Clinical Study Protocol	
Study Intervention	Sodium Zirconium Cyclosilicate (SZC), Lisinopril, and Valsartan
Study Code	D9488C00001
Version	2.0 (Amendment 1)
Date	08Jun2022

A Phase 3, International, Randomised, Double-blind, Placebo-controlled Study to Evaluate the Effect of Sodium Zirconium Cyclosilicate on Chronic Kidney Disease (CKD) Progression in Participants with CKD and Hyperkalaemia or at Risk of Hyperkalaemia

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Regulatory Agency Identifier Number(s):
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This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D9488C00001

Amendment Number: 1

Study Intervention: Sodium Zirconium Cyclosilicate (SZC), lisinopril, and valsartan

Study Phase: Phase 3

Short Title: Effect of Sodium Zirconium Cyclosilicate on Chronic Kidney Disease (CKD) Progression in Participants with CKD and Hyperkalaemia or at Risk of Hyperkalaemia

Acronym: STABILIZE-CKD

Study Physician name and contact information will be provided separately

International Coordinating Investigator:

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1 (version 2.0)	08Jun2022
Original protocol (version 1.0)	24Jun2021

Amendment 1 (Version 2.0) 08 June 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary reasons for this amendment are the following:

- Clarify that the primary endpoints (total and chronic eGFR slope) are co-primary and will be analysed as such, ie, both endpoints must be met for the study to be deemed successful.
- Implement the use of a race agnostic CKD-EPI eGFR formula (Delgado et al 2022, Inker et al 2021).
- Add a third stratification factor of SGLT2 inhibitor and/or finerenone use at randomisation.
- Allow inclusion of participants with Type 1 diabetes mellitus.
- Allow inclusion of participants on stable SGLT2 inhibitors or MRAs.

Changes to the protocol are listed below:

Section number and name	Description of change	Brief rationale
General	Corrected minor typographical and spelling errors throughout the protocol.	Improve the quality of the document.
Title Page	Added IND number 108951.	Provide IND regulatory identifier number.
1.1 (Synopsis)	Updated text to reflect changes made in the main body of the protocol.	Consistency with the main body of the protocol
2.1 (Study Rationale) 2.2.1 (Background Information on CKD) 2.2.3.1 (Facilitation of RAASi Treatment Optimisation) 11 (References)	Updated NICE 2014 link and reference to NICE 2021.	New NICE Guidelines for CKD (NG203) published 25 August 2021; last updated 24 November 2021.

Section number and name	Description of change	Brief rationale
1.3 (Schedule of Activities) Table 1 (Schedule of Activities During the Screening Period and Initiation and Run-in Phases) 4.1.1 (Screening Period [Up to 13 days])	Removed minimum interval of 7 days between screening Visit 1 and Visit 2. In Table 1, changed the study days for screening from -10 (window of ± 3 days) to -13 to -1 (no window).	Removed minimum interval of 7 days between Visit 1 and 2, so that Visit 2 can start as soon as results from the screening assessments and blood sampling are available.
1.3 (Schedule of Activities) Table 1 (Schedule of Activities During the Screening Period and Initiation and Run-in Phases) 4.1.2 (Initiation Phase [Up to 72 hours]) 4.1.3 (Run-in Phase [3 months/up to Day 90])	Removed requirement for participants who are hyperkalaemic at Visit 2 (Day 1) to have S-K measured at 24 hours post Day 1 dose (Visit 3a) during the initiation phase. Removed Visit 3a from the Schedule of Activities. NOTE: The original visit numbering will be retained.	To reduce participant and site burden.
1.3 (Schedule of Activities) Table 2 (Schedule of Activities During the Maintenance Phase and Follow-up)	Added footnote that "Week refers to the end of the week, eg: Week 6 is the end of the sixth week (ie, Day 43 [6 weeks × 7 days + 1 = 43]); Week 12 is the end of the twelfth week (ie, Day 85 [12 weeks × 7 days + 1 = 85]), etc."	Clarification.
3 (Objectives and Endpoints) Table 4 (Objectives and Endpoints) 4.2.2.1 (Rationale for the Primary Endpoints) 9.1 (Statistical Hypotheses)	The primary endpoints are co-primary. In Table 4, added footnote that "Both of the primary endpoints must be met in order for the study to be declared successful, ie, co-primary endpoints". In Section 9.1, revised as follows (bold indicates added text and strikethrough indicates deleted text): "Two **co-**primary hypotheses (corresponding to the evaluation of the difference in total and chronic eGFR slope, respectively) are defined in the study. ~~A fixed sequence MTP will be applied to the family of the primary hypotheses, with the hypothesis corresponding to difference in total slopes tested first and the~~	Total eGFR slope (measurements starting at randomisation) and chronic eGFR slope (measurements starting at 12 weeks after randomisation) will be evaluated as co-primary endpoints to mitigate the potential impact of the acute pharmacodynamic effects on efficacy assessments. The study will be deemed successful only if statistically significant differences in BOTH total and chronic eGFR slopes are demonstrated (using a 2-sided test and a significance level of 0.05 for both hypotheses).

Section number and name	Description of change	Brief rationale
	~~hypothesis corresponding to the difference in chronic slopes tested second.~~ Provided both **of the** primary hypotheses are rejected, the testing will proceed to the secondary hypotheses. ~~Similar to the primary hypotheses, a~~ **A** fixed sequence MTP will ~~also~~ be applied to the family of all secondary hypotheses, with the order in the sequence following the order specified in Table 4."	
4.2.3 (Rationale for Placebo Control During the Maintenance Phase)	Moved text in second paragraph to last paragraph and updated to "Potentially beneficial renoprotective treatments, including SGLT2 inhibitors **(ie, dapagliflozin and canagliflozin), finerenone, or any other medications in these 2 classes that are approved for CKD**, will not be withheld in the study" (bold indicates added text).	Moved text to last paragraph for better readability. Participants will receive SoC for any underlying medical conditions during the study. Dapagliflozin, canagliflozin, and finerenone are currently approved for CKD. Additionally, any other such medications approved for CKD subsequent to this amendment are allowed.
5.1 (Inclusion Criteria)	Criterion 2: Removed sentence specific to Japan, "For participants < 20 years of age and enrolled in Japan, a written informed consent should be obtained from the participant and his or her legally acceptable representative."	The age of adulthood in Japan is now 18 years, so consent of the participant's legally acceptable representative is no longer required.
5.1 (Inclusion Criteria) 8.1.1 (Assessments based on Laboratory Analyses; Table 9 [Laboratory Efficacy Variables]) 9.4.2.1 (Primary Endpoint[s]) 11 (References)	For inclusion in the study (criterion 3) and for the analysis of the primary endpoint, the race agnostic CKD-EPI eGFR formula (Delgado et al 2022, Inker et al 2021) will be used. The eGFR will also be calculated according to the original race adjusted CKD-EPI formula (Levey et al 2009) and may be used for sensitivity or supportive analyses	Revised per current recommendation of the NKF-ASN Task Force to use formulas that do not include race modifiers to estimate kidney function. Since there is a change in the eGFR CKD-EPI formula during the study, eGFR will be calculated using both formulas: the race agnostic CKD-EPI formula (Delgado et al 2022, Inker et al 2021) for the primary analysis and the race adjusted CKD-EPI formula (Levey et al 2009) for sensitivity or supportive analyses.

Section number and name	Description of change	Brief rationale
		Added literature references of Delgado et al 2022 and Inker et al 2021 to support CKD-EPI race agnostic eGFR formula.
5.1 (Inclusion Criteria)	Criterion 4 for UACR: Added "If the first sample does not fulfil eligibility criteria, a second sample can be obtained during the screening period; if so, the UACR measurement from the second sample must be within the eligibility range."	To mitigate variability in UACR measurements.
5.1 (Inclusion Criteria)	Criterion 8: "If on an SGLT2 inhibitor **(ie, dapagliflozin and canagliflozin), finerenone, or any other medications in these 2 classes that are approved for CKD**, the dose must have been stable for 3 months prior to screening (Visit 1)" (bold indicates added text).	Dapagliflozin, canagliflozin, and finerenone are currently approved for CKD. Criterion also applies to any other such medications approved for CKD subsequent to this amendment.
5.2 (Exclusion Criteria)	Criterion 3: Revised to "**Participants with a known history of** systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg ~~(confirmed by repeated measurement),~~ within 2 weeks prior to screening (Visit 1) **are excluded. In addition, any participant with systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg as measured at screening (Visit 1) and confirmed by repeated measurement is excluded**. Participants may be rescreened once blood pressure is controlled" (bold indicates added text; strikethrough indicates deleted text).	Revised to clarify exclusion of participants for uncontrolled blood pressure, ie, within 2 weeks prior to screening (history) or as measured at screening. Both conditions must not be met for participants to be eligible for the study.
5.2 (Exclusion Criteria)	Criterion 8: Removed exclusion of "Type 1 diabetes mellitus". NOTE: The original numbering of the exclusion criteria will be retained. (ie, 7, 9, 10, 11, etc).	To allow inclusion of Type 1 diabetes mellitus population in the study.

Section number and name	Description of change	Brief rationale
5.2 (Exclusion Criteria)	Criterion 22: Revised to "Treated with an MRA **not approved for CKD** within 3 months prior to screening (Visit 1)" (bold indicates added text).	Finerenone, a non-steroidal MRA, is approved for CKD. Participants on finerenone or any other MRAs approved for CKD are eligible for the study provided the dose is stable as per change to inclusion criterion 8.
5.2 (Exclusion Criteria)	Criterion 26: Added "Note: For participants taking a fixed combination of an ACEi or ARB with another agent (eg, calcium blockers or diuretics) as SoC, the investigator must make a judgment that it will be safe and efficacious for such participants to change to the study ACEi or ARB and to the other drug as separate agents."	All participants are required to switch to the study ACEi or ARB during the run-in phase. This note was added for investigator awareness to consider participants who are on the fixed combination of an ACEi or an ARB with another agent (eg, calcium blockers or diuretics) as SoC. Such participants are not excluded unless, based on investigator judgment, switching to the study ACEi or ARB and the other drug (eg, calcium blockers or diuretics) as separate agents (rather than a fixed combination) during the run-in phase could be a safety risk or may not be as efficacious.
6.1.1 (Investigational Products; Table 5 [Investigational Products])	Added lisinopril 2.5 and 10 mg and valsartan 80 mg unit dose strength(s) and a footnote that "In countries where lisinopril and valsartan will be supplied centrally through AstraZeneca, specific unit dose strengths will be confirmed to the countries".	To allow sourcing of lisinopril and valsartan at additional unit dose strengths.
6.1.1 (Investigational Products; Table 5 [Investigational Products])	Added footnote for single dose SZC and placebo "Further guidance and information are provided in the Pharmacy Manual". Added footnote for lisinopril and valsartan dosage levels that "the QD dose can be divided as long as the total daily dose is the prescribed dose, eg, valsartan 320 mg QD is equivalent to valsartan 160 mg BID." For SZC dosage level, revised to:	Clarification

Section number and name	Description of change	Brief rationale
	"Initiation Phase: S-K > 5 to ≤ 6.5 mmol/L (measured by L-Lab): Single dose contains 10 g SZC that should be suspended in 45 mL of water ~~and~~. **The 10 g SZC single dose should be** administered TID for up to 72 hours until normokalaemic (S-K 3.5-5.0 mmol/L)**; the total daily dose is 30 g SZC**" (bold indicates added text; strikethrough indicates deleted text).	
6.3.1 (The Process of Enrolment and Randomisation)	Added a third stratification factor for randomisation: SGLT2 inhibitor and/or finerenone use at randomisation.	To mitigate any baseline imbalance in the use of these agents.
6.5.1 (Prohibited and Restricted Concomitant Medication) Table 7 (Examples of Drugs that Should be Taken 2 hours Before or After SZC/Placebo to Avoid Possible Raised Gastric pH Drug Interactions)	Added section for "Interaction with Other Medicinal Products and Other Forms of Interaction" with subsections for "Effect of Other Medicinal Products on SZC" and "Effect of SZC on Other Medicinal Products". Updated text in subsection "Effect of SZC on Other Medicinal Products", including addition of tacrolimus. In Table 7, removed the following from the list of examples: • Anti-HIV drugs of amprenavir, delavirdine, and fosamprenavir • Antibiotics • antiepileptics • antimycotics of ioriconazole. • bisphosphonates • cardiac glycosides • immunosuppressants • intestinal anti-inflammatory agents • Iron preparations; • Tyrosine kinase inhibitors of acalabrutinib, gefitinib, pazopanib In Table 7, changed "antimyocotics" to "azole antifungals".	The list of examples in Table 7 is not exhaustive. The format, structure, and content of this section were updated to align with the SZC Core Data Sheet dated 22 March 2022.

Section number and name	Description of change	Brief rationale
8.2.2 (Vital Signs)	Removed requirement for 3 blood pressure readings separated by 2 minutes and for additional readings if first 2 readings differ by more than 5 mmHg.	To simplify the vital sign descriptions in the protocol.
9.2 (Sample Size Determination)	Added subsection for possible causes of missing data during the randomised treatment phase.	For clarity, to include details on the expected reasons for missing data, as well as a high-level description of the approaches for handling missing data in the analysis (with further details to be provided in the SAP)
9.4.2.1 (Primary Endpoint[s])	Removed the option of switching to a hypothetical intercurrent event strategy with respect to initiation of long-term potassium lowering agents.	This intercurrent event strategy will not be used for the primary efficacy analysis.
9.4.2.1 (Primary Endpoint[s])	Revised text to include additional details for covariance matrix, for sensitivity and subgroup analyses, and graphical illustrations of eGFR profiles over time.	For clarity, to include a high-level plan for sensitivity and subgroup analyses in the protocol (with further details to be provided in the SAP).
Appendix A 7 (Data Quality Assurance)	Last bullet, revised retention period for records and documents to 25 years (previously 15 years).	To align with updated AstraZeneca global retention and disposal schedule.
Appendix B2 (RAASi Dose Equivalence Table)	Added losartan starting dose of 25 mg and lisinopril starting dose of 2.5 mg to the list of examples in the footnote for doses that may differ per local labels.	Clarification.
Appendix B3 (Definitions of RAASi Adequate Dose)	Added footnote for adequate daily dose that “Normokalaemic participants with hypertension or primary glomerular diseases with nephrotic range proteinuria (> 3.5 g/24 hours) who are at high risk of hyperkalaemia, not taking maximal RAASi doses as per local label but currently receiving doses in the range considered adequate in this table can be included in the normokalaemic cohort if in the investigator’s judgment the current RAASi dose is not optimal for their condition. In these	To provide flexible wording so that such participants, eg, those with nephrotic range proteinuria who can benefit from higher doses of RAASi are not excluded because they are normokalaemic while receiving a dose within adequate range (but not maximal).

Section number and name	Description of change	Brief rationale
	participants, it is expected that RAASi doses will be up-titrated to maximal during the run-in phase.	
Appendix B3 (Definitions of RAASi Adequate Dose)	Added footnote for adequate daily dose column that "Where a range is indicated, any daily dose within that range is considered an adequate daily dose."	Clarification.
Appendix C (Instructions for Use of SZC/Placebo for Management of Serum Potassium During the Run-in and Maintenance Phases)	Added to the footnote to recheck S-K within 2 weeks if RAASi therapy is restarted at any dose or increased as per KDIGO 2020.	Clarification.

ACEi angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASN, American Society of Nephrology; BID, twice daily; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; HIV, human immunodeficiency virus; IND, investigational new drug; MRA, mineralocorticoid receptor antagonist; NICE, National Institute for Health and Care Excellence; MTP, multiple testing procedure; NKF, National Kidney Foundation; QD, once daily; RAASi, renin-angiotensin-aldosterone system inhibitor SGLT2, sodium-glucose cotransporter-2; SAP, statistical analysis plan; S-K, serum potassium; SoC, standard of care; SZC, sodium zirconium cyclosilicate; TID, three times daily; UACR, urine albumin-to-creatinine ratio.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase 3, International, Randomised, Double-blind, Placebo-controlled Study to Evaluate the Effect of Sodium Zirconium Cyclosilicate on Chronic Kidney Disease (CKD) Progression in Participants with CKD and Hyperkalaemia or at Risk of Hyperkalaemia

Short Title:

Effect of Sodium Zirconium Cyclosilicate on Chronic Kidney Disease (CKD) Progression in Participants with CKD and Hyperkalaemia or at Risk of Hyperkalaemia

Rationale:

Current clinical practice guidelines for patients with CKD recommend renin-angiotensin-aldosterone system inhibitor (RAASi) therapy, eg, angiotensin converting enzyme inhibitor (ACEi)/angiotensin II receptor blocker (ARB) therapy, as standard of care (SoC) to preserve kidney function and slow disease progression (KDIGO 2013, KDIGO 2020, NICE 2021, NKF 2012). However, hyperkalaemia limits the use of adequate ACEi/ARB therapy. The efficacy of sodium zirconium cyclosilicate (SZC) in correcting hyperkalaemia and maintaining normokalaemia long-term, irrespective of underlying morbidity (including CKD), and its favourable safety profile have been well demonstrated in the clinical programme. It is proposed that an efficacious and safe potassium binder such as SZC could facilitate the use of ACEi/ARB medications at doses that confer kidney outcomes benefit. Unlike other available treatments that bind potassium in the gastrointestinal tract (sodium polystyrene sulfonate, calcium polystyrene sulfonate, and patiromer), SZC has a high specificity for binding potassium ions and it possesses clinically important advantages over the currently available treatment options for hyperkalaemia. It is reasonable to assume that enabling the use of optimal ACEi/ARB therapy by SZC would confer renal benefit in treated patients. Further, the known effects of SZC on serum potassium (S-K), bicarbonate, and aldosterone levels would contribute to renoprotection.

This study will investigate whether SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan), is superior to placebo in slowing CKD progression (assessed as the reduction in participant's expected estimated glomerular filtration rate [eGFR] decline over time) in participants with hyperkalaemia or at high risk of hyperkalaemia.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan [a]), is superior to placebo in slowing CKD progression, assessed as the reduction in participant's expected eGFR decline over time	Co-primary [b] • Total slope: eGFR measurements starting at randomisation • Chronic slope: eGFR measurements starting at 12 weeks after randomisation
Secondary	
To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan [a]), is superior to placebo in reducing the incidence of the composite of kidney failure outcomes comprising: sustained ≥ 40% decline in eGFR, onset of ESKD, and death from kidney failure	• Time from randomisation to the first occurrence of any component in the composite of ° Sustained ≥ 40% decline in eGFR [c] ° Onset of ESKD (kidney transplantation, maintenance dialysis, or sustained low eGFR) [c] ° Death from kidney failure [c]
To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan [a]), is superior to placebo in reducing the incidence of lisinopril/valsartan dose decrease, in participants on lisinopril/valsartan at randomisation	• Time from randomisation to first lisinopril/valsartan dose decrease
To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan [a]), is superior to placebo in reducing albuminuria	• UACR measurements at scheduled visits after randomisation
To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan [a]), is superior to placebo in increasing serum bicarbonate levels	• Serum bicarbonate measurements at scheduled visits after randomisation
To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan [a]), is superior to placebo on maintenance of normokalaemia	• S-K level classification; normal (3.5-5.0 mmol/L) or non-normal (< 3.5 or > 5.0 mmol/L) at scheduled visits after randomisation

Objectives	Endpoints
Safety	
To assess the safety and tolerability of treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan [a]) as compared to placebo	Safety and tolerability will be evaluated in terms of AEs/SAEs, vital signs, clinical laboratory variables, and ECGs Assessments related to AEs cover: • Occurrence/frequency • Relationship to study intervention as assessed by the investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of study intervention

[a] In case of a local market valsartan shortage, irbesartan will be temporarily used instead.

[b] Both of the primary endpoints must be met in order for the study to be declared successful, ie, co-primary endpoints.

[c] Levin et al 2020; see Section 8.1.2.

ACEi, angiotensin converting enzyme inhibitor; AE, adverse event; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; SAE, serious adverse event; S-K, Serum potassium; SZC, Sodium zirconium cyclosilicate; UACR, urine albumin-to-creatinine ratio.

Overall Design

This is a Phase 3, international, randomised withdrawal, double-blind, parallel-group, placebo-controlled study, to evaluate the effect of SZC as adjunct to RAASi therapy (lisinopril or valsartan) in slowing CKD progression in participants with CKD and hyperkalaemia or at risk of hyperkalaemia.

Specifically, the study will include participants with hyperkalaemia (S-K > 5.0 to ≤ 6.5 mmol/L by central laboratory) who are on adequate or limited RAASi therapy due to hyperkalaemia, and participants with normokalaemia (S-K ≥ 3.5 to ≤ 5.0 mmol/L by central laboratory) who are on limited RAASi therapy due to high risk of hyperkalaemia. High risk of hyperkalaemia is defined as (1) participants with a previous medical history or record of hyperkalaemia within the prior 24 months who are on limited RAASi therapy despite indication in CKD; (2) participants in whom RAASi therapy is indicated in CKD but are on limited RAASi therapy and have S-K ≥ 4.7 to ≤ 5.0 mmol/L; and (3) participants in whom RAASi therapy has been discontinued or reduced to suboptimal doses because of hyperkalaemia.

The study will be conducted at up to 250 study sites in up to 16 countries.

Screening Period (Up to 13 days)

During the screening period, after signed informed consent is obtained, data required for determination of eligibility for the study will be collected and inclusion/exclusion criteria evaluated. Participants who fulfil the study eligibility criteria may proceed to the initiation phase. Participants who do not fulfil the study eligibility criteria are screen failures and may be rescreened once.

Initiation Phase (Up to 72 hours)

No changes will be made to the ACEi/ARB therapy during the initiation phase. The initial dosing of SZC will be based on the participant's S-K as measured by local laboratory on the same day as, or within 24 hours prior to, Day 1 (Visit 2); the S-K results MUST be available before any other Visit 2 procedures/assessments are performed.

Participants who are hyperkalaemic (S-K > 5.0 to ≤ 6.5 mmol/L [local laboratory]) will receive 10 g SZC three times daily (TID) starting on Day 1 (Visit 2). S-K will be measured by local laboratory at 48 hours (Day 3; Visit 3b) and subsequently at 72 hours (Day 4; Visit 3c) if normokalaemia (S-K ≥ 3.5 to ≤ 5.0 mmol/L) has not been previously achieved.

