Clinical Study Report Synopsis	
Drug Substance	Sodium Zirconium Cyclosilicate (SZC), Lisinopril, and Valsartan
Study Code	D9488C00001
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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

Study dates:
First subject enrolled: 30 September 2021
Last subject last visit: 07 February 2024
The analyses presented in this report are based on a clinical data lock date of 11 July 2024
Date of early study termination: 30 November 2023
The Sponsor discontinued the study early due to substantially increased enrolment timelines.

Phase of development: Therapeutic confirmatory (III)

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

Study Centres

This study was conducted at 286 sites across 20 countries, and participants were randomised at 198 sites in 18 countries. A total of 2463 participants were enrolled (consented).

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 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 to 5.0 mmol/L) or non-normal (< 3.5 or > 5.0 mmol/L) at scheduled visits after randomisation

Table S1 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 was temporarily used instead.

[b] Both of the primary endpoints had to 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 of the CSP (see Appendix 16.1.1).

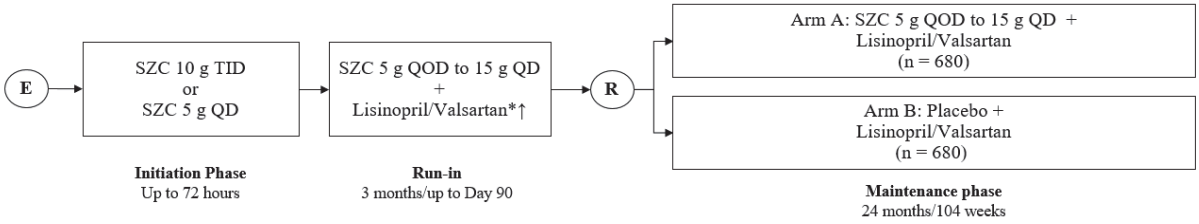
ACEi, angiotensin converting enzyme inhibitor; AE, adverse event; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CSP, Clinical Study Protocol; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; SAE, serious adverse event; S-K, serum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

Study Design

This was a Phase III, international, randomised withdrawal, double-blind, parallel-group, placebo-controlled study, to evaluate the effect of sodium zirconium cyclosilicate, hereafter abbreviated as SZC, as adjunct to renin-angiotensin-aldosterone system inhibitor (RAASi) therapy (lisinopril or valsartan) in slowing chronic kidney disease (CKD) progression in participants with CKD and hyperkalaemia or at risk of hyperkalaemia.

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

Figure S1 Study Design



*Participants on other ACEi or ARB were switched to lisinopril or valsartan.

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; E, eligibility criteria met; n, number of participants; QD, once daily; QOD, once every other day; R, randomisation, SZC, sodium zirconium cyclosilicate; TID, 3 times daily.

Screening Period (Up to 13 days)

During the screening period, after signed informed consent was obtained, data required for determination of eligibility for the study were collected and inclusion/exclusion criteria evaluated. Participants who fulfilled the study eligibility criteria proceeded to the initiation phase.

Initiation Phase (Up to 72 hours)

No changes were made to the angiotensin converting enzyme inhibitor/angiotensin II receptor blocker (ACEi/ARB) therapy during the initiation phase. The initial dosing of SZC was based on the participant's serum potassium (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 had to be available before any other Visit 2 procedures/assessments were performed.

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

As soon as possible after the participant was 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 entered the run-in phase (Visit 3d).

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

The aim of the run-in phase was to increase ACEi or ARB therapy stepwise to their maximum doses using lisinopril or valsartan as per local labels.

Maintenance Phase, Double-blind, Parallel Groups (Originally Planned to be 24 months/104 weeks)

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

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

Two safety visits occurred 2 and 7 (± 1) days after randomisation and included evaluation of S-K by local laboratory. A final safety follow-up visit was to be conducted at Week 105, one week after the participant's last dose of SZC/placebo, after which the participant exited the study.

On 30 November 2023, the Sponsor decided to discontinue the study early due to substantially increased enrolment timelines, which made it prohibitive to deliver study results within a

timeframe to meaningfully advance clinical practice. The decision to discontinue the study was not due to safety concerns.

As the study was terminated early, the post-randomisation mean time on SZC/placebo was approximately 8 to 9 months in the safety analysis set, maintenance phase (SAS-MP), versus (vs) planned 24 months.

