothesis 'the proportion of participants with normal serum potassium levels at visit 7 in the SZC group is not more than 10% lower than that in the standard treatment group' will be assessed if the null hypothesis is rejected. The superiority of SZC over a potassium-restricted diet in achieving normokalaemia (3.5 mEq/L≤sK<5.0 mEq/L) will be assessed with the same alpha (considered if it is >0%) if non-inferiority is proven. The second null hypothesis is that 'the proportion of participants with normal serum potassium levels at visit 7 in the SZC group is equal to that in the standard treatment group'. The alternative hypothesis that 'the proportion of participants with normal serum potassium levels at visit 7 in the SZC group is greater than that in the standard treatment group' will be assessed if the null hypothesis is rejected. These assessments will be conducted via a closed testing procedure without adjusting for multiplicity. The primary endpoint will be assessed using the FAS, whereas the sensitivity analysis will be conducted using the PPS. A sensitivity analysis is conducted to evaluate whether the results of the FAS differ from those of the PPS, particularly when patients with poor treatment adherence are excluded.

Participants who meet the discontinuation criteria 2–5 after receiving the initial dose of SZC are considered non-responders (ie, participants who are not normokalaemic at visit 7).

Analysis of the secondary endpoints

The proportion of normokalaemic (3.5 mEq/L≤sK<5.0 mEq/L) participants at visit 4 will be calculated. The participants who meet the discontinuation criteria 2–5 after receiving the initial dose of SZC by visit 4 are considered non-responders (who were not normokalaemic at visit 4).

Summary statistics (number of participants, mean, SD, minimum, median and maximum) for the serum potassium level at visit 7 in each group will be calculated. The adjusted mean change from baseline and SE in each group, the intergroup difference in the adjusted mean change from baseline, and its 95% CI will be determined by conducting an analysis of covariance (ANCOVA) for intergroup comparisons. ANCOVA will be performed with each endpoint as the response variable, and the treatment group and covariates (each endpoint measured at baseline and other background characteristics) as exploratory variables. Missing values will not be imputed. The secondary endpoints will be analysed using the FAS.

Analysis of the exploratory endpoints

The exploratory endpoints will be analysed using the statistical methods described in the SAP.

Analysis of the safety endpoints

A table of all adverse events and diseases containing the number and proportion of participants will be created for each group and period (SZC initial dose period (visit 1 (day 0)–visit 2 (day 3)), group intervention period (visit 2 (day 3)–visit 7 (days 28–42)) and safety follow-up period (4 weeks after visit 7 (days 28–42)) separately using the safety analysis set to analyse the safety endpoints.

Compensation for health damage and insurance

This study is conducted within the scope of approved treatment using an authorised drug that is commonly administered. Therefore, as a rule, special compensation is not provided, even if health damage is caused by the study drug. The management of such cases is identical to that of any health damage or medical incident occurring during routine medical care.

Data management

Data management will be conducted by the data management group of EviPRO Co.

The investigators should manage the data of the study subjects using the central registration number (anonymisation). The information obtained from the study subjects is collected using CRFs and questionnaires (DDRQOL-R, BDHQ and GSRS) at each visit. If correction of the data is required, record the content, date and the reason for the correction onto the CRF. The investigators should confirm that all data including the corrected ones are accurate and complete.

The data submitted by the CRFs or the questionnaires are entered into the database using the central registration number by the individuals responsible for the data management and electronically preserved.

Central registration numbers are used to identify study subjects. When transferring data of the study subjects in electronic form, approval from the person responsible for data management is required. In the case of the study subjects who discontinued the study, tests are conducted as much as possible, and enter the data till the study discontinuation into the database.

The data handling committee decides all the data handling including missing data and data deviating from the protocol, under a masking circumstance not to identify the study subject, prior to statistical analyses. In principle, missing values will not be supplemented unless specified in the individual analysis.

Handling and storage of samples and information

This study is conducted in accordance with the Personal Information Protection Law and other legislation/law and regulation. Unique information (initial, carte number) of study subjects is stored securely in the research institutions, and information that allows a person outside the research institution to identify the study subjects (such as names, addresses, telephone numbers, etc) is not included in the CRFs and registration database.

A central registration number is used when the data centre inquires about the data of the study subject to the research institution.

Anonymised data collected for the analysis is kept stored for future secondary studies such as meta-analysis. If the anonymised data is used for other studies, approval from the ethics review board is required prior to the study implementation.

All data from the results of this study and the achievement belong to the principal investigator.