In case the S-K result is not available for up to 24 hours after sample collection, the participant will be notified by phone as soon as possible after the S-K results are available, and the following instructions should be followed for SZC:

- Day 3 (Visit 3b): if the 48-hour S-K result is not available, the participant will take SZC 10 g TID for one additional day.
- Day 4 (Visit 3c): if the 48-hour S-K is > 5 to ≤ 6.5 mmol/L and the 72-hour S-K is not available, the participant will take SZC 10 g once daily (QD) for one day.

If normokalaemia is achieved after 48 or 72 hours of treatment with SZC, the participant will proceed to the run-in phase, during which SZC dosing will be initiated at 10 g QD. Participants who do not achieve normokalaemia after 72 hours of treatment will undergo a follow-up visit at 7 (± 2) days after the participant's last dose and exit the study.

Participants who are normokalaemic (S-K ≥ 3.5 to ≤ 5.0 mmol/L [local laboratory]) will receive SZC 5 g QD starting on Day 1 (Visit 2) for 48 hours. S-K will be measured by local laboratory at 48 hours (Day 3; Visit 3b). In case the S-K result is not available for up to 24 hours after sample collection, the participant will continue with a third day of SZC 5 g QD and will be notified by phone as soon as possible after the 48-hour S-K results are available.

If normokalaemia is maintained after 48 hours of treatment with SZC, the participant will proceed to the run-in phase, continuing to receive 5 g QD. Participants who do not maintain normokalaemia after 48 hours of treatment will undergo a follow-up visit at 7 (± 2) days after

the participant's last dose and exit the study. NOTE: Visit 3c is not applicable for participants who are normokalaemic at Visit 2.

Run-in Phase (3 months/up to Day 90)

As soon as possible after the participant is confirmed to be normokalaemic at the end of the initiation phase (based on local laboratory S-K results from Visits 3b or 3c), the participant will enter the run-in phase (Visit 3d).

Participants will receive open-label SZC and lisinopril or valsartan during the run-in phase.

Upon entering the run-in phase:

- Participants who are not on ACEi or ARB therapy will be started on lisinopril or valsartan on the first day of the run-in phase. The choice of drug class is per investigator judgment. One of the following starting doses will be used: lisinopril 10 mg QD (or 5 mg QD if eGFR ≥ 10 to ≤ 30 mL/min/1.73m^2 or if the participant is taking diuretics), or valsartan 80 mg QD.
- Participants who are on other ACEi or ARB therapy will be changed to lisinopril or valsartan on the first day of the run-in phase, keeping the corresponding drug class, ie, the ACEi will be changed to lisinopril and the ARB to valsartan. See Appendix B 1 and Appendix B 2 for guidance on the dosing equivalences among RAASi drugs and lisinopril/valsartan.
- Participants who are on lisinopril or valsartan will continue treatment at the same dose.

A participant cannot receive both lisinopril and valsartan simultaneously and should not take any other ACEi or ARB concomitantly with lisinopril or valsartan.

The aim of the run-in phase is to increase ACEi or ARB therapy stepwise to their maximum doses using lisinopril or valsartan as per local labels (see Sections 6.6.2 and 6.6.3).

At the end of the run-in phase (Day 90 [±3 days], Visit 6a), S-K will be measured by local laboratory. The participant will continue to receive the current prescribed dose of SZC until the S-K result is available. If normokalaemic (S-K ≥ 3.5 to ≤ 5.0 mmol/L), the participant will proceed to the maintenance phase of the study. If not normokalaemic, the participant will undergo a follow-up visit at 7 (± 2) days after the participant's last dose and exit the study.

NOTE: The study is designed to use valsartan as the ARB adjunct to SZC. However, if an actual shortage of valsartan in a local market jeopardises the ability of participants to enter or continue in the study, valsartan can be temporarily substituted with irbesartan until the shortage is resolved. See Appendix E for information on the use of irbesartan.

Maintenance Phase, Double-blind, Parallel Groups (24 months/104 weeks)

As soon as possible after the participant is confirmed to be normokalaemic at the end of the run-in phase (based on local laboratory S-K results from Visit 6a), the participant will enter the maintenance phase. The date of randomisation is Day 1 of the maintenance phase (Visit 6b).

Participants will be randomised in a 1:1 ratio to receive either SZC or matching placebo. The starting dose of SZC/placebo will be the same dose as the last dose of SZC during the run-in phase. Lisinopril and valsartan will be continued at the same doses assigned at the end of the run-in phase.

Two safety visits will occur 2 and 7 (±1) days after randomisation and will include evaluation of S-K by local laboratory. The investigator must ensure that the choice of date for randomisation will allow for these 2 safety visits to occur 2 and 7 (±1) days after randomisation, respectively. Participants will then be monitored for approximately 24 months (through Week 104) for efficacy and safety assessments. A final safety follow-up visit will be conducted at Week 105, one week after the participant's last dose, after which the participant will exit the study.

Disclosure Statement:

This is a treatment study with single arm open-label initiation and run-in phases followed by a randomised withdrawal maintenance phase with two parallel arms that is blinded to the participant, investigator, and Sponsor.

Number of Participants:

Approximately 3000 participants will be enrolled (screened) to achieve approximately 1500 participants receiving at least one dose of SZC during the initiation phase, consequently leading to a target of 1360 participants randomly assigned to SZC or placebo.

Note that "Enrolled" refers to a participant's, or their legally acceptable representative's, agreement to participate in the study following completion of the informed consent process.

Intervention Groups and Duration:

A participant is expected to be in the study for approximately 28 months, which includes up to 13 days for the screening period, 27 months for the intervention period, and 1 week for follow-up. The 27-month intervention period of the study consists of 3 phases, an initiation phase (up to 72 hours), a run-in phase (3 months/up to Day 90), and a maintenance phase (24 months/104 weeks).

The dose levels for SZC/placebo and lisinopril/valsartan that will be used in the study are:

- SZC: 5 g SZC every other day (QOD) by mouth (PO) or 5, 10, or 15 g SZC QD PO

- Placebo: 5 g placebo QOD PO or 5, 10, or 15 g placebo QD PO
- Lisinopril: 5, 10, 20, or 40 mg QD PO
- Valsartan: 40, 80, 160, 320 mg QD PO

See Section 6.6 for instructions on dose modification, including monitoring lisinopril/valsartan titration (Section 6.6.1) and management of abnormalities of S-K (Appendix C), lisinopril/valsartan dosing upon entry to and during the run-in phase (Section 6.6.2), strategy for lisinopril/valsartan up-titration during run-in phase visits (Section 6.6.3), use of SZC/placebo for management of S-K immediately after randomised withdrawal, ie, up to Week 6 of maintenance phase (Section 6.6.4), and additional unscheduled visits for titration of lisinopril/valsartan (Section 6.6.5).

Data Monitoring Committee:

An independent Data Monitoring Committee that is unblinded to treatment allocation will be responsible for safeguarding the interests of the participants throughout the study.

Statistical Methods

Statistical Hypotheses

Statistical testing will be performed for all primary and secondary hypotheses. In all cases, the null hypothesis will be that of no difference between the treatment arms (SZC vs placebo). The family-wise Type I error rate will be controlled in the strong sense over the families of the primary and the secondary hypotheses.

Two co-primary hypotheses (corresponding to the evaluation of the difference in total and chronic eGFR slope, respectively) are defined in the study. Provided both of the primary hypotheses are rejected, the testing will proceed to the secondary hypotheses. A fixed sequence MTP will be applied to the family of all secondary hypotheses, with the order in the sequence following the order specified in the Objectives and Endpoints table above.

Both of the co-primary hypotheses will be tested at a two-sided significance level of 0.05. In accordance with the fixed sequence MTP, significance for a hypothesis corresponding to a secondary endpoint will be declared if the corresponding two-sided p-value is smaller than 0.05, provided that all other preceding hypotheses in the sequence have been rejected.

Sample Size Determination

To allow for up to 20% missing eGFR data, it is planned to randomise 1360 participants to SZC or placebo. Assuming a two-sided test of a difference in slopes based on a linear mixed model, with a two-sided significance level of 0.05, is performed, approximately 1220 participants with complete eGFR data will provide a power of 91% for the evaluation of total slope. The power for the chronic slope will be approximately 85%. The evaluation of the chronic slope is assumed to start at 12 weeks. See Section 9.2 for further details including

assumptions for variability of eGFR measurements and missing data that form the basis of the sample size calculations.

Populations for analyses

Population/analysis set	Description
Enrolled	All participants who sign the ICF.
Safety analysis set, initiation phase (SAS-IP)	All participants receiving at least one dose of SZC during the initiation phase.
Safety analysis set, run-in phase (SAS-RIP)	All participants receiving at least one dose of SZC during the run-in phase.
Safety analysis set, maintenance phase (SAS-MP)	All randomised participants receiving at least one dose of SZC or placebo during the maintenance phase. Participants erroneously receiving incorrect SZC or placebo will be analysed according to the treatment arm they were randomised to.
Full analysis set (FAS)	All randomised participants.

ICF, informed consent form; SZC, Sodium zirconium cyclosilicate.

Efficacy:

The analysis of both primary and secondary efficacy endpoints will be performed according to the intention-to-treat principle and will be based on all randomised participants, regardless of whether they did or did not receive treatment or had any protocol deviations.

To evaluate both primary objectives, a linear mixed effects model will be used, with the eGFR values obtained at and after randomisation (total slope) and at and after 12-week visit (chronic slope) for a participant at a particular visit as the dependent variable. The following covariates will be included in the fixed effects part of the model:

- Time since randomisation
- Treatment
- Time and treatment interaction

Other covariates, as appropriate, might also be included and will be specified in the Statistical Analysis Plan. In addition, 2 random effects, intercept and time since randomisation, will be incorporated within a participant, with an underlying assumption of an unstructured covariance matrix between the two. A covariance matrix that assumes independence for the distribution of the residuals within each participant, but allows for different variability for different time points, will be applied, with a more general structure (eg, unstructured) used if issues with the model fit are encountered. An unstructured covariance matrix will also be assumed for the distribution of the residuals within each participant. The null hypothesis of no difference between SZC and placebo will be tested by considering the fixed effect of time and treatment interaction term in the model above (ie, the difference in slopes between the

2 treatment arms). The estimates of the slopes obtained from the model, as well as the difference between the two, and the corresponding SD estimates, will be presented. For the difference, the two-sided 95% confidence intervals and p-values will also be provided.

A number of sensitivity analyses of the primary endpoints will be performed. These will include, but might not be limited to, the following:

- A two-slope model (acute and chronic) with knot at 12 weeks post-randomisation (ie, using the same interval for the chronic slope as is utilised in the primary analysis). From this, estimates of the total and the chronic slope will be obtained. The purpose of this analysis is to evaluate the sensitivity of the results to the choice of approaching the primary objective via two separate models rather than a single combined one.
- A series of two-slope models (acute and chronic) with varying position of knots (the times of connection between acute and chronic slopes) other than 12 weeks. The purpose of this analysis is to evaluate the impact of the choice of 12 weeks as the start of the chronic eGFR profile on the estimate of the treatment effect.
- A shared parameter model that jointly models the eGFR profiles and time to ESKD or death. The purpose of this analysis is to evaluate the potential impact that the possibly informative drop-out caused by these 2 events has on the estimate of the effect of SZC.
- A tipping point analysis to explore the potential impact of data that are missing due to participant being lost to follow-up or entering a modified follow-up that precludes collection of eGFR measurements.
- A repeated measures model that includes the same covariates as the main analysis and utilises an unstructured (marginal) covariance matrix to reflect the dependence between observations obtained at different timepoints for the same participant.
- Same model as the one utilised for the main analysis, where missing eGFR values will be imputed as follows: if a participant is considered to enter ESKD through initiation of dialysis or kidney transplant, but no corresponding eGFR value is available, this will be imputed to a value that is less than 15 mL/min/1.73m^2.

In addition, graphical illustrations of eGFR profiles over time, eg, a scatter plot of eGFR values with a non-parametric smoothing curve in the respective treatment arm, will be provided to illustrate the plausibility of the assumption of a linear eGFR decline and the potential presence of acute effects.

The consistency of effect across subgroups defined by inclusion criterion 5 (Section 5.1) will be evaluated for the primary endpoint by obtaining effect estimates in each of these, along with the p-values for the test of the corresponding interaction. In addition, if the size of the subgroups allows, the subgroups in which the consistency of the main results will be evaluated will include, but might not be limited to the following: geographic region; diabetes at randomisation (yes/no); eGFR classification at randomisation; UACR classification at randomisation; adequate RAASi dose at screening (yes/no); adequate RAASi dose at randomisation (yes/no); CKD aetiology; SGLT2 inhibitor and/or finerenone use at

randomisation (yes/no). Further details of the subgroup analyses plan, including full specification of the groupings, will be provided in the SAP.

The eGFR will be calculated according to the race agnostic CKD-EPI formula (Delgado et al 2022, Inker et al 2021) for the main analysis of the primary endpoint. The eGFR will also be calculated according to the original race adjusted CKD-EPI formula (Levey et al 2009) and may be used for sensitivity or supportive analyses.

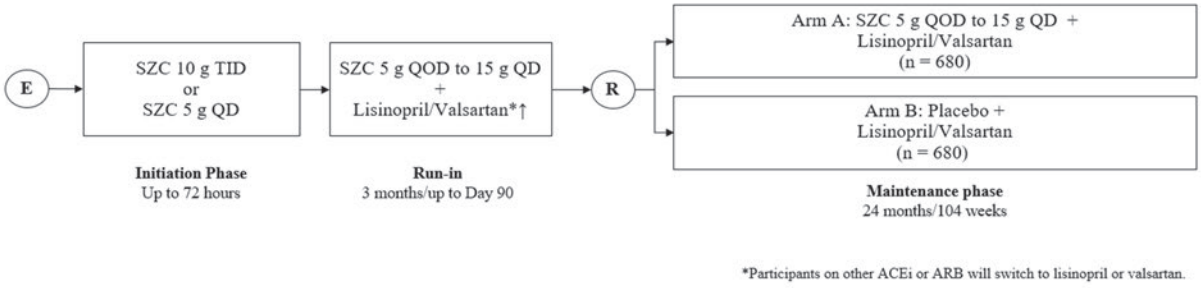
Safety

Safety analyses will be performed separately for the different phases of the study using the 3 safety sets defined above, as appropriate. Safety data will be presented primarily using descriptive statistics, by treatment arm and study phase.

1.2 Schema

The study design is presented in Figure 1.

Figure 1 Study Design



ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; E, eligibility criteria met; n, number of participants; QD, once daily; QOD, every other day; R, randomisation; SZC, Sodium zirconium cyclosilicate; TID, three times daily.

1.3 Schedule of Activities

The schedule of activities (SoA) during the screening period and initiation and run-in phases of the study is presented in Table 1. The SoA during the maintenance phase and at the final follow-up visit is presented in Table 2.

Table 1 Schedule of Activities During the Screening Period and Initiation and Run-in Phases

Study period/phase	Screening	Initiation [a]			Run-in [b]				FU [c]	ED [d]	ESD [e]	Details in CSP section or appendix
Visit	**1**	**2**	**3b**	**3c [f]**	**3d**	**4**	**5**	**6a**				
Study day	**-13 to -1**	**1**	**3 48h**	**4 72h**	**2, 3, 4, or 5**	**13**	**51**	**90**				
Window (days)						**± 3**	**± 3**	**± 3**				
Informed consent prior to any study-specific procedures	X											5.1, A 3
Enrolment in IRT/RTSM	X											6.3
SZC accountability [g]		X [h]			X	X	X	X [i]	X [i]	X [i]	X [i]	6, 6.2, 6.3, 6.4
Change to lisinopril/valsartan and assign dose					X							4.1.3, 6.6.2 B 1, B 2
Lisinopril/valsartan accountability [g]					X [h]	X	X	X	X [i]	X [i]	X [i]	6, 6.2, 6.3, 6.4
Participant population												
Inclusion/exclusion criteria	X											5.1, 5.2
Demography	X											8.9.2
Medical history	X											8.9.2
Height	X											8.2.1
Weight	X							X	X	X		8.2.1
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	6.5
AEs and other safety evaluations												
AEs/SAEs	X [j]	X	X	X	X	X	X	X	X	X	X	8.3
12-lead ECG	X											8.2.3
Vital signs (pulse and BP)	X	X	X	X	X	X	X	X	X	X		8.2.2
Complete physical examination	X											8.2.1
Brief physical examination						X	X		X	X		8.2.1

Table 1 Schedule of Activities During the Screening Period and Initiation and Run-in Phases

Study period/phase	Screening	Initiation [a]			Run-in [b]				FU [c]	ED [d]	ESD [e]	Details in CSP section or appendix
Visit	1	2	3b	3c [f]	3d	4	5	6a				
Study day	-13 to -1	1	3 48h	4 72h	2, 3, 4, or 5	13	51	90				
Window (days)						± 3	± 3	± 3				
Laboratory assessments												
Clinical chemistry, including eGFR (C-lab)	X											8.1.1, 8.2.4.1
Haemotology (C-lab)	X											8.2.4.1
S-K and S-Cr (L-lab) [k]		X [l]	X	X	X	X	X	X	X	X		8.9.1
UACR (C-lab)	X											8.1.1
Serum pregnancy test (POCBP only) (C-Lab)	X											8.2.4.1

[a] See Section 4.1.2 for details on the initiation phase.

[b] See Section 4.1.3 for details on the run-in phase.

[c] For participants who discontinue treatment during the initiation or run-in phases, the FU visit will be done 7 (± 2) days after the last dose of SZC during the initiation or run-in phases.

[d] For details regarding early treatment discontinuation, see Section 7.1.

[e] For details regarding ESD, see Section 7.2.

[f] Participants who are normokalaemic at Visit 2 (Day 1) will not attend Visit 3c.

[g] Accountability refers to collection/dispensation/re-dispensation of study intervention (SZC and lisinopril/valsartan).

[h] Dispensation only.

[i] Collection only.

[j] Only SAEs will be collected during screening.

[k] S-K and S-Cr samples collected and analysed by local laboratory at study visits and as part of routine clinical practice can also be used to adjust doses of SZC and lisinopril/valsartan.

[l] The S-K (L-lab) **result must** be available prior to performing any other assessments/procedures on Day 1. If necessary, the sample can be drawn 24 hours prior to Day 1 to ensure result is available on Day 1. If S-K is > 6.5 mmol/L or < 3.5 mmol/L, the participant is not eligible for the study (ie, screen failure) and must not be dosed (see Section 5.2, exclusion criterion 18 and Section 5.4).

AE, adverse event; BP, blood pressure; C-lab, central laboratory; CSP, clinical study protocol; ECG, electrocardiogram; ED, early discontinuation; ESD, early study discontinuation; eGFR, estimated glomerular filtration rate; FU, follow-up; h, hours; IRT/RTSM, interactive response technology/randomisation and trial supply management; L-lab, local laboratory; POCBP, participants of childbearing potential; SAE, serious adverse event; S-Cr, serum creatinine; S-K, serum potassium; SZC, Sodium zirconium cyclosilicate; UACR, urine albumin-to-creatinine ratio.

Table 2 Schedule of Activities During the Maintenance Phase and Follow-up

Study phase	Maintenance phase [a]																	FU	ED[d]	ESD[e]	Details in CSP section or appendix
Visit	6b [b]	7 [c]	8 [c]	9	10	11	12	13	14	15	16	17	18	19	20	21	22				
Maintenance phase day/week	Day			Week [f]																	
	1(R)	3	8	6	12	16	20	24	34	46	57	69	80	92	96	100	104	105			
Window (days)			± 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 2			
Randomisation in IRT/RTSM	X [b]																				6.3
SZC/placebo accountability [g]	X [h]			X	X	X	X	X	X	X	X	X	X	X	X	X	X [i]		X [i]	X [i]	6, 6.2, 6.3, 6.4
Lisinopril/ valsartan accountability [g]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X [i]		X [i]	X [i]	6, 6.2, 6.3, 6.4
Participant population																					
Weight										X							X	X	X		8.2.1
Concomitant medications	X	X	X	X	X	X	X	X		X		X		X	X	X	X	X	X	X	6.5
AEs and other safety evaluations																					
Complete physical examination	X																				8.2.1
Brief physical examination				X	X	X	X	X		X		X		X	X	X	X	X	X		8.2.1
12-lead ECG	X																				8.2.3
Vital signs (pulse and BP)	X	X	X	X	X	X	X	X		X		X		X	X	X	X	X	X		8.2.2
AEs/SAEs	X	X	X	X	X	X	X	X		X		X		X	X	X	X	X	X	X	8.3

Table 2 Schedule of Activities During the Maintenance Phase and Follow-up

Study phase	Maintenance phase [a]																	FU	ED[d]	ESD[e]	Details in CSP section or appendix
Visit	6b [b]	7 [c]	8 [c]	9	10	11	12	13	14	15	16	17	18	19	20	21	22				
Maintenance phase day/week	Day			Week [f]																	
	1(R)	3	8	6	12	16	20	24	34	46	57	69	80	92	96	100	104	105			
Window (days)			± 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 2			
Laboratory assessments																					
Clinical chemistry, including eGFR (C-lab)	X			X	X	X	X	X		X		X		X	X	X	X	X			8.1.1, 8.2.4.1
Haematology (C-lab)	X									X											8.2.4.1
Clinical chemistry (L-lab) [j]		X	X	X				X		X		X		X			X	X	X		8.2.4.2, 8.9.1
UACR (C-lab)	X							X									X				8.1.1

[a] See Section 4.1.4 for details on the maintenance phase.

[b] The participant must be confirmed normokalaemic (L-lab S-K) at the end of the run-in phase (Visit 6a) prior to randomisation. The date of randomisation is Day 1 of the maintenance phase. All assessments/procedures designated at this visit should be performed prior to randomising the subject, except for SZC/placebo and lisinopril/valsartan accountability.

[c] The investigator must ensure that Visits 7 and 8 occur 2 and 7 (±1) days after randomisation, respectively.

[d] For details regarding early treatment discontinuation, see Section 7.1.

[e] For details regarding ESD, see Section 7.2.

[f] Week refers to the end of the week, eg: Week 6 is the end of the sixth week (ie, Day 43 [6 weeks × 7 days + 1 = 43]); Week 12 is the end of the twelfth week (ie, Day 85 [12 weeks × 7 days + 1 = 85]), etc.

[g] Accountability refers to collection/dispensation/re-dispensation of study intervention (SZC/placebo and lisinopril/valsartan).

[h] Dispensation only.

[i] Collection only.