Target Population and Sample Size

The study included CKD participants with hyperkalaemia (S-K > 5.0 to ≤ 6.5 mmol/L by central laboratory) who were on adequate or limited RAASi therapy due to hyperkalaemia, and CKD participants with normokalaemia (S-K ≥ 3.5 to ≤ 5.0 mmol/L by central laboratory) who were on limited RAASi therapy due to high risk of hyperkalaemia. High risk of hyperkalaemia was defined as (1) participants with a previous medical history or record of hyperkalaemia within the prior 24 months who were on limited RAASi therapy despite indication in CKD; (2) participants in whom RAASi therapy was indicated in CKD but were on limited RAASi therapy and had S-K ≥ 4.7 to ≤ 5.0 mmol/L; and (3) participants in whom RAASi therapy had been discontinued or reduced to suboptimal doses because of hyperkalaemia. Refer to Appendix B 3 of the Clinical Study Protocol (see Appendix 16.1.1) for definitions of 'limited' and 'suboptimal' RAASi therapy. Participants had to have estimated glomerular filtration rate (eGFR) ≥ 25 and ≤ 59 mL/min/1.73m^2, and urine albumin-to-creatinine ratio (UACR) ≥ 200 and ≤ 5000 mg/g, as calculated by central laboratory at screening (Visit 1).

Approximately 3000 participants were to 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. This target allowed for up to 20% missing eGFR data.

As the study was terminated early, a total of 2463 participants were enrolled, of which 1112 participants were dosed in the initiation phase, and 716 participants were randomised in the maintenance phase.

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

The dose levels for SZC/placebo and lisinopril/valsartan used in the study were:

- SZC: 5 g SZC once every other day (QOD) by mouth (PO), or 5, 10, or 15 g SZC once daily (QD) PO, or 10 g 3 times daily 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.

For a list of participants receiving each batch of study treatment, refer to Appendix 16.1.6.

Duration of Treatment

A participant was originally expected to be in the study for approximately 28 months, which included 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 consisted 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).

Statistical Methods

The efficacy analyses were based on the full analysis set (FAS) that included all randomised participants. The safety analyses were based on the different Safety Analysis Sets, performed for each study phase, ie, the initiation, run-in, and maintenance phases, separately.

Data were summarised descriptively for each of the phases, by treatment arm (for the maintenance phase) and the overall total population.

In addition, time-to-event variables were summarised using Kaplan-Meier estimators of the cumulative distribution function.

All the efficacy analyses were aimed at evaluating the potential effect of SZC during the randomised treatment phase of the study (ie, the maintenance phase). To evaluate the primary objective, a linear mixed effects model was fitted for each of the primary endpoints. It was based on the eGFR values obtained at the scheduled visits at and after randomisation (total slope) and at and after the 12-week visit (chronic slope), respectively, as the dependent variable. Covariates included as fixed effects in the model were, among others: treatment (SZC vs placebo), time (continuous) since randomisation (days), and time and treatment interaction.

The null hypothesis of no difference between SZC and placebo was tested by considering the fixed effect of time and treatment interaction term in the model. The estimates of the mean slopes obtained from the model, as well as the estimate of the difference between the 2 slopes, together with 2-sided 95% confidence intervals (CIs), were presented. For the difference in slope, the corresponding p-value was also provided.

A limited number of sensitivity, supplementary, and supportive analyses of the main analyses of the primary endpoints were also performed.

Analyses of the secondary efficacy objectives included the estimates of the treatment effect (ie, difference between the 2 treatment arms) alongside the corresponding 95% CIs and a p-value.

As the study was terminated early, a decision was taken (before randomisation code disclosure) to take into account only those measurements in the models that were assessed up to Visit 17 (Week 69).

Safety was evaluated by summarising and listing adverse events (AEs) (including AEs leading to discontinuation of investigational product [DAEs], serious adverse events [SAEs], and SAEs with death as the outcome). The evaluation included tabulations by system organ class (SOC) and preferred term (PT), by intensity and causality. Separate analyses were performed to evaluate AEs related to oedema, hyperkalaemia, and hypokalaemia. Laboratory measurements, as well as vital signs were summarised in a descriptive manner and listed.