Monitoring

Monitoring is performed in accordance with the standard operating procedure of the monitoring by a third-party organisation, EviPRO Co. Regarding the quality of data, the principal investigator investigates the progress of the study through monitoring personnel periodically and the research conducted in compliance with the study protocol and the Ethical Guidelines for Medical and the Clinical Trial Act, and takes appropriate measures to prevent any deviation from the protocol. In addition, the monitoring personnel make a monitoring report and submit it periodically to the principal investigator. To ensure the safety of study subjects, adverse events and diseases are monitored and reported promptly.

Auditing

An audit is performed by a third-party organisation, EviPRO Co. An auditor performs it in accordance with the protocol and the standard operation procedure of audit of EviPRO Co to confirm whether this study has adhered to the study protocol appropriately as stated, by checking documents and records regarding the approval by the administrator of the medical institution, informed consent documents and forms, and the consistency of CRFs and medical records. The results will be reported by the auditor to the responsible investigator, the principal investigator and the heads of the participating institutions.

Modification of the study protocol

The principal investigator may consider modifications to the study protocol as needed.

When the modification of the study protocol is required, it is amended and revised based on the discussion of the principal investigator, the responsible investigators and the funder. After amendment or revision, the protocol should be promptly submitted to the certified review board to obtain approval.

Deviation from the protocol

When investigators need to deviate from or modify the study protocol to avoid an emergency risk to their study subjects or for other medically compelling reasons, the content and reason must be stated in the carte and the CRF. Investigators also monitor these study subjects as closely as possible during the study. Even if investigators deviate from the protocol, they must continue collecting the necessary information for this study as much as possible. For data handling, decisions are made by the data handling committees under blinded conditions.

Considerations for safety and disadvantages

Appropriate treatment and procedures are performed when adverse events occur, and the events are reported in accordance with 'Data Collection, Recording, and Reporting of Adverse Event and Disease'. To reduce burdens entailed on the study subjects, this study includes a minimum number of drugs inhibited to use or restricted the amount of use or when to use. Special blood tests are conducted using residual samples to reduce the burden caused by undergoing tests.

Study execution period

The study period is from 11 July 2023 (jRCT publication date) to 31 December 2026. The study registration period runs from 11 July 2023 (jRCT publication date) to 30 November 2025.

Ethics and dissemination

This study will be conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent will be obtained from all participants before commencing the study. This study has been approved by the Kyoto Prefectural University of Medicine Clinical Research Review Board and registered with the Japan Registry of Clinical Trials.

All data obtained from this study, including records of the results, raw data, and clinical study reports (including anonymised CRF), will be accessible to the principal investigator. However, the principal investigator agrees to provide the data to the funder upon request. The results of this study will be published in a peer-reviewed journal.

DISCUSSION

Dietary potassium restriction achieved through the implementation of a potassium-restricted diet prescribed by a registered nutritionist will be established as the standard treatment in this RCT. The non-inferiority of SZC to this treatment will be evaluated subsequently. Dietary restriction was selected as the comparator owing to the prevalence of its use. However, the current guidelines set forth by the KDIGO highlight a significant gap in the direct evidence supporting the efficacy of a potassium-restricted diet in managing hyperkalaemia. Moreover, KDIGO states that there is no direct evidence suggesting that increasing dietary potassium intake or liberalising potassium restrictions is safe.

Management of hyperkalaemia through dietary potassium restriction has some drawbacks. Increased dietary potassium, particularly from plant-based sources, potentially lowers the risk of mortality and disease progression in patients with CKD.[25] Therefore, whether increased potassium intake, particularly from plant-based diets and recipes, could decrease mortality risk and improve outcomes in these patients must be further evaluated. The increase in potassium intake facilitated by plant-based diets may aid in mitigating the progression of kidney disease.

The study included nutritional therapy in the control group, which complicates blinding, and this open-label design may introduce bias in the evaluation of the results. However, since the outcome is an objective measure for the normokalaemic participants, any potential bias in the interpretation of the results can be mitigated.

This trial specifically aims to include patients with T2DM owing to concerns that potassium-restricted diets could worsen glycaemic control.[26] Furthermore, dietary potassium restriction might lead to a poorer nutritional status, resulting in a decline in health-related quality of life (QOL).[27]

This trial aims to clarify the non-inferiority of SZC compared to potassium-restricted diets. By demonstrating the efficacy of SZC, this study suggests that integrating SZC into treatment regimens could facilitate the relaxation of strict dietary potassium limitations. This would improve glycaemic control and dietary QOL, which would be particularly advantageous for patients with T2DM, indicating a potential shift in the management paradigm for individuals at risk of developing hyperkalaemia.

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Patient and public involvement They will be given a simple summary of the study outcomes, written in Japanese, once the study has been completed.

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