[j] The minimum local laboratory clinical chemistry tests for safety monitoring will include sodium, potassium, bicarbonate, chloride (electrolytes) and urea nitrogen and creatinine (kidney). The S-K and S-Cr samples collected and analysed by local laboratory at study visits and as part of routine clinical practice can also be used to adjust doses of SZC/placebo and lisinopril/valsartan.

AE, adverse event; BP, blood pressure; C-lab, central laboratory; CSP, clinical study protocol; ECG, electrocardiogram; ED, early discontinuation; ESD, early study discontinuation; eGFR, estimated glomerular filtration rate; FU, follow-up; IRT/RTSM, interactive response technology/randomisation and trial supply management; L-lab, local laboratory; POCBP, participants of childbearing potential; R, randomisation; SAE, serious adverse event; S-Cr, serum creatinine; S-K, serum potassium; SZC, Sodium zirconium cyclosilicate; UACR, urine albumin-to-creatinine ratio.

2 INTRODUCTION

Sodium zirconium cyclosilicate, hereafter abbreviated as SZC, is an oral, non-polymer inorganic cation-exchanger that represents a novel therapy for the treatment of hyperkalaemia. SZC selectively captures potassium ions in exchange for sodium and hydrogen ions in the gastrointestinal tract, thereby reducing S-K concentration and removing potassium from the body through increased faecal excretion. SZC exerts its effect locally and it is not absorbed systemically. Clinical use is therefore not associated with systemic toxicity. The formulation developed for therapeutic use is an insoluble, free-flowing, odourless, tasteless, white powder for oral suspension.

2.1 Study Rationale

Current clinical practice guidelines for patients with CKD recommend RAASi therapy, eg, ACEi/ARB therapy, as SoC to preserve kidney function and slow disease progression (KDIGO 2013, KDIGO 2020, NICE 2021, NKF 2012). However, hyperkalaemia limits the use of adequate ACEi/ARB therapy. The efficacy of SZC in correcting hyperkalaemia and maintaining normokalaemia long-term, irrespective of underlying morbidity (including CKD), and its favourable safety profile have been well demonstrated in the clinical programme. It is proposed that an efficacious and safe potassium binder such as SZC could facilitate the use of ACEi/ARB medications at doses that confer kidney outcomes benefit. Unlike other available treatments that bind potassium in the gastrointestinal tract (SPS, CPS, and patiromer), SZC has a high specificity for binding potassium ions and it possesses clinically important advantages over the currently available treatment options for hyperkalaemia. It is reasonable to assume that enabling the use of optimal ACEi/ARB therapy by SZC would confer renal benefit in treated patients. Further, the known effects of SZC on S-K, bicarbonate, and aldosterone levels would contribute to renoprotection.

This study will investigate whether SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan), is superior to placebo in slowing CKD progression (assessed as the reduction in participant's expected eGFR decline over time) in participants with hyperkalaemia or at high risk of hyperkalaemia.

2.2 Background

2.2.1 Background Information on CKD

Chronic kidney disease is highly prevalent and an important contributor to morbidity and mortality around the world (GBD Chronic Kidney Disease Collaboration 2020). Approximately 850 million people have kidney disease worldwide and 1.2 million people died from it in 2017 (Jager et al 2019). The number of people receiving kidney replacement therapy exceeds 2.5 million globally and is projected to double to 5.4 million by 2030. However, in many countries, there is a shortage of kidney replacement services. In the US,

37 million people (15% of the adult population) are estimated to have CKD and over 726 thousand people are living with ESKD (CDC 2019).

People with CKD are at high risk for CV disease, and the presence of CKD often complicates treatment and worsens prognosis of CV disease. The SoC for slowing the progression of CKD includes treatment with ACEi/ARB therapy (KDIGO 2013, KDIGO 2020, NICE 2021, NKF 2012).

2.2.2 Background Information on SZC

The efficacy of SZC in correcting hyperkalaemia and maintaining normokalaemia long term, irrespective of underlying morbidity, and its favourable safety profile have been well documented in the clinical programme.

SZC has a rapid onset of effect and maintains normokalaemia for up to 12 months. SZC is highly selective for potassium ions and its use is not associated with any clinically significant changes in the concentrations of other electrolytes such as calcium or magnesium. Clinical studies in participants with hyperkalaemia consistently demonstrated that initial treatment with SZC 10 g TID for 24 hours up to 72 hours resulted in clinically meaningful S-K reduction with a majority of participants achieving normokalaemia within 24 to 48 hours. Moreover, participants with higher baseline S-K levels had greater reductions in S-K levels. Onset of efficacy was rapid with S-K reduction observed as early as 1 hour after dose intake. After correction of hyperkalaemia, continued maintenance treatment for 28 days with SZC 5 g, 10 g, or 15 g QD resulted in continued effective control of S-K within the normokalaemic range. The proportion of participants who remained normokalaemic at the end of treatment with SZC 5 g, 10 g, and 15 g QD increased dose-dependently (range: 71% to 85%) and was superior to placebo. In addition, long-term maintenance treatment of up to 12 months with SZC utilising a dose titration scheme with the starting dose of 5 g QD or 10 g QD, titrated to a maximum of 15 g QD or a minimum of 5 g QOD was effective in maintaining normokalaemia in the majority of participants.

The clinical studies included a broad population of participants with hyperkalaemia with a wide range of concomitant diseases and treatments including CKD, hypertension, heart failure, and/or diabetes, as well as concomitant RAASi treatment, recognizing that many patients with hyperkalaemia have a variety of underlying conditions; approximately 78% of participants in Study D9480C00002 (HARMONIZE Global; NCT02875834) and 66% of participants in Study ZS-004 (NCT02088073) had CKD and hyperkalaemia (Zannad et al 2020, Kosiborod et al 2014). Overall, SZC reduced S-K and maintained normokalaemia independently of the underlying conditions associated with hyperkalaemia, demonstrating similar efficacy in participants with CKD, heart failure, and diabetes mellitus, as well as in participants receiving concomitant RAASi treatment. In addition, SZC demonstrated similar efficacy across demographic subgroups, including age, sex, race, and geographic region.

Overall, the SZC clinical programme showed treatment with SZC to be safe and well tolerated. The overall rate of AEs and laboratory abnormalities were low and generally similar to those observed with placebo. Identified adverse drug reactions for SZC are oedema-related events (oedema, oedema peripheral, generalised oedema, fluid overload, fluid retention, hypervolaemia, localised oedema, and peripheral swelling) and hypokalaemia (see Section 2.3.1).

A detailed description of the chemistry, pharmacology, efficacy, and safety of SZC is provided in the Investigator's Brochure.

2.2.3 Rationale for the Use of SZC in Patients with CKD

2.2.3.1 Facilitation of RAASi Treatment Optimisation

Blockade of the RAAS with an ACEi or ARB remains the first-line therapy for both kidney and CV protection in patients with CKD (KDIGO 2013, KDIGO 2020, NICE 2021, NKF 2012). Optimal ACEi/ARB doses in CKD patients conferred further kidney outcomes benefit as compared to suboptimal doses (ROAD trial; Hou et al 2007).

However, RAASi treatment often leads to hyperkalaemia, and down-titration or discontinuation of ACEi/ARB therapy is common following an episode of hyperkalaemia and occurs in 38% and 47% of patients with mild and moderate hyperkalaemia (Epstein 2016). Down-titration or discontinuation of ACEi/ARB treatment in CKD patients are both similarly associated with an approximately doubling of mortality compared with patients maintained on maximum dose ACEi/ARB treatment (Epstein 2016). The number of patients not attaining optimal ACEi/ARB therapy or an optimal dosing regimen is significant, as shown in studies of patients with moderate to severe CKD in which approximately 30% of patients were not prescribed ACEi/ARB treatment (Shirazian et al 2015, Yildirim et al 2012). A study of CKD and heart failure patients receiving ACEi/ARB therapy also showed that 73.2% were on a suboptimal ACEi/ARB dose (Polson et al 2017).

2.2.3.2 Increased Serum Bicarbonate

SZC has also been found to consistently raise serum bicarbonate and this effect is likely to be due to ammonium binding and elimination in the gut by SZC (Ash et al 2015, Roger et al 2020). The observed increase in bicarbonate is a potential mechanism for nephroprotection by ameliorating acidosis, which is common in patients with CKD. Metabolic acidosis has been shown to be linked to CKD progression (Shah et al 2009) and bicarbonate therapy may slow its progression (Di Iorio et al 2019). Bicarbonate therapy has been suggested to provide kidney benefit to patients without overt acidosis (Mahajan et al 2010).

2.2.3.3 Correction of Hyperkalaemia with Maintenance of Normokalaemia and Reduction in Aldosterone

Hyperkalaemia may offset some of the renoprotective ACEi/ARB effect. In a post-hoc analysis of the RENAAL study data (Miao et al 2011), hyperkalaemia was associated with an increased risk for kidney events (hazard ratio of 1.22). Adjustment of the overall treatment effect for S-K level augmented the renoprotective effect of losartan from 21% to 35%, suggesting that the renoprotective effects of losartan are offset by its effect on S-K. Furthermore, mild to moderate hyperkalaemia may independently increase the risk of ESKD regardless of ACEi/ARB treatment (Provenzo et al 2018). The risk of ESKD also increased by 57% in patients with new-onset or persistent hyperkalaemia when there was non-use or discontinuation of ACEi/ARB treatment.

The adverse effects of hyperkalaemia on kidney function might be aldosterone mediated. Hyperkalaemia is known to increase aldosterone secretion (Himathongkam et al 1975). Furthermore, there is increasing evidence suggesting that aldosterone induces oxidative stress, inflammation, and fibrosis, resulting in CV and kidney injury (reviewed in Rüster et al 2006). Several SZC studies (ZS-005, ZS-004E, D9482C00001 [Japan long-term safety study] and D9480C00002 [HARMONIZE global]) have shown that serum aldosterone levels were reduced in response to SZC treatment. Treatment with finerenone, a selective MRA, resulted in lower risks of CKD progression and CV events than placebo in patients with type 2 diabetes and CKD (Bakris et al 2020). Thus, correction of hyperkalaemia and maintenance of normokalaemia together with reduction of aldosterone would potentially confer renoprotection.

2.2.3.4 Estimated GFR in Long-term Studies of SZC

In previous long-term studies (ZS-005 and D9482C00001 [Japan Long-Term Safety Study]), the effects of SZC were studied in patients with hyperkalaemia and comorbid conditions (73.5% and 93.3%, respectively) including CKD (defined as eGFR < 60 mL/min/1.73m^2) and followed up for one year. In patients with CKD at baseline, eGFR at the end of the one-year follow-up period was similar to the values observed at baseline. To a large degree, this was due to an acute improvement in eGFR following study initiation, followed by a decline that appeared to be slower than what would be expected in this population. However, as none of the studies were placebo-controlled, firm conclusions on causality cannot be made.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

This study has been designed with appropriate measures in place to monitor and minimise any potential health risks to participants. A DMC that is unblinded to treatment allocation will be responsible for safeguarding the interests of the participants throughout the study (Appendix A 5.2). To ensure the safety of all participants in AstraZeneca-sponsored studies,

reviews of all safety information from all ongoing clinical SZC studies are conducted as they become available.

Details of the risk assessment in this study are presented in Table 3. Refer to the Investigator's Brochure for detailed information on the risks of SZC. Refer to the applicable SmPC for lisinopril and valsartan for detailed information on the risks of these agents.

Table 3 Risk Assessment of SZC and the Use of SZC with Lisinopril or Valsartan as Background Interventions

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Hypokalaemia (S-K < 3.5 mmol/L)	Common for SZC (≥ 1/100 to < 1/10). In clinical trials, 4.1% of participants treated with SZC developed hypokalaemia.	Periodic monitoring of S-K and dose adjustment as necessary.
Oedema-related events (includes fluid overload, fluid retention, generalised oedema, hypervolaemia, localised oedema, oedema, oedema peripheral, peripheral swelling)	Common for SZC (≥ 1/100 to < 1/10). In clinical trials with SZC, the most commonly reported adverse reaction was oedema-related events which were reported by 5.7% of participants treated with SZC; 1.7%, 2.7%, 5.2%, and 14.3% of participants randomised to placebo, SZC 5 g, 10 g, or 15 g once daily up to one month, respectively.	Oedema management as per investigator's medical judgment and standard clinical practice.
Hyperkalaemia (S-K > 5.0 mmol/L)	Lisinopril/valsartan can cause hyperkalaemia (especially in patients with impaired renal function) because they inhibit the release of aldosterone. For participants randomised to placebo, there is risk of hyperkalaemia from lisinopril and valsartan.	Close monitoring of S-K after randomisation, including scheduled safety visits 2 and 7 days after randomisation. Down-titration/withdrawal of lisinopril/valsartan if significant hyperkalaemia persists. Rescue therapy available per standard of care/clinical practice. SZC/placebo dosing based on local laboratory S-K and instructions in Section 6.6 and Appendix C.

S-Cr, serum creatinine; S-K, serum potassium; SZC, Sodium zirconium cyclosilicate.

2.3.2 Benefit Assessment

Participants in this clinical study will potentially derive benefit from having their RAASi doses up-titrated although more participants receiving SZC are likely to maintain the higher beneficial doses compared to those on placebo. Further, patients receiving SZC may benefit from the other mechanisms (bicarbonate rise, control of hyperkalaemia, and aldosterone reduction). Should the study hypothesis prove true, participants treated with SZC may have delayed progression of CKD. All participants in this clinical study, irrespective of whether treated with SZC or placebo, will be receiving SoC and closer medical attention compared to ordinary medical practice.

2.3.3 Overall Benefit: Risk Conclusion

Considering the potential benefit implied and the measures implemented to minimise risk to participants in this study, the benefit-risk of the study is deemed favourable.

3 OBJECTIVES AND ENDPOINTS

The objectives and endpoints for the study are detailed in Table 4.

Table 4 Objectives and Endpoints

Objectives	Endpoints
Primary	
To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan [a]), is superior to placebo in slowing CKD progression, assessed as the reduction in participant's expected eGFR decline over time	Co-primary [b] • Total slope: eGFR measurements starting at randomisation • Chronic slope: eGFR measurements, starting at 12 weeks after randomisation
Secondary	
To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan [a]), is superior to placebo in reducing the incidence of the composite of kidney failure outcomes comprising: sustained ≥ 40% decline in eGFR, onset of ESKD, and death from kidney failure	• Time from randomisation to the first occurrence of any component in the composite of ° Sustained ≥ 40% decline in eGFR [c] ° Onset of ESKD (kidney transplantation, maintenance dialysis, or sustained low eGFR) [c] ° Death from kidney failure [c]
To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan [a]), is superior to placebo in reducing the incidence of lisinopril/valsartan dose decrease, in participants on lisinopril/valsartan at randomisation	• Time from randomisation to first lisinopril/valsartan dose decrease
To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan [a]), is superior to placebo in reducing albuminuria	• UACR measurements at scheduled visits after randomisation
To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan [a]), is superior to placebo in increasing serum bicarbonate levels	• Serum bicarbonate measurements at scheduled visits after randomisation
To determine if treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan [a]), is superior to placebo on maintenance of normokalaemia	• S-K level classification; normal (3.5-5.0 mmol/L) or non-normal (< 3.5 or > 5.0 mmol/L) at scheduled visits after randomisation

Table 4 Objectives and Endpoints

Objectives	Endpoints
Safety	
To assess the safety and tolerability of treatment with SZC, as adjunct to ACEi/ARB therapy (lisinopril or valsartan [a]), as compared to placebo	Safety and tolerability will be evaluated in terms of AEs/SAEs, vital signs, clinical laboratory variables, and ECGs Assessments related to AEs cover: • Occurrence/frequency • Relationship to study intervention as assessed by investigator • Intensity • Seriousness • Death • AEs leading to discontinuation of study intervention

[a] In case of a local market valsartan shortage, irbesartan will be temporarily used instead.
[b] Both of the primary endpoints must be met in order for the study to be declared successful, ie, co-primary endpoints.
[c] Levin et al 2020; see Section 8.1.2.

ACEi, angiotensin converting enzyme inhibitor; AE, adverse event; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; SAE, serious adverse event; S-K, Serum potassium; SZC, Sodium zirconium cyclosilicate; UACR, urine albumin-to-creatinine ratio.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, international, randomised withdrawal, double-blind, parallel-group, placebo-controlled study, to evaluate the effect of SZC as adjunct to RAASi therapy (lisinopril or valsartan) in slowing CKD progression in participants with CKD and hyperkalaemia or at risk of hyperkalaemia.

Specifically, the study will include participants with hyperkalaemia (S-K > 5.0 to ≤ 6.5 mmol/L by central laboratory) who are on adequate or limited RAASi therapy due to hyperkalaemia, and participants with normokalaemia (S-K ≥ 3.5 to ≤ 5.0 mmol/L by central laboratory) who are on limited RAASi therapy due to high risk of hyperkalaemia. High risk of hyperkalaemia is defined as (1) participants with a previous medical history or record of hyperkalaemia within the prior 24 months who are on limited RAASi therapy despite indication in CKD; (2) participants in whom RAASi therapy is indicated in CKD but are on limited RAASi therapy and have S-K ≥ 4.7 to ≤ 5.0 mmol/L; and (3) participants in whom RAASi therapy has been discontinued or reduced to suboptimal doses because of hyperkalaemia (see Section 5.1, inclusion criterion 5).

It is estimated that approximately 3000 participants at up to 250 study sites in up to 16 countries will be enrolled (screened) to reach the target of approximately 1360 randomised participants (see Section 9.2).

A participant is expected to be in the study for approximately 28 months, which includes up to 13 days for the screening period, 27 months for the intervention period, and 1 week for follow-up. The 27-month intervention period of the study consists of 3 phases, an initiation phase (up to 72 hours), a run-in phase (3 months/up to Day 90), and a maintenance phase (24 months/104 weeks).

An independent DMC that is unblinded to treatment allocation will be responsible for safeguarding the interests of the participants throughout the study (see Appendix A 5).

The overall study design is presented in Figure 1.

4.1.1 Screening Period (Up to 13 Days)

During the screening period, after signed informed consent is obtained, data required for determination of eligibility for the study will be collected and inclusion/exclusion criteria evaluated (Sections 5.1 and 5.2). Participants who fulfil the study eligibility criteria may proceed to the initiation phase. Participants who do not fulfil the study eligibility criteria are screen failures (see Section 5.4 for details on screen failures and rescreening).

4.1.2 Initiation Phase (Up to 72 hours)

No changes will be made to the ACEi or ARB therapy during the initiation phase. The initial dosing of SZC will be based on the participant's S-K as measured by local laboratory on the same day as, or within 24 hours prior to, Day 1 (Visit 2); the S-K results MUST be available before any other Visit 2 procedures/assessments are performed. If S-K < 3.5 or > 6.5 mmol/L, the participant is not eligible for the study (see exclusion criterion 18, Section 5.2).

Hyperkalaemic (S-K > 5.0 to ≤ 6.5 mmol/L [local laboratory]) at Visit 2

Participants will receive 10 g SZC TID starting on Day 1 (Visit 2). S-K will be measured by local laboratory at 48 hours (Day 3; Visit 3b) and subsequently at 72 hours (Day 4; Visit 3c) if normokalaemia (S-K ≥ 3.5 to ≤ 5.0 mmol/L) has not been previously achieved.

In case the S-K result is not available for up to 24 hours after sample collection, the participant will be notified by phone as soon as possible after the S-K results are available, and the following instructions should be followed for SZC:

- Day 3 (Visit 3b): if the 48-hour S-K result is not available, the participant will take SZC 10 g TID for one additional day.
- Day 4 (Visit 3c): if the 48-hour S-K is > 5 to ≤ 6.5 mmol/L and the 72-hour S-K is not available, the participant will take SZC 10 g QD for one day.

If normokalaemia is achieved after 48 or 72 hours of treatment with SZC, the participant will proceed to the run-in phase, during which SZC dosing will be initiated at 10 g QD. Participants who do not achieve normokalaemia after 72 hours of treatment will undergo a follow-up visit at 7 (± 2) days after the participant's last dose per the SoA (Section 1.3) and exit the study.

Normokalaemic (S-K ≥ 3.5 to ≤ 5.0 mmol/L [local laboratory]) at Visit 2

Participants will receive SZC 5 g QD starting on Day 1 (Visit 2) for 48 hours. S-K will be measured by local laboratory at 48 hours (Day 3; Visit 3b). In case the S-K result is not available for up to 24 hours after sample collection, the participant will continue with a third day of SZC 5 g QD and will be notified by phone as soon as possible after the 48-hour S-K results are available.

If normokalaemia is maintained after 48 hours of treatment with SZC, the participant will proceed to the run-in phase, continuing to receive 5 g QD. Participants who do not maintain normokalaemia after 48 hours of treatment will undergo a follow-up visit at 7 (± 2) days after the participant's last dose per the SoA (Section 1.3) and exit the study.

NOTE: Visit 3c is not applicable for participants who are normokalaemic at Visit 2.

4.1.3 Run-in Phase (3 months/up to Day 90)

As soon as possible after the participant is confirmed to be normokalaemic at the end of the initiation phase (based on local laboratory S-K results from Visits 3b or 3c), the participant will enter the run-in phase (Visit 3d).

Participants will receive open-label SZC and either lisinopril or valsartan. See Section 6.6.2 for instructions on lisinopril/valsartan starting doses. A participant cannot receive both lisinopril and valsartan simultaneously and should not take any other ACEi or ARB concomitantly with lisinopril or valsartan.

The aim of the run-in phase is to increase ACEi or ARB therapy stepwise to their maximum doses using lisinopril or valsartan as per local labels. See Section 6.6 for instructions on dose modification, including monitoring lisinopril/valsartan titration (Section 6.6.1) and management of abnormalities of S-K (Appendix C), lisinopril/valsartan dosing upon entry to and during the run-in phase (Section 6.6.2), strategy for lisinopril/valsartan up-titration during run-in phase visits (Section 6.6.3), and additional unscheduled visits for titration of lisinopril/valsartan (Section 6.6.5).

At the end of the run-in phase (Day 90 [±3 days], Visit 6a), S-K will be measured by local laboratory. The participant will continue to receive the current prescribed dose of SZC until the S-K result is available. If normokalaemic (S-K ≥ 3.5 to ≤ 5.0 mmol/L), the participant will proceed to the maintenance phase of the study. If not normokalaemic, the participant will

undergo a follow-up visit at 7 (± 2) days after the participant's last dose per the SoA (Section 1.3) and exit the study.