Study Population

This study was conducted at 286 sites across 20 countries, and participants were randomised at 198 sites in 18 countries. A total of 2463 participants were enrolled (consented). The first participant was screened (consented) on 30 September 2021. On 30 November 2023, AstraZeneca decided to discontinue the study early due to substantially increased enrolment timelines, which made it prohibitive to deliver study results within a timeframe to meaningfully advance clinical practice. Early study discontinuation visits started after 30 November 2023, and study data were collected until the end of each participant's last visit. The last participant last visit was 07 February 2024, and the clinical database was locked on 11 July 2024.

A summary of the disposition of participants in each phase is provided below:

- Of the 2463 participants enrolled, 1112 participants were dosed in the initiation phase (460 with SZC 10 g 3 times daily [TID] and 652 with SZC 5 g QD) and 1078 (96.9%) participants completed the initiation phase. A total of 34 (3.1%) participants (SZC 10 g TID: 13 [2.8%] participants; SZC 5 g QD: 21 [3.2%] participants) were withdrawn from the initiation phase.
- Of the 1078 participants who completed the initiation phase, 1049 participants were dosed with SZC or ACEi/ARB in the run-in phase, and 763 (72.7%) participants completed the run-in phase. A total of 286 (27.3%) participants discontinued in the run-in phase.
- Of the 763 participants who completed the run-in phase, 716 participants were randomised in the maintenance phase (361 to SZC and 355 to placebo), and 714 (99.7%) participants were dosed (SZC: 359 [99.4%] participants; placebo: 355 [100%] participants). Two participants, both randomised to receive SZC, were not treated. No participants completed the maintenance phase.

Participant demographic characteristics were generally balanced between the treatment groups in the FAS. Overall, 64.5% of participants were male, and the mean age was 64.0 years. Overall, 53.8% of participants were White, 38.1% were Asian, and 3.5% were Black or

African-American. Participant demographic characteristics in the initiation and run-in phases were generally similar to those in the maintenance phase.

Participant baseline characteristics including height, weight, and body mass index were balanced between the SZC and placebo groups in the FAS. Participant baseline characteristics in the initiation and run-in phases were generally similar to the maintenance phase.

Participant disease background characteristics and electrocardiogram variables were generally balanced between the SZC and placebo groups in the FAS, and were consistent with the expected profile of participants with CKD and hyperkalaemia or at risk of hyperkalaemia.

Summary of Efficacy Results

Co-primary Endpoints - Total Slope: eGFR Measurements Starting at Randomisation, and Chronic Slope: eGFR Measurements, Starting at 12 Weeks After Randomisation

The early termination of the study provides limitation on the pre-defined efficacy evaluation. In addition to only 716 out of the 1360 planned participants randomised, the planned follow-up time of 104 weeks was also substantially reduced. In particular, for the co-primary endpoints, measurements only up to 69 weeks were available, with only 44 (of 361) participants randomised to SZC having more than 1 year of follow up. This lack of follow up to 2 years provides in particular great limitation with regards to the evaluation of eGFR slopes.

Results for the main analysis of the co-primary endpoints for the FAS are:

- Mean eGFR total slope was -5.2975 mL/min/1.73 m^2/year in the SZC group vs -4.5622 mL/min/1.73 m^2/year in the placebo group (SZC vs placebo difference: -0.7354; 95% CI [-2.7311, 1.2604]; p-value = 0.4691).
- Mean eGFR chronic slope was -4.8705 mL/min/1.73 m^2/year in the SZC group vs -2.8285 mL/min/1.73 m^2/year in the placebo group (SZC vs placebo difference: -2.0421; 95% CI [-4.7156, 0.6314]; p-value = 0.1338).

Secondary Endpoints

The estimated hazard ratio (HR) of SZC vs placebo in time from randomisation to the first occurrence of any component in the composite of sustained ≥ 40% decline in eGFR, onset of end-stage kidney disease (ESKD), or death from kidney failure was 1.72 (95% CI [0.50, 5.90]; p-value = 0.390).

A nominally statistically significant time from randomisation to first RAASi dose decrease was observed, with a systematically shorter time in the placebo group compared to the SZC group, showing RAASi enablement by SZC (HR 0.34; 95% CI [0.25, 0.47]; p-value < 0.001). The Kaplan-Meier curves began to separate early and continued to separate over the course of the study.

A nominally statistically significant difference in mean UACR levels at Week 24 was observed, numerically in favour of placebo (difference in mean: 301.1 mg/g; 95% CI [23.15, 579.11]; p-value = 0.034).