NOTE: The study is designed to use valsartan as the ARB adjunct to SZC. However, if an actual shortage of valsartan in a local market jeopardises the ability of participants to enter or continue in the study, valsartan can be temporarily substituted with irbesartan until the shortage of valsartan is resolved.

Appendix E provides conversion information for changing from other ARBs or valsartan to irbesartan, dose equivalence ranges, irbesartan dose modification strategy, and other prescribing information about irbesartan.

During temporary treatment with irbesartan, the same procedures indicated for valsartan discontinuation (Section 7) and efficacy, safety, and other assessments (Section 8) must be followed.

As soon as the shortage is resolved, valsartan should be restarted at a dose determined by using the conversion table in Appendix B 1 unless in the investigator's judgment a change in dose is required. Every effort should be made to maximise the doses of valsartan and of irbesartan if the latter needs to be used because of a valsartan shortage.

4.1.4 Maintenance Phase, Double-blind, Parallel Groups (24 months)/104 weeks)

As soon as possible after the participant is confirmed to be normokalaemic at the end of the run-in phase (based on local laboratory S-K results from Visit 6a), the participant will enter the maintenance phase. The date of randomisation is Day 1 of the maintenance phase (Visit 6b).

Participants will be randomised in a 1:1 ratio to receive either SZC or matching placebo. The starting dose of SZC/placebo will be the same dose as the last dose of SZC during the run-in phase. Lisinopril and valsartan will be continued at the same doses assigned at the end of the run-in phase. As described in the run-in phase, if there is a shortage of valsartan in a local market, valsartan can be temporarily substituted with irbesartan until the shortage of valsartan is resolved (see Section 4.1.3 and Appendix E).

Two safety visits will occur 2 and 7 (±1) days after randomisation and will include evaluation of S-K by local laboratory. The investigator must ensure that the choice of date for randomisation will allow for these 2 safety visits to occur 2 and 7 (±1) days after randomisation, respectively. Participants will then be monitored for approximately 24 months (through Week 104) for efficacy and safety assessments. A final safety follow-up visit will be conducted at Week 105, one week after the participant's last dose, after which the participant will exit the study.

See Section 6.6 for instructions on dose modification, including monitoring lisinopril/valsartan titration (Section 6.6.1) and management of abnormalities of S-K (Appendix C), use of SZC/placebo for management of S-K immediately after randomised withdrawal, ie, up to Week 6 of maintenance phase (Section 6.6.4), and additional unscheduled visits for titration of lisinopril/valsartan (Section 6.6.5).

4.1.5 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with Good Clinical Practice, and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following:

- Obtaining consent for the mitigation procedures and document this in the source data.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, see Appendix F.

4.2 Scientific Rationale for Study Design

This is a randomised withdrawal, double-blind, placebo-controlled parallel-group study. Randomisation and double-blinding will minimise potential bias. The rationale for the randomised withdrawal design is to ensure that investigators up-titrate lisinopril/valsartan to their maximum doses during the run-in phase while participants are being treated with SZC to control S-K.

4.2.1 Rationale for the Study Population

The population included in this study comprises patients with moderate to severe CKD (eGFR ≥ 25 to ≤ 59 mL/min/1.73m^2) and albuminuria (UACR ≥ 200 and ≤ 5000 mg/g) with

hyperkalaemia or at risk of hyperkalaemia. The presence of a reduced eGFR together with significant albuminuria ensures that the selected population is at risk of progression of CKD and can potentially benefit from the proposed mechanisms of action of SZC. RAASi therapy, eg, ACEi/ARB treatment, is renoprotective and slows progression in early and advanced CKD patients. The low eGFR cut-off value is set at 25 mL/min/1.73m^2 to avoid enrolling patients with more advanced CKD who are at risk for rapid progression to ESKD, and who commonly cannot tolerate maximal ACEi/ARB doses because of the risk of further haemodynamic kidney impairment. In addition, including patients with very advanced kidney disease would detract from the ability to obtain meaningful long term eGFR slope data. Hyperkalaemia is a common reason for down-titration or discontinuation of ACEi/ARB therapy and constitutes the main barrier to attaining optimal therapy. SZC is likely to benefit this population by enabling optimisation of ACEi/ARB therapy in hyperkalaemic patients, and in patients at high risk of hyperkalaemia upon ACEi/ARB up-titration.

As indicated in Section 2.2.3, SZC may exert renoprotective effects in the proposed study population independently of ACEi/ARB optimisation (bicarbonate rise and potassium/aldosterone reduction). To study the effects of all potential SZC mechanisms of action, the proposed study patient population will include 2 subgroups of approximately equal size, based on S-K and RAASi therapy criteria, as follows:

- Hyperkalaemia and on adequate or limited RAASi therapy due to hyperkalaemia
- Normokalaemia and on limited RAASi therapy due to high risk of hyperkalaemia

The mechanisms underlying the potential benefit of SZC are relevant in all 2 subgroups (RAASi optimisation, acidosis correction, hyperkalaemia amelioration, and aldosterone reduction). The study population defined by the above eligibility criteria and study subgroups is considered well representative of a CKD population at risk of progression that is likely to benefit from treatment with SZC.

4.2.2 Rationale for the Endpoints

4.2.2.1 Rationale for the Primary Endpoints

The co-primary endpoints (ie, eGFR at and after randomisation and eGFR at and after 12-week visit) are appropriate for the objective of the study. These endpoints should reflect the combined results of the proposed SZC renoprotective mechanisms that include enabling the use of optimal ACEi/ARB therapy, and the anticipated effects on S-K, bicarbonate, and aldosterone levels as described in Section 2.2.3.

Data from observational cohorts as well as from randomised clinical studies support the validity of eGFR slope as a surrogate measure for kidney function decline (Astor et al 2011, Coresh et al 2014, Gansevoort et al 2011, Matsushita et al 2015, Turin et al 2013, Van der Velde et al 2011).

Furthermore, large observational and clinical studies have shown that an improvement in total eGFR slope predicts/translates into benefit on clinical kidney outcomes, for instance:

- In a patient-level meta-analysis of observational data from 122664 CKD participants with eGFR < 60 mL/min/1.73m^2, a reduction in eGFR slope decline by 0.75 mL/min/1.73m^2/year over 2 years was associated with a 30% lower risk of subsequent ESKD (Grams et al 2019).
- In a patient-level Bayesian meta-analysis including 47 clinical studies and 60620 participants (2018 NKF/FDA/EMA Workshop), a treatment effect of 0.75 mL/min/1.73m^2/year in the total eGFR slope predicts an average 27% lower hazard for the treatment benefit on the clinical endpoint (Inker et al 2019, Levey et al 2020).

It is the Sponsor's view that eGFR slope is a clinically relevant surrogate for CKD progression and use of eGFR slope allows faster and more efficient clinical trials in CKD. Due to the observed acute haemodynamic effects of RAASi and SZC on eGFR measures, both total eGFR slope and chronic eGFR slope are used in this study to mitigate the potential impact on kidney function assessment and minimise the risk of a type 1 error. Accordingly, this is expected to show a clinically relevant difference favouring SZC and will reflect a true effect on irreversible loss of kidney function.

4.2.2.2 Rationale for the Secondary Endpoints

The effect of SZC compared with placebo in reducing the incidence of the composite of kidney failure outcomes, comprising of ≥ 40% sustained decline in eGFR, onset of ESKD (kidney transplantation, maintenance dialysis, or sustained low eGFR), and death from kidney failure, will be evaluated to support analysis of the primary outcome measure. The components of the composite endpoint are based on international consensus definitions of clinical trial outcomes for kidney failure (Levin et al 2020). Additional secondary endpoints include time to lisinopril/valsartan dose decrease after randomisation, UACR, serum bicarbonate, and S-K levels, at scheduled visits after randomisation to further characterise the treatment effect of SZC/placebo and lisinopril/valsartan as well as the mechanisms of action of any renoprotective effects.

Standard safety parameters such as AEs/SAEs, vital signs, laboratory evaluations, and ECG will be evaluated to assess the safety profile of SZC compared to placebo as adjunct to lisinopril or valsartan.

4.2.3 Rationale for Placebo Control During the Maintenance Phase

It is hypothesised in this study that treatment of hyperkalaemia with SZC slows CKD progression. To date, no potassium binder has shown such a benefit in a randomised clinical study of patients with CKD. Therefore, other agents that treat hyperkalaemia in other clinical settings are not appropriate to use as controls in the proposed study.

The study protocol includes close monitoring of participant's status with frequent recording of AEs and SAEs, specific safety visits to monitor S-K, and the use of short-term rescue therapy for managing severe hyperkalaemia. During the randomised withdrawal of the maintenance phase, protocol-mandated safety visits will be required for all participants 2 and 7 (± 1) days after randomisation. Instructions for strict monitoring of S-K during this time and the use of SZC/placebo for management of S-K are provided in Section 6.6.4. Thus, participant safety and ethical considerations are preserved while the scientific hypothesis is being adequately and robustly tested.

Additionally, the randomised withdrawal design with placebo control has been safely used in previous RAASi and hyperkalaemia studies (eg, OPAL-HK) and is used in an ongoing global heart failure outcomes trial (DIAMOND, N = 2388). To mitigate the potential rebound hyperkalaemia risk in placebo participants, there will be rigorous monitoring of S-K during the randomised withdrawal and throughout the maintenance phase.

Treatment with SZC or placebo will be administered as adjunct to RAASi therapy (lisinopril or valsartan) in the study population. Participation in the study will not deprive participants from receiving therapies considered as necessary by the investigator. Participants will receive SoC for any underlying medical conditions during the study. Potentially beneficial renoprotective treatments, including SGLT2 inhibitors (ie, dapagliflozin and canagliflozin), finerenone, or any other medications in these 2 classes that are approved for CKD, will not be withheld in the study. Participants who require restricted medications that may interfere with the objectives of the study (eg, chronic treatment with a potassium binder) will be discontinued from study interventions.

4.3 Justification for Dose

4.3.1 Justification for Dose of SZC

The SZC doses selected for this study have been studied in the clinical development programme and are in line with the approved label(s). SZC 5, 10, and 15 g QD have been proven to be tolerable and efficacious doses during long-term therapy in prior SZC studies (see data on the maintenance phase for Studies ZS-004 and ZS-005 in the Investigator's Brochure). The SZC doses to be used in normokalaemic participants were also studied in a Phase 2 clinical trial (PRIORITIZE HF [Study D9484C00001; NCT03532009]) with no new safety concerns raised.

4.3.2 Justification for Dose of Lisinopril and Valsartan

Equivalence calculations for dosing lisinopril/valsartan during the run-in phase are based on the label recommendations for control of blood pressure as the primary indication. Appendix B 1 and Appendix B 2 detail the dosing equivalences among RAASi drugs that form the basis for determining the doses of lisinopril/valsartan to be used in the study and are

based on KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD (KDIGO 2020).

If participants are not already on maximum doses of lisinopril and valsartan upon entry into the run-in phase, stepwise dose adjustments to maximum doses as per local label will be done with close monitoring of S-K and S-Cr following clinical guidelines for RAASi therapy recommended by KDIGO guidelines (KDIGO 2020; see Section 6.6).

Any further dose increases of lisinopril/valsartan deemed clinically advisable after achieving the maximum tolerated dose during the early run-in phase should also follow KDIGO guidelines (KDIGO 2020). If necessary, dose reductions or discontinuation of lisinopril/valsartan are allowed as judged by the investigator, eg, because of hyperkalaemia, excessive (≥ 30%) rise in S-Cr, symptomatic hypotension, or other compelling medical reasons (KDIGO 2020).

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the scheduled follow-up visit after the maintenance phase, as indicated in the SoA (Section 1.3).

The end of the study globally is defined as the date of the last visit of the last participant.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

1 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Age

2 Must be ≥ 18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

3 Must have eGFR ≥ 25 and ≤ 59 mL/min/1.73m^2 as calculated by central laboratory (CKD-EPI formula; Delgado et al 2022, Inker et al 2021) at screening (Visit 1).

4 Must have UACR ≥ 200 and ≤ 5000 mg/g as calculated by central laboratory at screening (Visit 1). If the first sample does not fulfil eligibility criteria, a second sample can be

obtained during the screening period; if so, the UACR measurement from the second sample must be within the eligibility range.

5 Any of the following criteria, a or b, at screening (Visit 1):

(a) Cohort A: Hyperkalaemia (S-K > 5.0 to ≤ 6.5 mmol/L) as measured by the central laboratory, and on adequate* or limited** RAASi therapy due to hyperkalaemia.

(b) Cohort B: Normokalaemia (S-K ≥ 3.5 to ≤ 5.0 mmol/L) as measured by the central laboratory and on limited** RAASi therapy due to high risk of hyperkalaemia. High risk of hyperkalaemia is defined as:

(i) Participants with a previous medical history or record of hyperkalaemia within the prior 24 months, who are on limited** RAASi therapy despite indication in CKD.

(ii) Participants in whom RAASi therapy is indicated in CKD, who are on limited** RAASi therapy and have S-K ≥ 4.7 to ≤ 5.0 mmol/L.

(iii) Participants in whom RAASi therapy has been discontinued or reduced to suboptimal* doses because of hyperkalaemia.

*Adequate RAASi dose levels are defined in Appendix B 3; doses lower than these are considered as suboptimal.
**Limited RAASi therapy is defined as no or suboptimal RAASi therapy according to dosing guidance provided in Appendix B 3.

6 If on thiazide or loop diuretics, the dose must have been stable for 2 weeks prior to screening (Visit 1).

7 If on RAASi therapy, the dose must have been stable for one month prior to screening (Visit 1) and remain stable during screening.

8 If on an SGLT2 inhibitor (ie, dapagliflozin and canagliflozin), finerenone, or any other medications in these 2 classes that are approved for CKD, the dose must have been stable for 3 months prior to screening (Visit 1).

Reproduction and Contraception

Contraceptive use by participants of childbearing potential should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

9 Participants must be one-year postmenopausal, surgically sterile, or using one highly effective form of birth control (defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly). They should have been stable on their chosen method of birth control for a minimum of one month prior to screening (Visit 1) and willing to remain on the birth control until one month after the last dose of study intervention. See Section 5.3.3.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 New York Heart Association class III to IV congestive heart failure at the time of screening (Visit 1) or previous history of severe or symptomatic heart failure.

2 Myocardial infarction, unstable angina, stroke, or transient ischaemic attack within 3 months prior to screening (Visit 1).

3 Participants with a known history of systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg within 2 weeks prior to screening (Visit 1) are excluded. In addition, any participant with systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 95 mmHg as measured at screening (Visit 1) and confirmed by repeated measurement is excluded. Participants may be rescreened once blood pressure is controlled.

4 QTcF > 550 msec at screening (Visit 1).

5 History of QT prolongation associated with other medications that required discontinuation of that medication.

6 Congenital long QT syndrome.

7 Symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Participants with atrial fibrillation and heart rate controlled by medication are permitted.

9 Lupus nephritis or anti-neutrophil cytoplasmic antibody-associated vasculitis.

10 Change in renal function requiring hospitalisation or dialysis within 3 months prior to screening (Visit 1).

11 History of renal transplant (or anticipated need for renal transplant during the study).

12 Severe hepatic impairment, biliary cirrhosis, or cholestasis.

13 History of hereditary or idiopathic angioedema.

14 Any prior hypersensitivity to ACEi or ARB that in the investigator's judgment precludes use of lisinopril and valsartan/irbesartan. Prior hypersensitivity reactions to consider include, but are not limited to, development of angioedema, icterus, hepatitis, or neutropaenia or thrombocytopaenia requiring treatment modification.

15 Known hypersensitivity or previous anaphylaxis to SZC or to components thereof.

16 Any condition outside the CV and renal disease area such as, but not limited to, malignancy, with a life expectancy of less than 2 years based on investigator´s clinical judgment.

17 Active malignancy requiring treatment at the time of screening (Visit 1), except for successfully treated basal cell or treated squamous cell carcinoma.

18 S-K > 6.5 or < 3.5 mmol/L by local laboratory within 1 day prior to the scheduled first dose of SZC in the initiation phase.

19 Evidence of COVID-19 infection within 2 weeks prior to screening (Visit 1).

Prior/Concomitant Therapy

20 Treated with dual blockade of RAAS (combined use of an ACEi and ARB) within 3 months prior to screening (Visit 1).

21 Treated with an angiotensin receptor neprilysin inhibitor (ARNI; sacubitril/valsartan [Entresto®]) within 3 months prior to screening (Visit 1).

22 Treated with an MRA not approved for CKD within 3 months prior to screening (Visit 1).

23 Treated with aliskiren-containing products with 3 months prior to screening (Visit 1).

24 Treated with SPS (eg, Kayexalate, Resonium), CPS (Resonium Calcium), patiromer (Veltassa®), or SZC (Lokelma®) within 7 days prior to screening (Visit 1).

Prior/Concurrent Clinical Study Experience

25 Participation in another clinical study with an investigational product administered within one month prior to screening (Visit 1).

Other Exclusions

26 Not willing or not able to change to lisinopril or valsartan/irbesartan, the protocol-mandated RAASi study intervention. Note: For participants taking a fixed combination of an ACEi or ARB with another agent (eg, calcium blockers or diuretics) as SoC, the investigator must make a judgment that it will be safe and efficacious for such participants to change to the study ACEi or ARB and to the other drug as separate agents.

27 Previous dosing with SZC in the present study.

28 Currently pregnant (confirmed with positive pregnancy test at screening [Visit 1]) or breastfeeding.

29 Judgment by the investigator that the participant is unlikely to comply with study procedures, restrictions, and requirements.

30 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

No study-specific dietary restrictions are required. Study site personnel are encouraged to instruct participants to adhere to any dietary restrictions that apply for similar patients not participating in a study.

5.3.2 Caffeine, Alcohol, and Tobacco

No additional study-specific restrictions are required in the study, except restrictions applicable prior to a blood pressure measurement (see Section 8.2.2).

5.3.3 Contraception

Participants of childbearing potential must use one highly effective form of birth control. They should have been stable on their chosen method of birth control for a minimum of one month prior to screening (Visit 1) and remain on the birth control until one month after the last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician. Participants who are surgically sterile or those who are postmenopausal are not considered to be of childbearing potential.

- Surgical sterilisation includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy.
- Participants will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to screening (Visit 1) without an alternative medical cause.
- Highly effective birth control methods (defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly) include:
  - Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal).
  - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable).
  - Intrauterine device.
  - Intrauterine hormone-releasing system.
  - Bilateral tubal occlusion.
  - Vasectomised partner.
  - Heterosexual abstinence, true abstinence in line with the participant's preferred and usual lifestyle; however, periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently dosed in the initiation phase due to one or more of the eligibility criteria detailed in Sections 5.1 and 5.2 not being satisfied. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to

queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants will re-sign the ICF on the rescreening visit (ie, repeated Visit 1). All procedures from the screening period will be repeated.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to or medical device(s) utilised by a study participant according to the study protocol. For this study, the intervention refers to SZC or matching placebo and lisinopril/valsartan.

The intervention is expected to be dispensed during protocol specified visits (see SoA, Section 1.3), in the amount expected to account for its usage as per the investigator's prescription, including possible dose modifications that might occur before the next protocolised dispensation visit. Study intervention may also be dispensed at unscheduled visits.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

The study intervention (investigational products) to be administered in this study are presented in Table 5.

Table 5 Investigational Products

Intervention name/ Characteristic	SZC	Placebo	Lisinopril	Valsartan [a]
Type	Drug	Drug	Drug	Drug
Dose formulation	Powder for oral suspension in a sachet	Powder for oral suspension in a sachet	Tablet	Tablet or capsule
Unit dose strength(s)	5 or 10 g SZC	Placebo to match 5 or 10 g	2.5, 5, 10, or 20 mg [b]	40, 80, or 160 mg [b]
Dosage level(s)	Single dose will consist of 1-3 sachets [c] Initiation Phase: • S-K > 5 to ≤ 6.5 mmol/L (measured by L-Lab): Single dose contains 10 g SZC that should be suspended in 45 mL of water. The 10 g SZC single dose should be administered TID for up to 72 hours until normokalaemic (S-K 3.5-5.0 mmol/L); the total daily dose is 30 g SZC. • S-K ≥ 3.5 to ≤ 5 mmol/L (measured by L-Lab): Single dose contains 5 g SZC that should be suspended in 45 mL of water and administered QD for 48 hours Run-in and Maintenance Phases: • Single dose contains 5 g SZC administered QOD or 5, 10, or 15 g SZC administered QD that should be suspended in 45 mL of water	Single dose will consist of 1-3 sachets [c] Maintenance Phase: Single dose contains 5 g placebo administered QOD or 5, 10, or 15 g placebo administered QD that should be suspended in 45 mL of water	5, 10, 20, or 40 mg QD [d]	40, 80, 160, or 320 mg QD [d]
Route of administration	Oral	Oral	Oral	Oral

Table 5 Investigational Products

Intervention name/ Characteristic	SZC	Placebo	Lisinopril	Valsartan [a]
Use	Experimental	Placebo	Background intervention	Background intervention
IMP or NIMP	IMP	IMP	IMP	IMP
Provider	AstraZeneca	AstraZeneca	Local sourcing preferred. Under certain circumstances when local sourcing is not feasible, lisinopril may be supplied centrally through AstraZeneca.	Local sourcing preferred. Under certain circumstances when local sourcing is not feasible, valsartan may be supplied centrally through AstraZeneca.
Packaging and labelling	• Provided in sachet and labelled in accordance with GMP Annex 13 and per country regulatory requirement. Label text will be translated into local language. • For Japan: Labels will be prepared in accordance with GCP Ordinance. Details are specified in the document explaining the reconstitution procedures and other handling procedures for the investigational products.		• Provided in original package and labelled in accordance with GMP Annex 13 and per country regulatory requirement. Label text will be translated into local language.	

[a] If there is a shortage of valsartan in a local market, valsartan can be temporarily substituted with irbesartan until the shortage of valsartan is resolved. See Appendix E 4 for details on irbesartan.

[b] In countries where lisinopril and valsartan will be supplied centrally through AstraZeneca, specific unit dose strengths will be confirmed to the countries.

[c] Further guidance and information are provided in the Pharmacy Manual.

[d] For lisinopril and valsartan, the QD dose can be divided as long as the total daily dose is the prescribed dose, eg, valsartan 320 mg QD is equivalent to valsartan 160 mg BID.

BID, twice daily; GCP, Good Clinical Practice; GMP, Good Manufacturing Practice; IMP, investigational medicinal product; L-Lab, local laboratory; NIMP, non-investigational medicinal product; QD, once daily; QOD, every other day; S-K, serum potassium; SZC, Sodium zirconium cyclosilicate; TID, three times daily.

6.2 Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorised site staff may supply/dispense study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3 Measures to Minimise Bias: Randomisation and Blinding

6.3.1 The Process of Enrolment and Randomisation

An IRT/RTSM will be used for the assignment of unique participant numbers and randomisation codes in the study. The participant numbers will be obtained during screening for all participants, after the signature of the ICF, while the randomisation codes will be assigned only to the participants proceeding to the maintenance phase of the study. Before the study is initiated, detailed instructions describing the process of IRT/RTSM usage, including the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM, will be provided to each site in the IRT/RTSM user manual.

In case of rescreening, the rescreened participants should be assigned the same participant number as for the initial screening.

Study intervention will be dispensed at the study visits summarised in the SoA (Section 1.3) and can also be dispensed at unscheduled visits. Returned study intervention in unopened packets or sachets may be re-dispensed to the same participant. For study intervention that is sourced centrally, the IRT/RTSM will provide to the investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit. As the dosing regimen in the initiation phase is dependent on the participant's local S-K value obtained prior to the first SZC dose, this value will have to be provided to the system before any SZC is dispensed.

Direct-to-participant delivery of study intervention may be implemented where local regulations allow; instructions will be provided to the applicable investigator site(s) regarding dispensation of study intervention (ie, specific visits and delivery methods).

The study will aim at recruiting a certain minimum number of participants in the 2 cohorts described in inclusion criterion 5 (Section 5.1) as follows:

(a) Cohort A: Hyperkalaemia (S-K > 5.0 to ≤ 6.5 mmol/L) and on adequate or limited RAASi treatment due to hyperkalaemia; one half of all enrolled participants.
(b) Cohort B: Normokalaemia (S-K ≥ 3.5 to ≤ 5.0 mmol/L) and on limited RAASi treatment due to high risk of hyperkalaemia; one third of all enrolled participants.

During the study, sites will be notified if the number of participants recruited in a particular cohort approaches a point where further recruitment in the cohort would hinder the achievement of the desired number of participants in the other cohort.

In this study, the randomisation will be stratified by 3 factors: country; inclusion criterion 5 (Section 5.1) categorisation as given above; and SGLT2 inhibitor and/or finerenone use at randomisation.

6.3.2 Break of the Blind

The randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. The IRT/RTSM will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention (ie, SZC/placebo) will affect the immediate management of the participant's condition, the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination.

If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The investigator should document and report the action to AstraZeneca, without revealing the treatment given to participant to the AstraZeneca staff.

AstraZeneca retains the right to break the randomisation code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

6.3.3 Potentially Treatment-revealing Data

The following information will be considered as potentially treatment revealing during the maintenance phase of the study:

- S-K (central laboratory)
- Serum bicarbonate (central laboratory)
- SZC/placebo dose
- Lisinopril/valsartan/irbesartan dose

To minimise the risk of revealing the treatment, the AstraZeneca study team will be blinded to the above.

The investigator site will be blinded to the central laboratory results/values of S-K and serum bicarbonate. However, if the S-K or serum bicarbonate laboratory results/values fall outside of the reference range with potential critical implications for the participant, the investigator and a pre-identified Sponsor contact will be notified.

Additional information about preserving the blind and maintaining study integrity will be detailed in another document. The clinical management of an individual participant is considered to have minimal risk of bias.

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date of dose administration in the clinic will be recorded in the source documents.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed primarily by counting returned sachets/tablets/capsules during the site visits and documented in the source documents.

A record of the number and strength of SZC/placebo sachets (5 or 10 g) and the number and strength of lisinopril/valsartan/irbesartan tablets/capsules dispensed to and returned by each participant must be maintained and reconciled with study intervention and compliance records. This information will be recorded in the source documents, together with the dates of the dispensation and return. In addition, the prescribed SZC/placebo and lisinopril/valsartan/irbesartan treatment, in terms of dosing and time of titration, will be recorded.

For the purpose of study reporting, compliance to SZC/placebo treatment regimen will then be evaluated by means of comparison between the number and type of sachets estimated to be taken by the participant, and the recorded prescription.

6.5 Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy. Medication other than that described in the subsections below, which is considered necessary for the participant's safety and wellbeing, may be given at the discretion of the investigator.

6.5.1 Restricted Concomitant Medication

Restricted medications are listed in Table 6. Restricted medications taken outside the conditions as specified in the "Instruction" column, due to, eg, compelling medical reasons that necessitate such an action, will be considered as disallowed medications, the use of which constitutes a protocol deviation.

Table 6 Restricted Medications

Type of medication/treatment	Instruction
Potassium binders including SPS, CPS, patiromer sorbitex calcium (Veltassa®)	Only permitted to be used as short-term rescue therapy to treat an AE of severe hyperkalaemia (recommended if S-K > 6.0 mmol/L)
ACEi/ARB other than the study ACEi/ARB	Not permitted concomitantly with any ACEi/ARB study drug after the initiation phase

ACEi, angiotensin converting enzyme inhibitor; AE, adverse event; ARB, angiotensin II receptor blocker; CPS, calcium polystyrene sulfonate; SPS, sodium polystyrene sulfonate; S-K, serum potassium.

Interaction with Other Medicinal Products and Other Forms of Interaction

Effect of Other Medicinal Products on SZC

As SZC is not absorbed or metabolised by the body, there are no expected effects of other medicinal products on the pharmacological action of SZC.

Effect of SZC on Other Medicinal Products

As SZC is not absorbed or metabolised by the body and does not meaningfully bind other medicinal products, there are limited effects on other medicinal products.

SZC can transiently increase gastric pH by absorbing hydrogen ions that can lead to changes in solubility and absorption kinetics for co-administrated drugs with pH-dependent bioavailability. Therefore, SZC should be administered at least 2 hours before or 2 hours after oral medications with clinically meaningful gastric pH dependent bioavailability.

Examples of drugs that should be taken 2 hours before or after SZC/placebo to avoid possible raised gastric pH drug interactions are listed in Table 7.

Table 7 Examples of Drugs that Should be Taken 2 hours Before or After SZC/Placebo to Avoid Possible Raised Gastric pH Drug Interactions

Class of Drug	Drugs
Azole antifungals	Ketoconazole, itraconazole, posaconazole
Anti-HIV drugs	Atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir, rilpivirine
Tyrosine kinase inhibitors	Erlotinib, dasatinib, nilotinib

HIV, human immunodeficiency virus; SZC, Sodium zirconium cyclosilicate.

SZC/placebo can be co-administered without spacing of dosing times with oral medications that do not exhibit pH-dependent bioavailability.

In a clinical drug-drug interaction study conducted in healthy subjects, co-administration of SZC with amlodipine, dabigatran, clopidogrel, atorvastatin, furosemide, glipizide, warfarin, losartan, or levothyroxine did not result in clinically meaningful drug-drug interactions. No dose adjustments or separation of the time of dosing are required for these drugs.

In another drug-drug interaction study in healthy volunteers, co-administration of SZC 15 g with tacrolimus 5 mg resulted in a decreased tacrolimus area under the concentration-time curve and maximum observed concentration by 37% and 29%, respectively. Therefore, tacrolimus should be taken at least 2 hours before or after SZC/placebo. In the same study, co-administration of SZC and cyclosporin did not show a clinically meaningful interaction.

See Appendix D for drug interactions for lisinopril and valsartan.

6.5.2 Rescue Medication

Rescue therapy for controlling hyperkalaemia is defined as any short-term (24 to 48 hours) therapeutic intervention during the run-in and maintenance phases, that is considered necessary as per the investigator's judgment and in accordance with local practice patterns to reduce S-K in the setting of an AE of severe hyperkalaemia. Rescue therapy is recommended

in general if S-K > 6.0 mmol/L unless otherwise specified in the protocol (see Section 6.6.4). Rescue therapy may include, but is not limited to, insulin/glucose, beta adrenergic agonists, sodium bicarbonate as well as dialysis, or other forms of renal replacement treatments, and other potassium binders including SPS, CPS, patiromer sorbitex calcium (Veltassa®) given for short-term control of severe hyperkalaemia. SZC/placebo must be temporarily discontinued while rescue therapy is administered.

All potassium binders other than SZC are considered restricted medications and can be used only for short-term rescue. They must not be used for chronic treatment during the study. Any participant who receives chronic treatment with potassium binders other than SZC/placebo must be discontinued from SZC/placebo study intervention.

Rescue medication for hyperkalaemia will not be provided as part of study medications.

6.5.3 COVID-19 Vaccination

COVID-19 vaccination of participants during the study is permitted as per national/local guidelines and provided the vaccine is licensed by country health authorities including emergency use authorisation by the FDA or similar authorisation by other regulatory agencies. The specific vaccine used (brand name) and each dose administered after enrolment should be recorded as concomitant medication. Adverse events suspected of being related to vaccinations should be reported as for any other AEs. Vaccines which are still in development, ie, in study, not yet approved, are not permitted.

6.6 Dose Modification

The investigator should rely primarily on local laboratories to make rapid or urgent decisions regarding clinical management. This includes monitoring of electrolytes (eg, S-K), renal function (eg, S-Cr), and other parameters that may be needed for appropriate CKD clinical management as per investigator's discretion.

The S-K and S-Cr samples collected and analysed by local laboratory as per the SoA (Section 1.3) or as part of routine clinical practice can also be used to adjust doses of SZC/placebo and lisinopril/valsartan.

During the run-in and maintenance phases, SZC/placebo can be titrated in the range 5 g QOD to 15 g QD. Lisinopril overall dose range/titration steps for this study are 5, 10, 20, or 40 mg QD; valsartan dose range/titration steps are 40, 80, 160, or 320 mg QD (see Table 8). In case of valsartan shortage, see Appendix E for irbesartan information. Temporary discontinuations of SZC/placebo or lisinopril/valsartan are permitted as part of the dosing regimen.

If at any point in the study lisinopril/valsartan treatment is reduced or temporarily discontinued, the investigator should make every effort to restart and maximise the dose of these agents once the cause of the reduction or discontinuation has resolved.

Instructions for dose modification and monitoring and management of S-K during the study are provided in the subsections below.

6.6.1 Monitoring Lisinopril/Valsartan Titration During the Run-in and Maintenance Phases

Anytime during the run-in and maintenance phases, if lisinopril/valsartan doses are increased (or decreased or discontinued because of hyperkalaemia), participants will be called for additional local laboratory S-K sampling after 2 weeks, or earlier, as per investigator's judgment. This includes dose changes that occur during scheduled study visits and during unscheduled visits corresponding to usual clinical care. This aligns with KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD (KDIGO 2020, Practice Point 1.2.2), which indicates that changes in S-K, S-Cr, and blood pressure should be monitored within 2 to 4 weeks of initiation or increase in the dose of an ACEi or ARB, and earlier laboratory monitoring may be indicated for participants at high risk of hyperkalaemia due to low eGFR, history of hyperkalaemia, or borderline high S-K concentration. Appendix C provides instructions for the use of SZC/placebo to manage abnormalities in S-K levels found in such visits.

All local S-K values that trigger either an SZC/placebo or lisinopril/valsartan dose modification should be specified in the clinical record. If lisinopril or valsartan doses need to be reduced or discontinued for reasons other than abnormalities in S-K, the reason should also be recorded (eg, rise in S-Cr > 30%, low blood pressure, AE).

6.6.2 Lisinopril/Valsartan Dosing Upon Entry to and During the Run-in Phase

Upon entering the run-in phase:

- Participants who are not on ACEi or ARB therapy will be started on lisinopril or valsartan on the first day of the run-in phase at the starting dose (STEP 1) indicated in Table 8. The choice of drug class is per investigator judgment.
- Participants who are on other ACEi or ARB therapy at the starting daily dose will be changed to lisinopril or valsartan on the first day of the run-in phase at the starting dose (STEP 1) indicated in Table 8, keeping the same drug class.
- Participants who are on other ACEi or ARB therapy with daily doses in the mid-range or at maximum will be changed to lisinopril or valsartan on the first day of the run-in phase, keeping the same drug class, following the RAASi dose equivalence guidance in Appendix B 1 and Appendix B 2.
- Participants who are on lisinopril or valsartan will continue treatment at the same dose.

The following dose steps in Table 8 should be used for up-titration of lisinopril and valsartan:

Table 8 Lisinopril and Valsartan Dose Titration Steps

Dose steps (daily dose)	Lisinopril (mg)[a]	Valsartan (mg) [a]
STEP 1 – Starting dose	10 (5) [b]	80
STEP 2	20	160
STEP 3	40	320

[a] Starting dose and dose range may differ per local labels. For example, in Japan, where starting and/or maximum doses are lower than specified above, the following would apply:
- STEP 1: lisinopril 10 mg; valsartan 40 mg
- STEP 2: lisinopril 20 mg; valsartan 80 mg
- STEP 3: lisinopril 20 mg; valsartan 160 mg

[b] If lisinopril starting dose is 5 mg (eg, if eGFR ≥ 10 to ≤ 30 mL/min/1.73m^2, or participant is on diuretics, or per local label), stepwise increase in these cases may require an additional step: 5, 10, 20 and 40 mg.

eGFR, estimated glomerular filtration rate.

As per Section 4.1.3, if temporary use of irbesartan is necessary due to local market shortage, see Appendix E for further details, including conversion information for changing from valsartan or other ARBs to irbesartan, ARB dose equivalence ranges, dose modification strategy for irbesartan, and other prescribing information about irbesartan.

6.6.3 Strategy for Lisinopril/Valsartan Up-Titration During the Run-in Phase Visits

Review of concurrent drugs and dietary potassium intake should be performed in all cases of hyperkalaemia before a decision is made to reduce or withdraw lisinopril/valsartan therapy. Whenever lisinopril/valsartan is temporarily discontinued because of hyperkalaemia and these agents are already at the lowest possible dose, every effort should be made to reinitiate them as soon as possible at the investigator's discretion and following a review of concurrent drugs and dietary potassium intake. In this case starting doses of lisinopril/valsartan should be used. Suitability of lisinopril/valsartan up-titration based on other clinical parameters, such as S-Cr and blood pressure, is left to the investigator's clinical judgment (KDIGO 2020). At any step during the study if hypokalaemia (S-K < 3.5 mmol/L) occurs, see Appendix C for further actions.

Visit 4 (Day 13 ± 3 days)

- If S-K is ≥ 3.5 and < 4.7 mmol/L, and if not already on maximum dose, increase lisinopril/valsartan one step; follow 2 weeks later with a local laboratory measurement of S-K.
- If S-K is ≥ 4.7 and ≤ 5.5 mmol/L, increase SZC to 15 g QD, repeat S-K in 48 hours and follow instructions in Appendix C; if lisinopril/valsartan is increased one step based on these instructions, follow 2 weeks later with a local laboratory S-K measurement.

- If S-K is > 5.5 and ≤ 6.0 mmol/L, temporarily discontinue lisinopril/valsartan, increase SZC to 15 g QD, repeat S-K in 48 hours and follow instructions in Appendix C. After 48 hours:
  - If S-K is ≥ 3.5 and < 4.7 mmol/L, restart lisinopril/valsartan at previous dose.
  - If S-K is ≥ 4.7 and ≤ 5.0 mmol/L, restart lisinopril/valsartan at lower dose if available. If lower dose is not available, consider reinitiating lisinopril/valsartan at starting dose 2 weeks after visit or permanently discontinue lisinopril/valsartan as per investigator judgment.
  - If S-K is > 5.0 and ≤ 6.0 mmol/L, reduce or permanently discontinue lisinopril/valsartan per investigator judgment.
  - If S-K is > 6.0 mmol/L, permanently discontinue lisinopril/valsartan, continue short-term rescue therapy as per SoC.
- If S-K > 6.0, temporarily discontinue lisinopril/valsartan, increase SZC to 15 g QD, repeat S-K in 48 hours, consider short-term rescue therapy as per SoC. Per Appendix C, after 48 hours:
  - If S-K is ≥ 3.5 and < 4.7 mmol/L, restart lisinopril/valsartan at previous dose.
  - If S-K is ≥ 4.7 and ≤ 5.0 mmol/L, restart lisinopril/valsartan at lower dose if available. If lower dose is not available, consider reinitiating lisinopril/valsartan at starting dose 2 weeks after visit or permanently discontinue lisinopril/valsartan as per investigator judgment.
  - If S-K is > 5.0 and ≤ 6.0 mmol/L, reduce or permanently discontinue lisinopril/valsartan per investigator judgment.
  - If S-K is > 6.0 mmol/L, permanently discontinue lisinopril/valsartan, continue short-term rescue as per SoC.
- Follow 2 weeks after any dose adjustment with a local laboratory S-K measurement or earlier if clinically indicated.

<u>Unscheduled visit for monitoring of lisinopril/valsartan up-titration 2 weeks after Visit 4 (or earlier if clinically indicated)</u>

- If S-K is ≥ 3.5 and < 4.7 mmol/L, increase lisinopril/valsartan one step (if not already maximal); follow 2 weeks later with a local laboratory measurement of S-K.
- If S-K is ≥ 4.7 mmol/L, follow instructions in Appendix C; chosen path depending on whether SZC is at maximum dose or not.

Up-titration of lisinopril/valsartan should be continued following the above stepwise scheme until the maximum dose has been achieved.

It is generally expected to take up to 3 up-titration steps and up to 6 weeks (2 weeks for each step) for a participant to reach the maximum lisinopril/valsartan dose during the run-in phase.

6.6.4 Use of SZC/Placebo for Management of Serum Potassium Immediately after Randomised Withdrawal (Up to Week 6 of Maintenance Phase)

At Visit 6b, the participant is randomised to SZC or placebo (ie, to withdraw SZC and receive placebo), at the same dose as the last dose of SZC during the run-in phase. Lisinopril/valsartan is continued at the same dose received at the end of the run-in phase. As the investigator and the participant are blinded to the SZC/placebo treatment assignment, specific instructions for management of S-K during the period immediately following randomisation are provided below. All participants must return for Visit 7 exactly 2 days after randomisation.

Note: Use Table 8 for STEP-wise dose adjustments and Section 6.5.2 for information about rescue therapy.

Visit 7 (2 days after Visit 6b/randomisation)

- If S-K ≥ 3.5 and ≤ 5.0 mmol/L, continue lisinopril/valsartan at the same dose; the participant must return 5 (± 1) days later to Visit 8 for a local S-K laboratory measurement.
- If S-K is > 5.0 and ≤ 5.5 mmol/L and SZC/placebo IS NOT at maximum of 15 g QD, increase SZC/placebo to 15 g QD AND reduce lisinopril/valsartan one step. If lisinopril/valsartan is at the lowest dose, pause dosing and assess re-initiation of these agents at starting doses (STEP 1) during the next visit. The participant must return 5 (± 1) days later to Visit 8 for a local S-K laboratory measurement.
- If S-K is > 5.0 and ≤ 5.5 mmol/L and SZC/placebo IS at maximum of 15 g QD, reduce lisinopril/valsartan one step. If lisinopril/valsartan is at the lowest dose (STEP 1), pause dosing and assess re-initiation of these agents at STEP 1 starting doses during the next visit. The participant must return 5 (± 1) days later to Visit 8 for a local S-K laboratory measurement.
- If S-K is > 5.5 mmol/L and:
  - Lisinopril/valsartan is at the lowest dose, permanently discontinue lisinopril/valsartan and consider short-term rescue therapy and management of hyperkalaemia as per SoC at the investigator's discretion and local practice. Follow up at Visit 8 for monitoring of local S-K laboratory value.
  - Lisinopril/valsartan is at mid-range (STEP 2) or maximum dose (STEP 3), pause lisinopril/valsartan and SZC/placebo, and give short-term rescue therapy as per SoC at the investigator's discretion (24 to 48 hours rescue treatment); re-start SZC/placebo after rescue and increase to 15 g QD if not already at maximum. Follow up at Visit 8 for monitoring of local S-K laboratory value.

Visit 8 (5 [±1] days after Visit 7)

- If S-K is ≥ 3.5 and ≤ 5.0 mmol/L and lisinopril/valsartan treatment has continued at any dose since Visit 7, the dose will remain unchanged, and the participant will follow the SoA (Section 1.3) to return for Visit 9.

- If S-K is ≥ 3.5 and ≤ 5.0 mmol/L and lisinopril/valsartan treatment was paused on Visit 7, but no rescue was given, re-initiate these agents at starting doses (STEP 1). Follow up 5 (± 1) days later in an unscheduled visit for a local S-K laboratory measurement.
- If S-K is ≥ 3.5 and ≤ 5.0 mmol/L WITH rescue given at Visit 7 (but not during past 72 hours), consider re-initiating lisinopril/valsartan at starting dose (STEP 1). If rescue was continued during past 72 hours, permanently discontinue lisinopril/valsartan and return to SoC as per local practice. Follow up 5 (± 1) days later in an unscheduled visit for a local S-K laboratory measurement.
- If S-K is > 5.0 WITH rescue given at Visit 7, permanently discontinue lisinopril/valsartan and return to SoC as per local practice.
- If S-K is > 5.0 and ≤ 5.5 mmol/L and no rescue was given at Visit 7 and SZC/placebo IS NOT at maximum of 15 g QD, increase SZC/placebo to 15 g QD AND reduce lisinopril/valsartan one step. If lisinopril/valsartan is at the lowest dose (STEP 1), pause dosing and assess re-initiation of these agents at starting doses during the next visit. The participant must return 5 (± 1) days later to an unscheduled visit for a local S-K laboratory measurement.
- If S-K is > 5.0 and ≤ 5.5 mmol/L and no rescue was given at Visit 7 and SZC/placebo IS already at 15 g QD, reduce lisinopril/valsartan one step. If lisinopril/valsartan is at the lowest dose (STEP 1), pause dosing and assess re-initiation of these agents at STEP 1 starting doses during the next visit. The participant must return 5 (± 1) days later to an unscheduled visit for a local S-K laboratory measurement.
- If S-K is > 5.5 mmol/L and no rescue was given at Visit 7 and:
  - Lisinopril/valsartan is at the lowest dose (STEP 1), permanently discontinue lisinopril/valsartan and consider short-term rescue therapy and management of hyperkalaemia as per SoC at the investigator's discretion and local practice. Follow up 5 (± 1) days later to an unscheduled visit for a local S-K laboratory measurement.
  - Lisinopril/valsartan is at mid-range (STEP 2) or maximum dose (STEP 3), pause lisinopril/valsartan and SZC/placebo, consider short-term rescue therapy as per SoC at the investigator's discretion; re-start SZC/placebo after rescue and increase to 15 g QD if not already at maximum. Follow up 5 (± 1) days later to an unscheduled visit for a local S-K laboratory measurement.