A nominally statistically significant higher mean serum bicarbonate in SZC vs placebo was consistently observed across time points up to and including Week 46 after randomisation. The mean serum bicarbonate least squares mean difference (SZC – placebo) ranged from 1.0 to 1.7 mmol/L, with the Week 6 difference being the highest.

Mean S-K values were numerically lower across the time points post-randomisation in the SZC group compared with the placebo group (mean S-K ranges: 4.50 to 4.74 mmol/L in the SZC group vs 4.88 to 5.03 mmol/L in the placebo group).

Summary of Safety Results

Exposure: In the 714 participants in the SAS-MP, the total duration of exposure to SZC/placebo in the maintenance phase ranged from 3 to 670 days in the SZC group and 2 to 674 days in the placebo group. Total median duration of exposure was 24 days higher in the SZC group (SZC: 227 days; placebo: 203 days). The mean time on SZC (including interruptions) was 262.5 days and the mean time on placebo (including interruptions) was 247.3 days, corresponding to a mean time on SZC/placebo of approximately 8 to 9 months.

In the maintenance phase, the median duration of exposure to SZC 5, 10, and 15 g doses was 128 days, 144 days, and 168.5 days, respectively. Approximately 53% of the SZC participants received the highest dose (15 g QD) at least once during the maintenance phase, vs approximately 72% of the participants who received placebo.

Adverse Events: In the initiation phase, 27 (4.1%) participants who received SZC 5 g QD experienced an AE vs 16 (3.5%) participants who received SZC 10 g TID. AEs leading to discontinuation, dose reduction, or possibly related to SZC were generally balanced between the dosing regimens, and there were no SAEs.

In the run-in phase, 416 (39.7%) participants experienced an AE. SAEs occurred in 54 (5.1%) participants, and one participant (0.1%) died.

In the maintenance phase, 201 (56.0%) participants in the SZC group experienced an AE vs 229 (64.5%) participants in the placebo group. AEs leading to discontinuation of lisinopril/valsartan, and possibly related to lisinopril/valsartan, were both more frequent in the placebo group, whereas AEs possibly related to SZC were more frequent in the SZC group. SAEs occurred in 66 (18.4%) participants in the SZC group vs 42 (11.8) participants in the placebo group; 6 SAEs led to death (SZC: 4 [1.1%] participants; placebo: 2 [0.6%] participants).

Numerical differences between the treatment groups were observed for the most common AEs. The proportions of participants with AEs of hypokalemia (12.5% vs 0.3%), hypertension (5.8% vs 3.9%), oedema peripheral (5.3% vs 1.7%), coronavirus disease 2019 (COVID-19) (3.3% vs 2.5%), hypotension (3.3% vs 2.3%), diarrhoea (3.3% vs 2.0%), acute kidney injury (3.1% vs 1.7%), nasopharyngitis (3.1% vs 1.7%), and constipation (3.1% vs 0.8%) were numerically higher in the SZC group; the proportion of participants with AEs of hyperkalaemia was higher in the placebo group (placebo: 26.8% vs SZC: 7.0%).

A numerical imbalance between the treatment groups was also observed in cardiac disorders (SOC) (SZC: 24 [6.7%] participants; placebo: 14 [3.9%] participants); the proportions of participants with AEs of acute left ventricular failure (0.3% vs 0), cardiac failure (0.6% vs 0), cardiac failure acute (1.4% vs 0), cardiac failure chronic (0.6% vs 0), and cardiac failure congestive (0.8% vs 0) were numerically higher in the SZC group. These findings are consistent with a recently conducted pooled analysis that demonstrated an increase in the risk of heart failure (HF) worsening in participants with pre-existing HF treated with SZC.

Deaths: There were no SAEs with an outcome of death in the initiation phase.

In the run-in phase, 1 (0.1%) participant had an SAE (PT ischaemic stroke) which led to death, and was not considered to be related to study treatment.

In the maintenance phase, 6 participants had SAEs with an outcome of death (SZC: 4 [1.1%)] participants; placebo: 2 [0.6%] participants). SAEs with an outcome of death in the SZC group were PTs of anal abscess, ischaemic stroke, pulmonary embolism, and death (reported as: PPD) (1 [0.1%] participant each). SAEs with an outcome of death in the placebo group were PTs of haemorrhagic stroke, and accidental death (reported as: PPD PPD) (1 [0.1%] participant each). None of the SAEs with an outcome of death were considered to be related to study treatment.

Serious Adverse Events: There were no SAEs in the initiation phase.