Unscheduled Visit (5 [± 1] days after Visit 8)

- If S-K is ≥ 3.5 and ≤ 5.0 mmol/L and lisinopril/valsartan was paused at Visit 8, restart lisinopril/valsartan at starting dose and schedule follow-up visits as per KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD (KDIGO 2020, Practice Point 1.2.2); the participant will in addition follow the SoA (Section 1.3) and return for Visit 9.
- If S-K is > 5.0 mmol/L, permanently discontinue lisinopril/valsartan if on treatment, and consider short-term rescue therapy and management of hyperkalaemia as per SoC at the investigator's discretion and local practice.

6.6.5 Additional Unscheduled Visits for Titration of Lisinopril/Valsartan Doses During the Run-in and Maintenance Phases

If at any time the participant exhibits any evidence of poor RAASi tolerability, which may include, but is not limited to, local laboratory S-K > 5.0 mmol/L, hypotension, or clinically significant decline of eGFR (per investigator judgment), down-titration of lisinopril/valsartan may be considered per investigator judgment. Similarly, if eGFR is < 20 mL/min/1.73m^2, down-titration of lisinopril/valsartan will be at the investigator's discretion.

If at any point in the study an unexpected intercurrent clinical event causes lisinopril/valsartan dose to be reduced or temporarily discontinued, the investigator should make every effort to restart and maximise the dose of these agents once the event has resolved. The stepwise approach described above beginning in Visit 4 should be used if the participant cannot be restarted immediately on the same dose given prior to the event.

6.7 Intervention After the End of the Study

Not applicable. Individual physicians may manage each of their study participants according to local laboratory values and the local SoC.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

At any time, participants are free to discontinue study intervention or withdraw from the study, without prejudice to further treatment.

7.1 Discontinuation of Study Intervention

7.1.1 Permanent Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) any or all study intervention (SZC, placebo, lisinopril, and valsartan).

Note that permanent discontinuation from study intervention is NOT the same as withdrawal from the study. If, upon discontinuation of study intervention, the participant choses to withdraw from the study entirely, procedures described in Section 7.2 should be followed.

Participants should be discontinued from study intervention in the following situations as detailed below:

- Situations applicable to all study interventions
  - Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment.
  - Initiation of dialysis or kidney transplantation occurring prior to randomisation.

  - Severe non-compliance with the CSP.
  - Pregnancy (See Section 8.3.7).
- Additional situations applicable to SZC/placebo
  - An AE that, in the opinion of the investigator or the Sponsor, contraindicates further dosing with SZC/placebo.
  - Local laboratory S-K < 3.5 or > 6.5 mmol/L at any time during the initiation phase (applicable only for initiation phase).
  - Local laboratory S-K < 3.0 mmol/L at any time during the study; the participant should immediately receive appropriate medical intervention.
  - Absolute QTc > 550 ms, or an increase in QTc interval > 60 ms from baseline to > 500 ms is reached; the participant should immediately receive appropriate medical intervention. The QTcF algorithm is recommended. All participants meeting the QTc > 500 msec criterion on study intervention should immediately have potassium assessed, if not already done within 1 hour of performing the ECG.
  - Chronic use of potassium binders other than SZC.
- Additional situations applicable to lisinopril/valsartan
  - An AE that, in the opinion of the investigator or the Sponsor, contraindicates further dosing with lisinopril/valsartan, including, but not limited to, angioedema, jaundice, or marked elevations of hepatic enzymes.
  - Severe hyperkalaemia as per titration algorithm (see Appendix C).
  - Advanced CKD with low eGFR (eg, sustained eGFR < 20 mL/min/1.73m^2).

7.1.1.1 Procedures for Permanent Discontinuation of Study Intervention

The following general procedures should be followed when study intervention is discontinued.

- The Investigator should instruct participants to contact the site before or at the time study intervention is stopped. A participant who decides to discontinue study intervention will always be asked about the reason(s) and the presence of any AEs.
- If at any time during the course of the study, discontinuation of lisinopril/valsartan or SZC/placebo is deemed advisable by the Sponsor for safety reasons, the study physician will promptly discuss with the principal investigator to agree on discontinuing these agents and further actions to take to ensure the participant's safety.
- With the exception of the initiation phase, the participant should attend an ED visit if any study intervention is discontinued. The ED visit should take place as soon as possible after discontinuation and can be combined with a scheduled visit, if appropriate. See the SoA (Section 1.3) for data to be collected at the time of the ED visit. It is possible for a participant to have more than one ED visit (ie, if SZC/placebo or lisinopril/valsartan are discontinued at different times).
- The time and the reason for discontinuation of any study intervention will be recorded.

- Participants discontinuing study intervention should be given locally available SoC therapy, at the discretion of the investigator.

Additional procedures to be followed when a participant is discontinued from study intervention are described below for each phase of the study:

- Initiation Phase
  - If SZC is discontinued, the participant should attend a follow-up Visit 7 (± 2) days after the last dose of SZC. This is the last visit in the study for the participant. See the SoA (Section 1.3) for data to be collected at the follow-up visit.
- Run-in Phase
  - If any study intervention (SZC or lisinopril/valsartan) is discontinued, the other study intervention must be discontinued. See NOTE.
  - The participant should attend an ED visit.
  - The participant should attend a follow-up Visit 7 (± 2) days after the last dose of study intervention. This is the last visit in the study for the participant. See the SoA (Section 1.3) for data to be collected at the follow-up visit.
- Maintenance Phase
  - If either SZC/placebo or lisinopril/valsartan is discontinued:
    - The participant may remain on the other study intervention. See NOTE.
    - The participant should attend an ED visit.
    - The participant must remain in the study and attend all subsequent visits as planned.
  - If both SZC/placebo and lisinopril/valsartan are discontinued:
    - The participant should attend an ED visit.
    - It is preferred that the participant remain in the study and attend all subsequent visits as planned.
    - If the participant is unwilling to remain in the study and attend all subsequent visits as planned, it is acceptable to offer modified follow-up. Modified follow-up options include, but are not limited to, modified visit schedule, telephone contact, or allowing the investigator to check medical records for information about the participant's health status.

NOTE: Participants who are started on lisinopril and who subsequently develop any common nonserious side effects (eg, cough), can change to valsartan at a comparable dose range per Appendix B 1 at the investigator's discretion. If this happens, the participant will complete an ED visit when lisinopril is permanently discontinued. The participant can continue to receive SZC/placebo (and valsartan) in the study.

7.1.2 Temporary Discontinuation

Temporary discontinuation (hold) of study intervention is allowed for the following situations:

- Situations applicable to all study intervention
  - Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment.
  - An AE temporarily precluding further therapy with SZC/placebo or lisinopril/valsartan
- Additional situations applicable to SZC/placebo
  - Hypokalaemia
- Additional situations applicable to lisinopril/valsartan
  - Hyperkalaemia as described in Appendix C and Section 6.6.4
  - Symptomatic hypotension
  - Rise in S-Cr > 30% within 2 weeks from previous dose increase visit
  - eGFR < 20 mL/min/1.73m^2

Temporary discontinuation of any study intervention should not be a reason for permanent discontinuation and the participant should be allowed to resume treatment as soon as, in the opinion of the investigator, the participant's condition is stable, and the participant wishes to resume. The time and reason for temporary discontinuation, as well as the time of the re-initiation of treatment, will be recorded.

Temporary discontinuation of SZC or lisinopril/valsartan in the run-in phase does not preclude randomisation provided the participant meets the requirement to proceed to the maintenance phase (Section 4.1.3).

7.1.3 Procedures for Erroneously Dosed or Randomised Participants

Participants who fail to meet the eligibility criteria for the study (Sections 5.1 and 5.2) or fail to meet requirements for entering any phases of the study (Sections 4.1.2, 4.1.3, and 4.1.4) will not, under any circumstances, enter that phase. There can be no exceptions to this rule. If a participant does not meet all the study eligibility criteria or the requirements for entering a study phase but is dosed in error, or incorrectly randomised, then the investigator should inform the AstraZeneca Study Physician immediately. A discussion should then occur between the AstraZeneca Study Physician and the investigator regarding whether to continue or discontinue the participant from treatment (see Section 7.1.1). The AstraZeneca Study Physician must ensure all decisions are appropriately documented. If the participant initiates the first phase of the study on a higher dose than indicated by the CSP (ie, 10 g TID rather than 5 g QD) due to a mistake in the initial S-K evaluation, then this should be considered an overdose, and the procedures detailed in Section 8.4 should be followed.

7.2 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request without prejudice to further treatment. In exceptional circumstances, the participant may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons.

A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or collecting information from medical records).

At the time of withdrawal from the study, if possible, an ESD visit should be conducted per SoA (Section 1.3). The participant will discontinue the study intervention, if applicable, and be withdrawn from the study at that time.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team. If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

7.3 Lost to Follow up

A participant will be considered lost to follow up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for any of the required study visits:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Unscheduled visits may occur in-between scheduled visits for evaluation of a participant's clinical status. Assessments and activities that may be performed at such visits may include, but are not limited to, local or central laboratory measurements, collection of AEs/SAEs, study intervention dose adjustment, dispensation of study intervention, or other assessments deemed clinically necessary by the investigator.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria (Sections 5.1 and 5.2). The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Similarly, the evaluation of normokalaemia must be completed before the entry into the run-in and the maintenance phases, with the results recorded as appropriate (see Sections 4.1.2, 4.1.3, and 8.9.1).

The following efficacy, safety (including AEs and SAEs), and other assessments apply also for irbesartan if used instead of valsartan because of a shortage of the latter. See Appendix E 8 for irbesartan overdose information.

8.1 Efficacy Assessments

8.1.1 Assessments Based on Laboratory Analyses

Laboratory efficacy variables are shown in Table 9.

Table 9 Laboratory Efficacy Variables

Primary endpoint	Secondary endpoint
• eGFR [a] (S-Creatinine)	• eGFR [a] (S-Creatinine) • UACR [b] (U-Albumin and U-Creatinine) • S-Potassium • S-Bicarbonate

[a] The eGFR will be derived by race agnostic CKD-EPI equation (Delgado et al 2022, Inker et al 2021) and calculated by central laboratory for the analysis of the primary endpoint. The race adjusted eGFR will also be calculated and may be used for sensitivity or supportive analyses (Levey et al 2009).

[b] The UACR will be calculated by central laboratory.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; S, serum; U, urine; UACR, urine albumin-to-creatinine ratio.

Analyses will be performed at a central laboratory contracted by AstraZeneca; the timing of the samples is indicated in the SoA (Section 1.3). For instructions on the sampling process, see Section 8.2.4.1.

8.1.2 Other Efficacy Assessments

Composite Outcome

The components of the composite of kidney failure outcomes are defined below, based on Levin et al 2020:

- Sustained percent decline in eGFR, defined as percent decline in eGFR of ≥ 40% from the point of randomisation over at least 4 weeks, as evidenced by 2 consecutive central laboratory measurements taken at least 4 weeks apart. The start date of the event is the date of the first central laboratory measurement.
- Onset of ESKD:
  - Kidney transplantation, defined as receipt of a kidney transplant or
  - Maintenance dialysis, defined as dialysis performed for at least 4 weeks, or
  - Sustained low eGFR, defined as eGFR < 15 mL/min/1.73m^2 over at least 4 weeks, as evidenced by 2 consecutive central laboratory measurements taken at least 4 weeks apart.
- Death from kidney failure, defined as the participant dies, AND kidney replacement therapy was never started (irrespective of reason), AND advanced CKD is the underlying cause of death.

The central laboratory will notify the site if there is ≥ 40% decline in eGFR compared to the point of randomisation or if eGFR is < 15 mL/min/1.73m^2. A central laboratory re-sampling should be done at an unscheduled visit after at least 4 weeks, and preferably no later than 6 weeks, after the first sampling.

Whether an event of death qualifies as death from kidney failure will be determined by the investigator and indicated in the source documentation and eCRF. Similarly, the initiation of renal replacement therapy (kidney transplantation or maintenance dialysis) will be recorded by the investigator in the source documentation and eCRF.

Lisinopril/Valsartan Dosing Pattern

The prescribed dose, the start, and the stop dates, as well as the timing of the dose titration of lisinopril/valsartan will be recorded and used to determine the time to the first dose change to a dose that is smaller than that taken at the point of randomisation.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

8.2.1 Physical Examinations

A complete physical examination will include an assessment of general appearance, respiratory system, CV system, abdomen, skin, head, and neck (including ears, eyes, nose and throat), lymph nodes, thyroid gland, musculoskeletal system (including spine and extremities), and neurological system.

A brief physical examination will include an assessment of general appearance, respiratory system, CV system, and abdomen.

New or worsening abnormalities may qualify as AEs; see Section 8.3 for details.

Height will be assessed using locally available tools without the participant wearing shoes. Weight will be assessed using the same scale (properly maintained and calibrated), and with the participant wearing a similar amount of clothes (eg, underwear only or light indoor clothing only) at each time.

8.2.2 Vital Signs

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

For all participants, blood pressure and pulse measurements should be preceded by at least 5 minutes of rest in a supine or sitting position in a quiet setting without distractions (eg, television, cell phones) and should be taken before any blood sampling (unless otherwise noted in the SoA; Section 1.3). The participant should be relaxed with the arm outstretched and supported. Blood pressure should be measured in the upper arm in either the supine or sitting position. No shift from one position to another should be made during the study. The participant should also abstain from caffeine for at least one hour prior to the measurements.

Systolic and diastolic blood pressure will be measured by an adequately trained health care professional. Measurements with a calibrated sphygmomanometer are preferred. If not available, another device calibrated carefully in proportion to a mercury sphygmomanometer is preferred. The use of aneroid manometers should be avoided. An appropriate cuff size must be used to ensure accurate measurement.

8.2.3 Electrocardiograms

A 12-lead ECG will be performed with a properly maintained and calibrated machine. The recording should be done after the participant has been lying down to rest for at least

5 minutes. For participants with pacemakers, ECG variables should be read manually. ECG may also be performed according to clinical judgment and should be performed in connection with hypokalaemia (S-K < 3.0 mmol/L) or hyperkalaemia (S-K > 6 mmol/L), or as indicated based on any symptoms or clinical events (eg, cardiac arrhythmia).

The following ECG parameters should be collected: PR interval, RR interval, QRS duration, QT and QTcF intervals, and heart rate. An overall evaluation of the ECG results should also be performed.

8.2.4 Clinical Safety Laboratory Assessments

8.2.4.1 Clinical Safety Central Laboratory Assessments

Blood samples for determination of clinical chemistry, haematology, and pregnancy will be taken at the visits indicated in the SoA (Section 1.3).

Analyses will be performed at a central laboratory contracted by AstraZeneca. Sites will be provided with ready-to-use laboratory kits, as well as appropriate instructions/manuals, where procedures for collection, processing, and sending samples to the central laboratory will be described.

All serum samples should be examined, and any haemolysed samples must be re-drawn.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator.

The laboratory variables listed in Table 10 will be measured.

Table 10 Central Laboratory Safety Variables

Haematology/haemostasis (whole blood)
Haemoglobin (Hb)
Leucocyte count
Leucocyte differential count (absolute count)
Platelet count
Clinical chemistry (serum)
Bilirubin, total, direct and indirect
Alkaline phosphatase (ALP)
Alanine transaminase (ALT)
Aspartate transaminase (AST)
Gamma glutamyl transferase (GGT)
Lactate dehydrogenase (LDH)
Urea nitrogen
Creatinine
Glucose
Uric acid
Calcium
Phosphorus
Total protein
Albumin
Globulin
Triglycerides
Cholesterol
Creatine kinase (CK)
Sodium
Potassium
Bicarbonate
Chloride
Magnaesium
Pregnancy test (serum)
Human chorionic gonadotropin (HCG)

8.2.4.2 Clinical Safety Local Laboratory Assessments

Blood samples for determination of clinical chemistry for local laboratory safety monitoring will be taken at the visits indicated in the SoA (Section 1.3).

All serum samples should be examined, and any haemolysed samples must be re-drawn.

Additional safety samples may be collected, if clinically indicated at the discretion of the investigator.

The minimum laboratory variables listed in Table 11 will be measured for safety monitoring. Additional variables may be measured if clinically indicated at the discretion of the investigator.

Table 11 Local Laboratory Safety Variables

Clinical chemistry (serum)
Urea nitrogen
Creatinine
Sodium
Potassium
Bicarbonate
Chloride

8.3 AEs and SAEs

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix G.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the start of first dose of study intervention (Visit 2 of initiation phase) throughout the treatment period and including the follow-up period.

Serious AEs will be recorded from the time of signing of the ICF.

If the investigator becomes aware of an SAE with a suspected causal relationship to the Study intervention that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the Sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse Event Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity (mild, moderate, or severe). For event of hypokalaemia, mild intensity refers to S-K ≥ 3.0 to < 3.5 mmol/L, moderate intensity ≥ 2.5 to < 3.0 mmol/L, and severe intensity < 2.5 mmol/L.
- Whether the AE is serious or not
- Whether the AE required rescue therapy for severe hyperkalaemia or not
- Whether the AE fulfils the criteria of death from kidney failure or not
- Investigator causality rating against each study intervention, SZC, SZC/placebo, and lisinopril/valsartan (yes or no)
- Action taken with regard to each study intervention
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.3.3 Causality Collection

The investigator should assess causal relationship between each study intervention and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable

possibility that the event may have been caused by the study intervention?' for each study intervention (SZC, SZC/placebo, lisinopril/valsartan).

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes.'

A guide to the interpretation of the causality question is found in Appendix G.

8.3.4 AEs Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 AEs Based on Examinations and Tests

The results from the CSP-mandated laboratory tests and vital signs will be summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention or are considered to be clinically relevant as judged by the investigator (which may include but is not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Hypokalaemia leading to a temporary or a permanent discontinuation of SZC or SZC/placebo should be reported as an AE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 Reporting of SAEs

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives **within 1 day, ie, immediately but no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site within 1 calendar day of initial receipt for fatal and life-threatening events and **within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE **within 1 calendar day, ie, immediately but no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix G.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for SZC and is the applicable SmPC for lisinopril and valsartan.

8.3.7 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- Pregnancy discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

8.3.7.1 Maternal Exposure

If a participant becomes pregnant during the study, all study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives **within 1 day, ie, immediately but no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.6) and **within 30 days** for all other pregnancies.

8.3.7.2 Paternal Exposure

There is no restriction on fathering children or donating sperm during the study.

8.3.8 Medication Error

Medication error reporting is only required for SZC and SZC/placebo.

The definition of a medication error can be found in Appendix G 4.

If a medication error occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives **within 1 day, ie, immediately but no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed **within 1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.3.6) and **within 30 days** for all other medication errors.

8.4 Overdose

8.4.1 SZC or SZC/Placebo

For participants entering the initiation phase being hyperkalaemic (based on local laboratory S-K), any dose of SZC > 30 g within 1 day or continuation of the correction dose (10 g TID) for more than 72 hours will be considered an overdose. For participants entering the initiation phase being normokalaemic (based on local laboratory S-K), any dose of SZC > 5 g within

1 day will be considered an overdose. If the overdose is discovered during the initiation phase, the dosing regimen should immediately be corrected to the one pre-specified by the CSP.

During the run-in and maintenance phases, any dose of SZC or SZC/placebo > 15 g within 1 day will be considered an overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on SZC or SZC/placebo occurs during the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, **but no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see section 8.3.6) and **within 30 days** for all other overdoses.

8.4.2 Lisinopril/Valsartan

During the run-in and maintenance phases, any dose of valsartan or lisinopril greater than the prescribed daily dose is considered an overdose with potential risks, and safety monitoring as per SoC shall take place.

An overdose with associated SAEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.6).

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix H.

8.5.1 Pharmacokinetics

Pharmacokinetic samples are not collected in this study.

8.5.2 Immunogenicity

Immunogenicity samples are not collected in this study.

8.5.3 Pharmacodynamics

Pharmacokinetic samples are not collected in this study.

8.6 Human Biological Sample Biomarkers

Samples for biomarker analysis will not be collected in this study.

8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

8.8 Medical Resource Utilisation and Health Economics

Medical resource utilisation and health economics data are not collected in this study.

8.9 Other Assessments

8.9.1 Local Laboratory Measurements

The S-K will be measured by local laboratory to determine if a participant can proceed into the next phase of the study (see Section 4.1). The S-K and S-Cr measurements obtained from the local laboratories will also be used to determine the need for dose adjustments (SZC/placebo and lisinopril/valsartan; see Section 6.6). Finally, local laboratories will be used for safety purposes to evaluate S-K in the period following the randomisation and throughout the maintenance phase.

For determination of SZC starting dose at Visit 2/Day 1 of the initiation phase, the local laboratory sample can be taken on the same day as the visit, or the day before.

For dose titration during the run-in and maintenance phases, the local laboratory samples can be taken on the same day as a scheduled or unscheduled visit, or the day before (excluding Visits 7 and 8); for Visits 7 and 8, the samples must be taken on the same day as the scheduled visit and not the day before.

Data results from local S-K laboratory samples should be obtained as soon as possible after sample collection, but no later than 24 hours after the sample collection. If dose adjustments are required, the investigator will inform the participant either by phone or during a visit, depending on the time point when the laboratory results are available.

8.9.2 Demography and Medical History

Demography will include basic background participant information such as age, sex, and race. Collection of medical history will include history of nicotine use (former, current, never smoker) and an overview of relevant medical conditions, including CKD etiology.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Statistical testing will be performed for all primary and secondary hypotheses. In all cases, the null hypothesis will be that of no difference between the treatment arms (SZC vs placebo). The family-wise Type I error rate will be controlled in the strong sense over the families of the primary and the secondary hypotheses.

Two co-primary hypotheses (corresponding to the evaluation of the difference in total and chronic eGFR slope, respectively) are defined in the study. Provided both of the primary hypotheses are rejected, the testing will proceed to the secondary hypotheses. A fixed sequence MTP will be applied to the family of all secondary hypotheses, with the order in the sequence following the order specified in Table 4.

Both of the co-primary hypotheses will be tested at a two-sided significance level of 0.05. In accordance with the fixed sequence MTP, significance for a hypothesis corresponding to a secondary endpoint will be declared if the corresponding two-sided p-value is smaller than 0.05, provided that all other preceding hypotheses in the sequence have been rejected.

9.2 Sample Size Determination

Approximately 3000 participants will be enrolled (screened) to achieve approximately 1500 participants receiving at least one dose of SZC during the initiation phase, consequently leading to a target of 1360 participants randomly assigned to SZC or placebo.

Note that “enrolled” refers to a participant’s, or their legally acceptable representative’s, agreement to participate in the study following completion of the informed consent process.

The assumptions for variability of the eGFR measurements between and within participants used in the calculation below are taken from the DECLARE study (D1693C00001 [NCT01730534]): between-participant SD (ie, SD of the random slopes) of 2.6 and within-participant SD (ie, SD of the residuals) of 7.7. The difference in slopes in the 2 treatment arms is assumed to be 0.75, a magnitude that is deemed clinically relevant. For the purpose of sample size determination, it is also assumed that no acute effects are present, ie, that the decline in eGFR over time in both treatment arms is well-approximated by a single line with a particular slope.

Given this, and assuming a two-sided test of a difference in slopes based on a linear mixed model, with a two-sided significance level of 0.05, is performed, then approximately 1220 participants with complete eGFR data will provide a power of 91% for the evaluation of total slope. This is true provided the following time points for eGFR assessment, in terms of weeks since randomisation, are observed for each participant as a minimum: 0 (randomisation), 6, 12, 16, 20, 24, 46, 69, 92, 96, 100, and 104.

Under the same assumptions (ie, a difference in slopes of 0.75, no acute effect), the power for the chronic slope will be approximately 85%. The evaluation of the chronic slope is assumed to start at 12 weeks.

It is expected that approximately 20% of the eGFR data will be missing. As the eGFR data is correlated within participant, it is assumed that the data points available for a participant will provide information on the missed evaluations, and 20% of missed data would roughly correspond to approximately 10% of randomised participants with no eGFR data available. Hence, 1360 participants will be randomised in the maintenance phase.

Possible Causes for Missing Data during the Randomised Treatment Phase

The initial expectation that approximately 20% of eGFR measurements during the randomised treatment phase will be missing, is largely inferred from DAPA-CKD (Heerspink et al 2020). Death from any cause and ESKD were identified as the 2 potential main contributors for missing eGFR data. Looking at the placebo group in the aforementioned publication, it is expected that approximately 7% of participants will reach ESKD during the 2 years of randomised treatment phase, and approximately 6% of participants will die; this is a conservative assumption as some participants will likely experience both of these events. It should be noted that the DAPA-CKD study had a somewhat healthier patient population that included patients with eGFR between 25 and 75 mmol/L (10% of the patient population in the study had an eGFR > 60 mmol/L). In addition, the hyperkalaemia requirement in the STABILIZE-CKD study might lead to a lower baseline eGFR in general, so a somewhat larger percentage of missing data due to the reasons mentioned above is expected. The expectation is that approximately 15% of the missing values will originate from ESKD or death.

In addition to these 2 major reasons, it is expected that data points will also be missing due to a number of smaller issues, such as participants not attending visits, blood samples not being analysable, and participants either discontinuing the study or discontinuing treatment and choosing an alternative follow-up option that precludes blood sampling. The magnitude of such smaller issues is difficult to predict, but it is expected that they might, cumulatively, lead to an additional 5% of the data points being missing, which would, together with ESKD and death, add up to approximately 20% of missing data.

9.3 Populations for Analyses

The populations for analysis are defined in Table 12.

Table 12 Populations for Analysis

Population/analysis set	Description
Enrolled	All participants who sign the ICF.
Safety analysis set, initiation phase (SAS-IP)	All participants receiving at least one dose of SZC during the initiation phase.
Safety analysis set, run-in phase (SAS-RIP)	All participants receiving at least one dose of SZC during the run-in phase.
Safety analysis set, maintenance phase (SAS-MP)	All randomised participants receiving at least one dose of SZC or placebo during the maintenance phase. Participants erroneously receiving incorrect SZC or placebo will be analysed according to the treatment arm they were randomised to.
Full analysis set (FAS)	All randomised participants.

ICF, informed consent form; SZC, Sodium zirconium cyclosilicate.

9.4 Statistical Analyses

The SAP will be finalised prior to data base lock and will provide a complete description of all the planned statistical analyses, including the analyses of the secondary objectives, sensitivity and complementary analyses of the primary objective, descriptions of supportive data overviews, and procedures for handling of missing data. The complementary analyses will eg, include an exploration of the potential effect that temporarily switches from valsartan to irbesartan have on the efficacy evaluation. This section is primarily a summary of the planned statistical analysis of the primary objective(s).

Analyses will be performed by AstraZeneca or its representatives.

9.4.1 General Considerations

The Full Analysis Set will be used for the efficacy evaluations, while the different safety analysis sets will be used for the safety evaluation, performed for each study phase separately.

9.4.2 Efficacy

The analysis of both primary and secondary efficacy endpoints will be performed according to the intention-to-treat principle and will be based on all randomised participants, regardless of whether they did or did not receive treatment or had any protocol deviations.

9.4.2.1 Co-primary Endpoint(s)

Estimand

Population: Participants satisfying the inclusion and the exclusion criteria of the study and achieving normokalaemia after a 3-month run-in period, while on SZC treatment regimen, during which lisinopril/valsartan dose optimisation has been attempted.

Intervention: SZC and placebo, while receiving lisinopril/valsartan, as guided by the CSP.

Population-level summary: Difference in population-level eGFR slopes between SZC and placebo.

Intercurrent events: In general, the intercurrent events that lead to a potential change in the measurements profile, but for which post-intercurrent event data are available (eg, treatment discontinuation, introduction of eGFR altering concomitant therapy), will be ignored, and all eGFR data obtained, both pre and post the intercurrent event will be used in the primary analysis. This would correspond to a treatment policy approach as per ICH E9 (R1) and align with the intention-to-treat principle. The exception to this rule will be the events for which it could be argued that, after experiencing these, a participant ceases to belong to the population of interest, namely onset of ESKD as defined in Section 8.1.2. For such an event, any data collected post event occurrence will be excluded from the analysis of the primary objective.

Analysis

To evaluate both primary objectives, a linear mixed effects model will be used, with the eGFR values obtained at and after randomisation (total slope) and at and after 12-week visit (chronic slope) for a participant at a particular visit as the dependent variable. The following covariates will be included in the fixed effects part of the model:

- Time since randomisation
- Treatment
- Time and treatment interaction

Other covariates, as appropriate, might also be included and will be specified in the SAP. In addition, 2 random effects, intercept and time since randomisation, will be incorporated within a participant, with an underlying assumption of an unstructured covariance matrix between the two. A covariance matrix that assumes independence for the distribution of the residuals within each participant, but allows for different variability for different time points, will be applied, with a more general structure (eg, unstructured) used if issues with the model fit are encountered. An unstructured covariance matrix will also be assumed for the distribution of the residuals within each participant. The null hypothesis of no difference between SZC and placebo will be tested by considering the fixed effect of time and treatment interaction term in the model above (ie, the difference in slopes between the 2 treatment arms). The estimates of

the slopes obtained from the model, as well as the difference between the two, and the corresponding SD estimates, will be presented. For the difference, the two-sided 95% confidence intervals and p-values will also be provided.

A number of sensitivity analyses of the primary endpoints will be performed. These will include, but might not be limited to, the following:

- A two-slope model (acute and chronic) with knot at 12 weeks post-randomisation (ie, using the same interval for the chronic slope as is utilised in the primary analysis). From this, estimates of the total and the chronic slope will be obtained. The purpose of this analysis is to evaluate the sensitivity of the results to the choice of approaching the primary objective via two separate models rather than a single combined one.
- A series of two-slope models (acute and chronic) with varying position of knots (the times of connection between acute and chronic slopes) other than 12 weeks. The purpose of this analysis is to evaluate the impact of the choice of 12 weeks as the start of the chronic eGFR profile on the estimate of the treatment effect.
- A shared parameter model that jointly models the eGFR profiles and time to ESKD or death. The purpose of this analysis is to evaluate the potential impact that the possibly informative drop-out caused by these 2 events has on the estimate of the effect of SZC.
- A tipping point analysis to explore the potential impact of data that are missing due to participant being lost to follow-up or entering a modified follow-up that precludes collection of eGFR measurements.
- A repeated measures model that includes the same covariates as the main analysis and utilises an unstructured (marginal) covariance matrix to reflect the dependence between observations obtained at different timepoints for the same participant.
- Same model as the one utilised for the main analysis, where missing eGFR values will be imputed as follows: if a participant is considered to enter ESKD through initiation of dialysis or kidney transplant, but no corresponding eGFR value is available, this will be imputed to a value that is less than 15 mL/min/1.73m^2.

In addition, graphical illustrations of eGFR profiles over time, eg, a scatter plot of eGFR values with a non-parametric smoothing curve in the respective treatment arm, will be provided to illustrate the plausibility of the assumption of a linear eGFR decline and the potential presence of acute effects.

The consistency of effect across subgroups defined by inclusion criterion 5 (Section 5.1) will be evaluated for the primary endpoint by obtaining effect estimates in each of these, along with the p-values for the test of the corresponding interaction. In addition, if the size of the subgroups allows, the subgroups in which the consistency of the main results will be evaluated will include, but might not be limited to the following: geographic region; diabetes at randomisation (yes/no); eGFR classification at randomisation; UACR classification at randomisation; adequate RAASi dose at screening (yes/no); adequate RAASi dose at randomisation (yes/no); CKD aetiology; SGLT2 inhibitor and/or finerenone use at

randomisation (yes/no). Further details of the subgroup analyses plan, including full specification of the groupings, will be provided in the SAP.

The eGFR will be calculated according to the race agnostic CKD-EPI formula (Delgado et al 2022, Inker et al 2021) for the main analysis of the primary endpoint. The eGFR will also be calculated according to the original race adjusted CKD-EPI formula (Levey et al 2009) and may be used for sensitivity or supportive analyses.

9.4.2.2 Secondary Endpoint(s)

The analysis of the secondary objectives will be presented in the SAP.

9.4.3 Safety

Safety analyses will be performed separately for the different phases of the study using the 3 safety sets defined above, as appropriate. Safety data will be presented primarily using descriptive statistics, by treatment arm and study phase.

Adverse Events

Adverse events will be coded using the most recent version of the MedDRA that will have been released for execution at AstraZeneca.

A high-level overview of AEs will be presented for each treatment group and will include the number and percentage of participants with any AE, AEs with outcome of death, SAEs, and AEs leading to discontinuation of SZC/placebo or lisinopril/valsartan.

Adverse events will be presented for each treatment group by system organ class and/or preferred term, covering number and percentage of participants reporting at least one event and number of events where appropriate. Similar tables will be created for SAEs, discontinuations due to AE, and AEs with the outcome of death. Separate AE tables will be provided to illustrate AE pattern with respect to causal relationship as assessed by the investigator, as well as the intensity of AEs. Key information will be presented for participants with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of SZC/placebo. Adverse events occurring during the screening period will be presented in a listing.

Vital Signs, Laboratory Evaluations, and ECG

The distribution of the measurements over time will be illustrated by presenting the summary statistics (mean, SD, median, minimum, maximum) of the values obtained at the study visits, as well as change from baseline to each of the respective visits. The occurrence of extreme measurements, eg, measurements falling outside pre-defined criteria at any point during a study phase, or measurements judged to be abnormal by the investigator, will be summarised by means of frequencies and percentages.

Events of Hypokalaemia and Oedema

A tabulated overview of oedema-related AEs will be presented, with oedema-related AE defined through the following preferred terms: fluid overload, fluid retention, generalised oedema, hypervolaemia, localised oedema, oedema, oedema peripheral, peripheral swelling.

Instances of S-K < 3.5 mmol/L at particular visits, as well as the number and percentage of participants with S-K < 3.5 mmol/L at any point during a study phase, will be tabulated. Instances of S-K < 3.0 and < 2.5 mmol/L will be presented in a similar manner.

9.5 Interim Analyses

There are no interim analyses planned in this study.

9.6 Data Monitoring Committee

An independent DMC that is unblinded to treatment allocation will be responsible for safeguarding the interests of the participants throughout the study. For details on the DMC, see Appendix A 5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organisation (CRO) but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the Sponsor of a serious adverse event (SAE) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will

review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

Participants who are rescreened are required to sign a new ICF.

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

A 5.1 Executive Committee

Together with AstraZeneca, the Executive Committee will be responsible for the final overall study design, including the development of the study protocol and any protocol amendments needed during the study, liaison with the Data Monitoring Committee (DMC), as needed, development of the charter, and supervision, interpretation, and reporting (presentations at international congresses and publications in peer reviewed journals) of the study.

The Executive Committee will make recommendations to AstraZeneca with regard to early stopping or modifications of the study based on the information received from the DMC. The Executive Committee will be comprised of designated international academic leaders and non-voting members of the Sponsor and will operate under an Executive Committee charter.

A 5.2 Data Monitoring Committee

An independent DMC will be appointed. The DMC will be responsible for monitoring the progress of the study with respect to randomisation, compliance, and follow up, as well as for reviewing the unblinded data for evidence of benefit or harm. The DMC can make recommendations to the Sponsor and the Executive Committee to alter or terminate all or part of the trial. A DMC charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the Executive Committee.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic case report form (eCRF) unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections, and provide direct access to source data documents.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the in the Monitoring Plan and Clinical Trial Agreement.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in ICH GCP Section 1.52 Source Documents.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B RAASi Therapy Considerations for Inclusion into the Study and Dosing of Lisinopril and Valsartan

B 1 Guide for Change of Other RAASi therapy into an Equivalent Dose Range for Lisinopril or Valsartan

Other ACEi or ARB SoC dose [a]	Lisinopril (mg) [b]	Valsartan (mg) [b]
None or starting daily dose	10 (5) [c]	80
Mid-range daily dose (doses between starting and maximum dose if applicable)	20 (10) [c]	160
Maximum daily dose	20 (20) [c]	160

[a] See Appendix B 2 for starting, mid-range (if applicable), and maximum daily dose of each individual ACEi/ARB drug.

[b] Starting dose may differ per local labels. For example, in Japan, where starting doses are lower than specified above, the following would apply:

- Starting: lisinopril 10 mg; valsartan 40 mg
- Mid-range: lisinopril 20 mg; valsartan 80 mg
- Maximum: lisinopril 20 mg; valsartan 160 mg

[c] If eGFR ≥ 10 to ≤ 30 mL/min/1.73m^2 or participant is on diuretics, or per local label, lisinopril starting, mid-range, and maximum are 5, 10, and 20 mg, respectively.

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; SoC, standard of care.

For subsequent up-titration of lisinopril or valsartan during the run-in phase, see Sections 6.6.2 and 6.6.3.

B 2 RAASi Dose Equivalence Table

Drug	Starting daily dose	Mid-range daily dose (if applicable)	Maximum daily dose
ARB			
Valsartan [a]	80 mg	160 mg	320 mg
Losartan [a]	50 mg	-	100 mg
Olmesartan	20 mg	-	40 mg
Azilsartan	20 – 80 mg	40 mg	80 mg
Candesartan	16 mg	-	32 mg
Irbesartan [a]	150 mg	-	300 mg
Telmisartan	40 mg	-	80 mg
ACEi			
Lisinopril [a]	10 mg	20 mg	40 mg
Ramipril CrCl < 40 mL/min: 25% of normal dose	2.5 mg	5 mg, 10 mg	20 mg
Perindopril [b] CrCl < 30 mL/min: not recommended	2 mg	4 mg	8 mg
Benazepril	10 mg CrCl < 30 mL/min: 5 mg	20 mg, 40 mg	80 mg
Captopril CrCl 10-50 mL/min: 75% of normal dose CrCl < 10 mL/min: 50% of normal dose	12.5 – 25 mg bid to tid	12.5 mg tid 25 mg, 37.5 mg bid to tid 50 mg bid	Usually 50 mg tid (may go up to 450 mg)
Enalapril	5 mg CrCl ≤ 30 mL/min: 2.5 mg	10 mg, 20 mg	40 mg
Fosinopril	10 mg	20 mg, 40 mg	80 mg
Quinapril	10 mg CrCl 61-89 mL/min: 10 mg CrCl 30-60 mL/min: 5 mg CrCl 10-29 mL/min: 2.5 mg	20 mg, 40 mg	80 mg
Trandolapril	1 mg CrCl < 30 mL/min: 0.5 mg	2 mg	4 mg

NOTE: Dosage recommendations are based on KDIGO guidelines (KDIGO 2020)/information from package inserts registered in the United States and may differ across countries and regulatory authorities.

[a] Doses may differ per local labels. For example, valsartan starting dose can be 40 mg; losartan starting dose can be 25 mg; irbesartan starting dose can be 50 or 75 mg; irbesartan maximum dose can be 200 mg (eg, Japan); lisinopril starting dose can be 2.5 or 5 mg.

[b] Refers to perindopril erbumine (tablet strength may differ depending on perindopril salt).

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; bid, twice daily; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; tid, three times daily.

B 3 Definitions of RAASi Adequate Dose

Renin-angiotensin-aldosterone system inhibitor (RAASi) adequate dose levels are defined below. Doses lower than the ones listed below are considered as suboptimal.

The definition of "limited RAASi therapy" for purposes of inclusion in the study (Section 5.1) = no or suboptimal RAASi.

ARB	Adequate daily dose [a, b]	ACEi	Adequate daily dose [a, b]
Valsartan	160 - 320 mg	Lisinopril	20 - 40 mg
Losartan	50 - 100 mg	Ramipril CrCl < 40 mL/min: 25% of normal dose	10 - 20 mg
Olmesartan	40 mg	Perindopril [c] CrCl < 30 mL/min: not recommended	8 mg
Azilsartan	40 - 80 mg	Benazepril	20 - 80 mg
Candesartan	32 mg	Captopril CrCl 10-50 mL/min: 75% of normal dose CrCl < 10 mL/min: 50% of normal dose	37.5 bid - 50 mg tid
Irbesartan	300 mg	Enalapril	10 - 40 mg
Telmisartan	80 mg	Fosinopril	20 - 80 mg
		Quinapril	20 - 80 mg
		Trandolapril	2 - 4 mg

NOTE: Adequate dose level definitions are based on KDIGO guidelines (KDIGO 2020)/information from package inserts registered in the United States and may differ across countries and regulatory authorities.

[a] Normokalaemic participants with hypertension or primary glomerular diseases with nephrotic range proteinuria (> 3.5 g/24 hours) who are at high risk of hyperkalaemia, not taking maximal RAASi doses as per local label but currently receiving doses in the range considered adequate in this table can be included in the normokalaemic cohort if in the investigator's judgment the current RAASi dose is not optimal for their condition. In these participants, it is expected that RAASi doses will be up-titrated to maximal during the run-in phase.

[b] Where a range is indicated, any daily dose within that range is considered an adequate daily dose.

[c] Refers to perindopril erbumine (tablet strength may differ depending on perindopril salt).

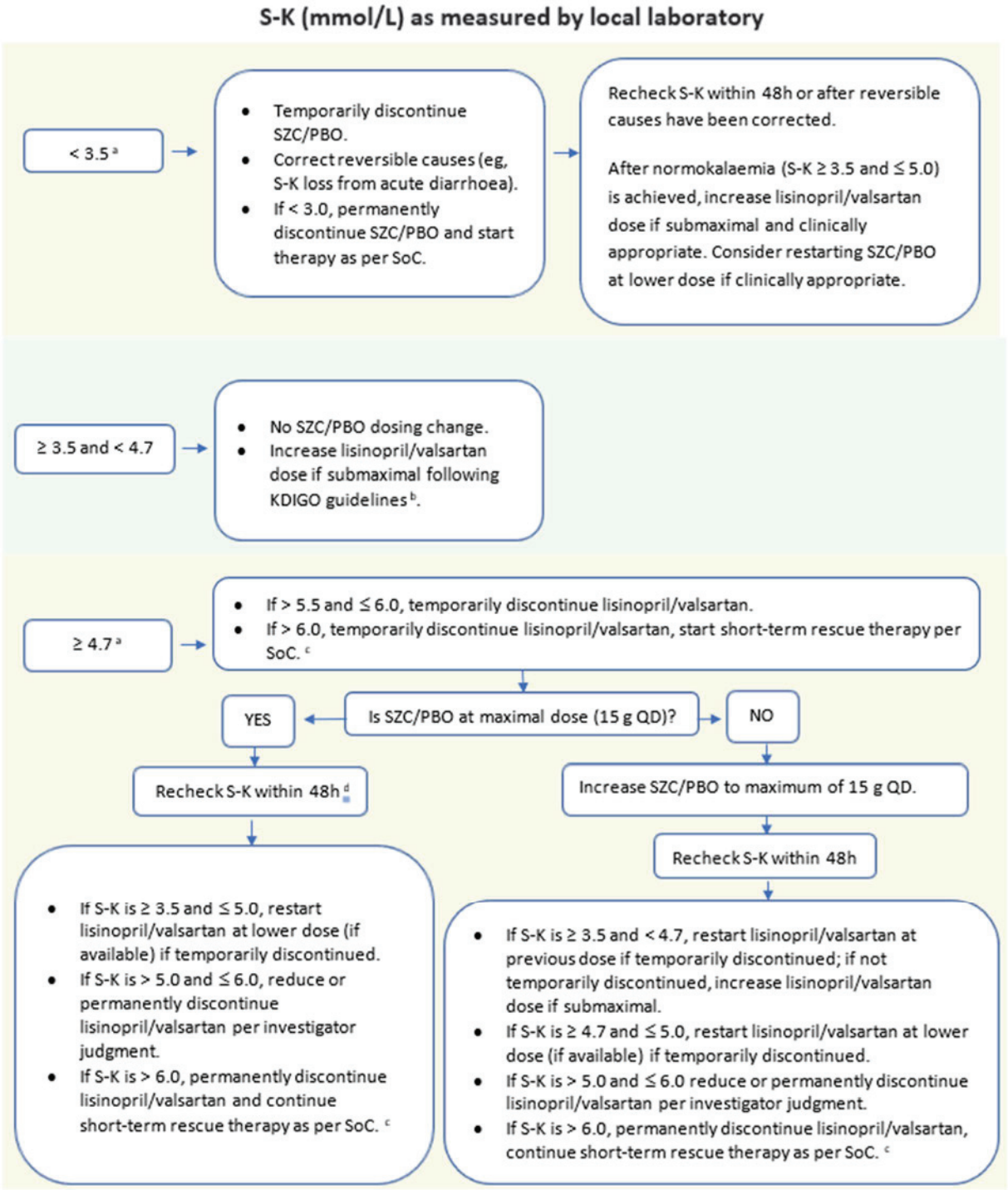
ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; bid, twice daily; CrCl, creatinine clearance; RAASi, renin-angiotensin-aldosterone system inhibitor; tid, three times daily.