In the run-in phase, 54 (5.1%) participants had an SAE. The most common SAEs by PT were pneumonia (4 [0.4%] participants) and hypertension (3 [0.3%] participants).

In the maintenance phase, a numerically higher proportion of participants in the SZC group had an SAE (SZC: 66 [18.4%] participants; placebo: 42 [11.8%] participants). The most common SAEs by PT in the SZC group were acute kidney injury (SZC: 6 [1.7%] participants; placebo: 3 [0.8%] participants), cardiac failure acute (SZC: 5 [1.4%] participants; placebo: 0 participants), pneumonia (SZC: 4 [1.1%] participants; placebo: 0 participants), hyperkalaemia (SZC: 3 [0.8%] participants; placebo: 3 [0.8%] participants), hypertension (SZC: 3 [0.8%] participants; placebo: 1 [0.3%] participant) and CKD (SZC: 3 [0.8%] participants; placebo: 1 [0.3%] participant).

Adverse Events Leading to Discontinuation of SZC/Placebo: In the initiation phase, 1 (0.2%) participant in the SZC 10 g TID group had a DAE (PT: abdominal pain) vs 2 (0.3%) participants in the SZC 5 g QD group with PT hyperkalaemia.

In the run-in phase, 26 (2.5%) participants had a DAE; the most frequent DAEs were hypokalaemia (9 [0.9%] participants), and hyperkalaemia, pleural effusion, and oedema peripheral (2 [0.2%] participants each).

In the maintenance phase, 17 (4.7%) participants in the SZC group had a DAE vs 15 (4.2%) participants in the placebo group; hypokalemia was the most frequent DAE (SZC: 10 [2.8%] participants; placebo: 0 participants).

Clinical Laboratory Evaluation: No clinically meaningful differences between the SZC and placebo groups over time, or in change from baseline over time, in haematology variables were noted. No clinically meaningful treatment-emergent haematology abnormalities were noted.

No clinically meaningful differences between the SZC and placebo groups over time, or in change from baseline over time, in clinical chemistry variables were noted. No clinically meaningful treatment-emergent clinical chemistry abnormalities were noted.

UACR was not collected as part of the safety clinical laboratory assessment; however, an increase in UACR was observed with SZC as part of the efficacy analyses (see Summary of Efficacy results [Secondary Endpoints] section above).

Vital Signs and Other Observations Related to Safety: No clinically meaningful differences between the SZC and placebo groups in change from baseline in vital sign variables over time were noted. No clinically meaningful treatment-emergent vital signs abnormalities were noted.

One pregnancy was reported during the study.

Conclusion(s)

This study was terminated early and randomised 716 participants (vs 1360 planned). The post-randomisation mean time on SZC/placebo was approximately 8 to 9 months in the SAS-MP (vs planned 24 months).

- Efficacy:
  - The small sample sizes, short follow up, and small number of eGFR measurements preclude any meaningful conclusions on eGFR slopes.

- The low number of events on hard renal outcomes (ie, sustained ≥ 40% decline in eGFR, onset of ESKD, or death from kidney failure) preclude any meaningful conclusions.
- Evidence of RAASi enablement by SZC was observed: a nominally statistically significant and systematically shorter time from randomisation to first RAASi dose decrease was observed in the placebo group vs the SZC group; the Kaplan-Meier curves separated early and continued to separate over the course of the study.
- A nominally statistically significant difference in mean UACR levels at Week 24 post-randomisation was observed, numerically in favour of placebo (difference in mean: 301.1 mg/g; 95% CI [23.15, 579.11]; p value = 0.034).
- The SZC group had a nominally statistically significant higher mean serum bicarbonate vs the placebo group across the maintenance phase time points up to and including Week 46.
- The SZC group had lower mean S-K values vs the placebo group across the maintenance phase time points.

- Safety:
  - In the maintenance phase, a higher proportion of participants in the SZC group had AEs of hypokalaemia vs placebo (12.5% vs 0.3%).
  - A numerical imbalance of cardiac disorders was observed, with a higher incidence of HF AEs in participants treated with SZC vs placebo. These findings are consistent with a recently conducted pooled analysis that demonstrated an increase in the risk of HF worsening in participants with pre-existing HF treated with SZC.
  - An increase in UACR was observed with SZC as part of the efficacy analyses.
  - Otherwise, the safety profile of SZC in the study was largely consistent with pre-trial data.