Appendix C Instructions for Use of SZC/Placebo for Management of Serum Potassium During the Run-in and Maintenance Phases

Anytime during the run-in and maintenance phases, if lisinopril/valsartan doses are increased (or decreased or discontinued because of hyperkalaemia), participants will be called for additional local laboratory serum potassium (S-K) sampling after 2 weeks or earlier if in the investigator's judgment this is indicated. This includes dose changes that occur during scheduled study visits and during unscheduled visits corresponding to usual clinical care. This aligns with KDIGO 2020 Clinical Practice Guideline for Diabetes Management in chronic kidney disease (CKD) (KDIGO 2020, Practice Point 1.2.2), which indicates that changes in S-K, serum creatinine (S-Cr), and blood pressure should be monitored within 2 to 4 weeks of initiation or increase in the dose of an angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB), and earlier laboratory monitoring may be indicated for participants at high risk of hyperkalaemia due to low estimated glomerular filtration rate, history of hyperkalaemia, or borderline high S K concentration. Instructions for the use of SZC/placebo for management of S-K at such visits during the run-in and maintenance phases are provided below.

In addition, other appropriate monitoring as per routine clinical practice during renin-angiotensin-aldosterone system inhibitor (RAASi) therapy in CKD (eg, S-Cr) should be performed. Refer to KDIGO 2020, which states that, in regard to renal function, initiation or up-titration of RAASi therapy can be done as long as S-Cr does not rise > 30% from pre-dosing value.

If at any point in the study lisinopril/valsartan treatment is reduced or temporarily discontinued, the investigator should make every effort to restart and maximise the dose of these agents once the cause of the reduction or discontinuation has resolved.



Note: If a lower dose of a study intervention (SZC/placebo or lisinopril/valsartan) is not available, temporary or permanent discontinuation should follow at the investigator's discretion depending on the participant's clinical condition. Also note that similar actions as algorithm above should be followed for irbesartan in case of temporary valsartan shortage.

[a] After actions in a panel are completed: recheck S-K within 2 weeks if RAASi therapy is restarted at any dose or increased (see KDIGO 2020); otherwise, recheck S-K at investigator's discretion; and proceed as per Appendix C per new S-K values.

[b] KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD (KDIGO 2020).

[c] SZC/placebo must be temporarily discontinued when rescue therapy is administered. Once rescue therapy is completed (typically within a few hours), SZC/placebo can be resumed at the maximum dose (if not already at maximum dose).

[d] If S-K is ≥ 4.7 and ≤ 5.0 mmol/L, and the participant is on SZC 15 QD and a stable dose of lisinopril/valsartan, a S-K re-check at 48h and further actions may not be necessary. This decision is left to the investigator's clinical judgment.

CKD, chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; PBO, placebo; QD, once daily; S-K, serum potassium; SoC, standard of care; SZC, Sodium zirconium cyclosilicate.

Appendix D Drug Interactions for Lisinopril and Valsartan

D 1 Drug Interactions for Lisinopril

Drug Interactions for Lisinopril

Type of medication/treatment	Instruction
Antihypertensive agents	When combined with other antihypertensive agents (eg, glyceryl trinitrate and other nitrates, or other vasodilators), additive falls in BP may occur. Concomitant use with aliskiren-containing products is contraindicated in participants with diabetes mellitus or renal impairment (eGFR < 60 mL/min/1.73m^2). Concomitant use of ACEi, ARB, or aliskiren is associated with a higher frequency of AEs and increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACEi, ARB, or aliskiren is therefore not recommended.
Sacubitril/valsartan	Concomitant use with sacubitril/valsartan is contraindicated as this increases the risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of lisinopril. Treatment with lisinopril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan.
mTOR inhibitors (eg, temsirolimus, sirolimus, everolimus), NEP inhibitors (eg, racecadotril), vildagliptin, or tissue plasminogen activator	Concomitant use may increase the risk of angioedema (eg, swelling of the airways or tongue, with or without respiratory impairment). Caution should be used when starting racecadotril, mTOR inhibitors and vildagliptin in a patient already taking lisinopril.
Diuretics	Antihypertensive effects are usually additive. Participants already on diuretics and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of BP when lisinopril is added. The possibility of symptomatic hypotension with lisinopril can be minimised by discontinuing the diuretic prior to initiation of treatment with lisinopril. In some patients with bilateral renal artery stenosis or with a stenosis of the artery to a solitary kidney, where renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. Diuretics should be discontinued, and renal function should be monitored during the first weeks of lisinopril therapy.
Potassium-sparing diuretics (eg, spironolactone, triamterene or amiloride), potassium supplements, potassium-containing salt substitutes, and other drugs that may increase serum potassium levels, eg, trimethoprim and co-trimoxazole (trimethoprim/sulfamethoxazole)	Concomitant use is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of S-K.

Drug Interactions for Lisinopril

Type of medication/treatment	Instruction
Ciclosporin	Hyperkalaemia may occur during concomitant use. Monitoring of S-K is recommended.
Heparin	Hyperkalaemia may occur during concomitant use. Monitoring of S-K is recommended.
Lithium	Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACEi. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased lithium toxicity with ACEi. Concomitant use is not recommended, but if the combination proves necessary, careful monitoring of serum lithium levels is recommended.
NSAIDs including acetylsalicylic acid ≥ 3 g/day	When administered simultaneously (ie, acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in S-K, especially in participants with poor pre-existing renal function. These effects are usually reversible. The combination should be administered with caution, especially in the elderly. Participants should be adequately hydrated, and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.
Gold	Nitritoid reactions (symptoms of vasodilatation including flushing, nausea, dizziness, and hypotension, which can be very severe) following injectable gold (eg, sodium aurothiomalate) have been reported more frequently in patients receiving ACEi.
Tricyclic antidepressants/antipsychotics/ anaesthetics	May result in further reduction of BP. In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Lisinopril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.
Sympathomimetics	May reduce the antihypertensive effects of lisinopril.
Antidiabetics, eg, insulins, oral hypoglycaemic agents	Epidemiological studies have suggested that concomitant administration of ACEi and antidiabetic medicines (insulins, oral hypoglycaemic agents) may cause an increased blood glucose lowering effect with risk of hypoglycaemia. This phenomenon appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment. In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with lisinopril.

Drug Interactions for Lisinopril

Type of medication/treatment	Instruction
Acetylsalicylic acid, thrombolytics, beta-blockers, nitrates	May be used concomitantly with acetylsalicylic acid (at cardiologic doses), thrombolytics, beta-blockers, and/or nitrates.

ACEi, angiotensin converting enzyme inhibitor; AE, adverse event; ARB, angiotensin II receptor blocker; BP, blood pressure; COX-2, cyclooxygenase-2; eGFR, estimated glomerular filtration rate; mTOR, mammalian target of rapamycin; NEP, neutral endopeptidase; NSAID, Non-steroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone system; S-K, serum potassium.

D 2 Drug Interactions for Valsartan

Drug Interactions for Valsartan

Type of medication/treatment	Instruction
Dual blockade of RAAS with ARB, ACEi, or aliskiren	Concomitant use with aliskiren-containing products is contraindicated in participants with diabetes mellitus or renal impairment (eGFR < 60 mL/min/1.73m^2). Concomitant use of ACEi, ARB, or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACEi, ARB, or aliskiren is therefore not recommended.
Lithium	Concomitant use is not recommended. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACEi or ARB. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further.
Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels	Concomitant use is not recommended. If considered necessary, monitoring of S-K is advised.
NSAIDs, including selective COX-2 inhibitors, acetylsalicylic acid > 3 g/day, and non-selective NSAIDs	Caution required with concomitant use. Attenuation of the antihypertensive effect may occur. Concomitant use may lead to an increased risk of worsening of renal function and an increase in S-K. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the participant.
Transporters	Caution required with concomitant use. Co-administration of inhibitors of the uptake transporter (eg, rifampin, ciclosporin) or efflux transporter (eg, ritonavir) may increase the systemic exposure to valsartan. Exercise appropriate care when initiating or ending concomitant treatment with such drugs.

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; COX-2, cyclooxygenase-2; eGFR, estimated glomerular filtration rate; NSAID, Non-steroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone system; S-K, serum potassium.

Appendix E Temporary Irbesartan Use in the Event of a Local Valsartan Shortage

Refer to this Appendix only if valsartan needs to be temporarily substituted with irbesartan during valsartan shortage.

The study is designed to use valsartan as the selected ARB therapy adjunct to SZC. However, if an actual shortage of valsartan in a local market jeopardises the ability of participants to enter or continue in the study, valsartan can be temporarily substituted with irbesartan until the shortage of valsartan is resolved.

During treatment with irbesartan, the same procedures indicated for valsartan discontinuation (Section 7) and efficacy, safety, and other assessments (Section 8) must be followed.

As soon as the shortage is resolved, valsartan should be restarted at a dose determined by using the conversion table in Appendix B 1, unless in the investigator's judgment a change in dose is required. Every effort should be made to maximise the doses of valsartan and of irbesartan if the latter needs to be used because of a valsartan shortage.

E 1 Benefit/Risk Assessment for Irbesartan

See Section 2.3 for the overall benefit/risk assessment of the study.

Details of the risk assessment for irbesartan in this study are presented below. The risk assessment is similar to valsartan. Refer to the applicable SmPC for irbesartan for detailed information on the risks of this agent.

Risk Assessment of Irbesartan as Background Intervention

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Hyperkalaemia (S-K > 5.0 mmol/L)	Irbesartan can cause hyperkalaemia (especially in patients with impaired renal function) because it inhibits the release of aldosterone. For participants randomised to placebo, there is risk of hyperkalaemia from irbesartan	Close monitoring of S-K after randomisation, including scheduled safety visits 2 and 7 days after randomisation. Down-titration/withdrawal of irbesartan if significant hyperkalaemia persists. Rescue therapy available per standard of care/clinical practice. SZC/placebo dosing based on local laboratory S-K and instructions in Section 6.6 and Appendix C.

S-Cr, serum creatinine; S-K, serum potassium; SZC, Sodium zirconium cyclosilicate.

E 2 Overall Benefit: Risk Conclusion of Use of Irbesartan

Irbesartan is an ARB with comparable RAASi effects to valsartan, and a similar therapeutic and safety profile. The use of irbesartan as temporary substitution for valsartan does not impact the favourable Benefit/Risk assessment of the study.

E 3 Justification for Dose of Irbesartan

Equivalence calculations for dosing irbesartan during the run-in phase is based on the label recommendations for control of blood pressure as the primary indication. Appendix B 2 details the dosing equivalences among RAASi drugs that form the basis for determining the doses of irbesartan to be used in the study and are based on KDIGO 2020 Clinical Practice Guideline for Diabetes Management in CKD (KDIGO 2020).

If participants are not already on maximum doses of irbesartan upon entry into the run-in phase, stepwise dose adjustments to maximum doses as per local label will be done with close monitoring of S-K and S-Cr following clinical guidelines for RAASi therapy recommended by KDIGO guidelines (KDIGO 2020; see Section 6.6).

Any further dose increases of irbesartan deemed clinically advisable after achieving the maximum dose during the early run-in phase should also follow KDIGO guidelines (KDIGO 2020). If necessary, dose reductions or discontinuation of irbesartan are allowed as judged by

the investigator, eg, because of hyperkalaemia, excessive (≥ 30%) rise in S-Cr, symptomatic hypotension, or other compelling medical reasons (KDIGO 2020).

E 4 Investigational Medicinal Product (Irbesartan)

See Section 6.1 for the study interventions (investigational products) SZC/placebo, lisinopril/valsartan of the study.

The study intervention (investigational product) irbesartan to be administered in this study during valsartan shortage is presented below.

Intervention name/ Characteristic	**Irbesartan**
Type	Drug
Dose formulation	Tablet
Unit dose strength(s) [a]	75, 150, or 300 mg
Dosage level(s) [a]	75, 150, or 300 mg QD
Route of administration	Oral
Use	Background intervention
IMP or NIMP	IMP
Provider	Local sourcing preferred. Under certain circumstances when local sourcing is not feasible, irbesartan may be supplied centrally through AstraZeneca.
Packaging and labelling	Provided in original package and labelled in accordance with GMP Annex 13 and per country regulatory requirement. Label text will be translated into local language.

[a] For Japan, dose levels are 50, 100, or 200 mg QD with unit dose strengths 50 or 100 mg.
GMP, Good Manufacturing Practice; IMP, investigational medicinal product; NIMP, non-investigational medicinal product; QD, once daily.

E 5 Guide for Change of Other RAASi therapy into an Equivalent Dose Range for Irbesartan

In the situation that valsartan is not available when a participant should enter the run-in phase, the following instructions will be followed.

- Participants who are not on ACEi or ARB therapy upon entering the run-in phase, and per investigator's judgement are to be initiated on an ARB will be started on irbesartan on the first day of the run-in phase (starting dose as per table below).
- Participants who are on ARB therapy other than irbesartan at screening will have their therapy changed to irbesartan upon entering the run-in phase. See Appendix B 2 for guidance on the dosing equivalences among ARB drugs and irbesartan.

- Participants who are on irbesartan will continue treatment at the same dose.

A participant cannot receive both lisinopril and irbesartan simultaneously and should not take any other ACEi or ARB concomitantly with irbesartan.

The table below applies also for dose equivalent conversion of valsartan to irbesartan at any stage of the study beyond the run-in phase.

Other ARB SoC dose [a]	**Irbesartan (mg)** [b]
None or starting daily dose	75
Mid-range daily dose (doses between starting and maximum dose if applicable)	150
Maximum daily dose	150

[a] See Appendix B 2 for starting, mid-range (if applicable), and maximum daily dose of each individual ARB drug including valsartan.

[b] Starting dose may differ per local labels. For example, in Japan, the following would apply:
- Starting: Irbesartan 50 mg if applicable
- Mid-range: Irbesartan 100 mg if applicable
- Maximum: Irbesartan 100 mg if applicable

ARB, angiotensin II receptor blocker; SoC, standard of care.

For subsequent up-titration of irbesartan during the run-in phase, see Appendix E 6.

E 6 Irbesartan Dose Titration Steps

Upon entering the run-in phase:

Every effort should be made to increase irbesartan to its maximum dose during the run-in phase. The following dose steps should be used for up-titration:

Dose steps (daily dose)	**Irbesartan (mg)** [a]
STEP 1	75
STEP 2	150
STEP 3	300

[a] Starting dose and dose range may differ per local labels. For example, in Japan, the following would apply:
- STEP 1: Irbesartan 50 mg if applicable
- STEP 2: Irbesartan 100 mg if applicable
- STEP 3: Irbesartan 200 mg if applicable

For up-titration and dose modification strategy of irbesartan during the run-in and maintenance phases, see Sections 6.6.3, 6.6.4, 6.6.5 and follow the same recommendations as for valsartan.

E 7 Drug Interactions for Irbesartan

Drug Interactions for Irbesartan

Type of medication/treatment	Instruction
Diuretics and other antihypertensive agents	Other antihypertensive agents may increase the hypotensive effects of irbesartan. Prior treatment with high dose diuretics may result in volume depletion and a risk of hypotension when initiating therapy with irbesartan. Intravascular volume depletion/symptomatic hypotension should be corrected before the administration of irbesartan.
Dual blockade of RAAS with ARB, ACEi, or aliskiren	Concomitant use with aliskiren-containing products is contraindicated in participants with diabetes mellitus or renal impairment (eGFR < 60 mL/min/1.73m^2). Concomitant use of ACEi, ARB, or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACEi, ARB, or aliskiren is therefore not recommended.
Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other medicinal products that may increase potassium levels (eg, heparin)	Concomitant use is not recommended.
Lithium	Concomitant use is not recommended. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACEi. Similar effects have been very rarely reported with irbesartan so far. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.
NSAIDs (ie, selective COX-2 inhibitors, acetylsalicylic acid > 3 g/day, and non-selective NSAIDs)	Caution required with concomitant use, especially in the elderly. Attenuation of the antihypertensive effect may occur. Concomitant use may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in S-K, especially in patients with poor pre-existing renal function. Patients should be adequately hydrated, and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.
Repaglinide	Irbesartan has the potential to inhibit OATP1B1. Dose adjustment of antidiabetic treatment such as repaglinide may be required.

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; COX-2, cyclooxygenase-2; eGFR, estimated glomerular filtration rate; NSAID, Non-steroidal anti-inflammatory drugs; OATP1B1, organic anion transporting polypeptide 1B1; RAAS, renin-angiotensin-aldosterone system; S-K, serum potassium.

E 8 Irbesartan Overdose

During the run-in and maintenance phases, any dose of irbesartan greater than the prescribed daily dose is considered an overdose with potential risks, and safety monitoring as per SoC shall take place.

An overdose with associated SAEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.6).

Appendix F Management of Study Procedures During the COVID-19 Pandemic

F 1 Introduction

Safeguarding the health and wellbeing of our participants and ensuring the continued supply of our medicines to participants remains of paramount importance for AstraZeneca through the ongoing coronavirus disease 2019 (COVID-19) outbreak.

F 2 Risk Assessment for COVID-19 Pandemic

Sodium Zirconium Cyclosilicate (SZC) is a potassium binder acting in the gastrointestinal tract and is not absorbed. No additional risk from COVID-19 is expected due to SZC.

Lisinopril (angiotensin-converting enzyme inhibitor) and valsartan (angiotensin receptor blocker) are oral renin-angiotensin-aldosterone system inhibitors (RAASi) drugs indicated for the treatment of hypertension, heart failure, and post-myocardial infarction state. Because angiotensin converting enzyme 2 is the receptor that allows coronavirus entry into cells and this receptor may be upregulated during RAASi therapy, the use of these drugs has been extensively monitored and studied during the COVID-19 pandemic. A comprehensive systematic review of a 1.4 million patient nationwide registry that provides the best available information on RAASi therapy during the pandemic has shown that these drugs are not associated with a higher likelihood of a positive test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, greater disease severity, or increased hospitalisations and mortality (Savarese et al 2020). Therefore, no additional risk from COVID-19 is expected due to lisinopril or valsartan.

However, the risk of exposure to infected people cannot be completely excluded during study participation as the participants may need to expose themselves to public areas (eg, commute to the site) and have additional human contact (eg, with site staff).

F 2.1 Measures to Mitigate the Risks Associated with COVID-19

National laws and local recommendations regarding the pandemic will be strictly adhered to.

F 3 COVID-19 at Screening

It is important that participants with possible ongoing or not completely resolved COVID-19 infection are not to be started on treatment in the study. If the participant has evidence of COVID-19 within 2 weeks prior to screening (Visit 1) (eg, a positive COVID-19 test or a clinical risk that has not been satisfactorily excluded), the participant should not be enrolled.

F 4 Suspected COVID-19 After Screening

F 4.1 Participant is Severely Ill or Hospitalised

If the participant becomes symptomatic after screening and has suspected COVID-19 (regardless of any SARS-CoV-2 test results that may be available), and is severely ill and/or hospitalised, the participant may temporarily or permanently discontinue study intervention at the discretion of the site investigator.

F 4.2 Participant is NOT Severely Ill or Hospitalised

If the participant becomes symptomatic after enrolment and has suspected COVID-19 (regardless of whether any SARS-CoV-2 test results are available or not) and is NOT severely ill and/or hospitalised, the investigator should determine if continuation of treatment with study intervention is in the best interest of the participant.

If feasible and where local regulations allow, remote visits (telemedicine, phone contact) may be considered for follow-up purposes.

F 5 Study Interruptions due to COVID-19

F 5.1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete on-site study visits and assessments and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Section F 5.2. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note: in the case of verbal reconsent, the informed consent form should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

F 5.2 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix the term telemedicine visit refers to remote contact with the study participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, visits that are scheduled to be on-site may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow adverse events and concomitant medication to be reported and documented.

F 5.3 Data Capture During Telemedicine Visits

Data collected during telemedicine visits will be captured by a qualified healthcare professional from the study site.

Appendix G Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

G 1 Definition of Adverse Events

An adverse event (AE) is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

G 2 Definition of Serious Adverse Events

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse events for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability, or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (eg, neutropaenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation.
- Development of drug dependency or drug abuse.

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix G 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for

several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix G 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix G 2.

G 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related.'

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

G 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding Interactive Response Technology [IRT]/Randomisation and Trial Supply Management [RTSM] errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM – including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or SoC medication in open-label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Appendix H Handling of Human Biological Samples

H 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at the site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire lifecycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample lifecycle.

H 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented, and study site is notified.

H 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) **(https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx)** classifies infectious substances into three categories: Category A, Category B, or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to them occurs, are capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt – Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.

Appendix I Abbreviations

Abbreviation or special term	Explanation
ACEi	angiotensin converting enzyme inhibitor
AE	adverse event
ARB	angiotensin II receptor blocker
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	coronavirus disease 2019
CPS	calcium polystyrene sulfonate
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	cardiovascular
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
ED	early discontinuation
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ESD	early study discontinuation
ESKD	end stage kidney disease
FDA	Food and Drug Administration
ICF	informed consent form
ICH	International Council for Harmonisation
IRT	Interactive Response Technology
KDIGO	Kidney Disease: Improving Global Outcomes
MRA	mineralocorticoid receptor antagonist
MTP	multiple testing procedure
QD	once daily
QOD	once every other day
QTcF	QT interval corrected using Fridericia's formula
RAAS	renin-angiotensin-aldosterone system
RAASi	renin-angiotensin-aldosterone system inhibitor
RTSM	Randomisation and Trial Supply Management
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Abbreviation or special term	Explanation
S-Cr	serum creatinine
SD	standard deviation
SGLT2	sodium-glucose cotransporter-2
S-K	serum potassium
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SoC	standard of care
SPS	sodium polystyrene sulfonate
SZC	sodium zirconium cyclosilicate
TID	three times daily
UACR	urine albumin-to-creatinine ratio
US	United States

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