Clinical trial results:
An Open-Label, Randomised, Phase 4 Study of Continuing Sodium Zirconium Cyclosilicate (SZC) after Discharge in Participants with Chronic Kidney Disease treated for Hyperkalaemia

Summary

EudraCT number	2021-003527-14
Trial protocol	IT ES FR NL BE
Global end of trial date	10 December 2024

Results information

Result version number	v1
This version publication date	31 October 2025
First version publication date	31 October 2025

Trial information

Trial identification

Sponsor protocol code	D9480C00023

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05347693
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	151 85, Södertälje, Sweden,
Public contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 18772409479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 January 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 December 2024
Global end of trial reached?	Yes
Global end of trial date	10 December 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of continuing SZC as part of the discharge medications, compared to standard of care (SoC), in maintaining normokalaemia (NK)

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH / GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 March 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Spain: 145
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Netherlands: 1
Worldwide total number of subjects	186
EEA total number of subjects	180

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	38
From 65 to 84 years	126
85 years and over	22

Subject disposition

Recruitment

Recruitment details:

A total of 186 participants were screened from 28 study sites across 6 countries.

Pre-assignment

Screening details:

Of 186 participants entering the inpatient phase, 137 were randomized 1:1 to Arm A or B for the outpatient phase; one did not receive treatment.

The remaining 49 were not randomized due to consent withdrawal, eligibility issues, screening failure, death, or other reasons.

Pre-assignment period milestones

Number of subjects started	186
Number of subjects completed	137

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 3
Reason: Number of subjects	Adverse event, serious fatal: 2
Reason: Number of subjects	Consent withdrawn by subject: 10
Reason: Number of subjects	Physician decision: 5
Reason: Number of subjects	Withdrawn in error: 1
Reason: Number of subjects	Participant was discharged from hospital: 1
Reason: Number of subjects	screening failure: 8
Reason: Number of subjects	Failure to meet inclusion/ exclusion criteria: 19

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Outpatient Period - Arm A: SZC

Arm description:

Participants discharged with SZC, as per local label, to manage hyperkalaemia (HK) until 7 days before the end of the study.

Arm type	Experimental
Investigational medicinal product name	Sodium zirconium cyclosilicate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension in sachet
Routes of administration	Oral use

Dosage and administration details:

As per local label

Arm title	Outpatient Period - Arm B: Standard of Care (SoC)

Arm description:

SZC was withdrawn and participants discharged with SoC, as per local practice, to manage HK until the end of study.

Arm type	SoC

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	Outpatient Period - Arm A: SZC	Outpatient Period - Arm B: Standard of Care (SoC)
Started	68	69
Received at least 1 treatment	68	68
Completed	42	56
Not completed	26	13
Adverse event, serious fatal	6	2
Consent withdrawn by subject	8	5
Development of withdrawal criteria: Severe HK	-	1
Adverse event, non-fatal	9	-
Compliance unmonitored; complex circumstances	1	-
Start of dialysis	-	1
Started dialysis on 16 Feb 2023	1	-
Lost to follow-up	-	1
The participant entered hemodialysis	-	1
Scheduled hemodialysis	1	-
Severe HK	-	1
Relocated; unable to attend study visits	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Of 186 participants entering the inpatient phase, 137 were randomized 1:1 to Arm A or B for the outpatient phase.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	137	137	
Age Categorical			
Age at Screening			
Units: Participants			
18-64 years	27	27	
65-84 years	93	93	
>=85 years	17	17	
Age Continuous			
Age at Screening			
Units: Years			
arithmetic mean	72.5		
standard deviation	± 10.56	-	
Sex: Female, Male			
Units: Participants			
Female	41	41	
Male	96	96	
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	31	31	
Not Hispanic or Latino	100	100	
Other category	6	6	
Race/Ethnicity, Customized			
Units: Subjects			
White	129	129	
Black or African American	0	0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
American Indian or Alaskan Native	0	0	
Other	0	0	
Multiple	0	0	
Not reported	7	7	
Country			
Units: Subjects			
Belgium	2	2	
Spain	117	117	
France	6	6	
United Kingdom	2	2	
Italy	9	9	
Netherlands	1	1	

Subject analysis sets	
Subject analysis set title	Outpatient Period - Arm A: SZC (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants were randomized and discharged with SZC, as per local label, to manage HK until 7 days before the end of the study.

Subject analysis set title	Outpatient Period - Arm B: SoC (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants were randomized and had SZC withdrawn and were discharged with SoC, as per local practice, to manage HK until the end of study.

Subject analysis set title	Outpatient Period - Arm A: SZC (SSR)
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Set Randomized (SSR) includes all randomized participants who received at least 1 dose of SZC post-discharge. Participants in this arm were discharged with SZC, as per local label, to manage HK until 7 days before the end of the study.

Subject analysis set title	Outpatient Period - Arm B: SoC (SSR)
Subject analysis set type	Safety analysis

Subject analysis set description:

Includes all randomised participants who had SZC withdrawn and was discharged with SoC, as per local practice, to manage HK until the end of study.

Reporting group values	Outpatient Period - Arm A: SZC (FAS)	Outpatient Period - Arm B: SoC (FAS)	Outpatient Period - Arm A: SZC (SSR)
Number of subjects	68	69	68
Age Categorical			
Age at Screening			
Units: Participants			
18-64 years	14	13	14
65-84 years	45	48	45
>=85 years	9	8	9
Age Continuous			
Age at Screening			
Units: Years			
arithmetic mean	72.8	72.2	72.8
standard deviation	± 10.25	± 10.92	± 10.25
Sex: Female, Male			
Units: Participants			
Female	25	16	25
Male	43	53	43
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	21	10	21
Not Hispanic or Latino	43	57	43
Other category	4	2	4
Race/Ethnicity, Customized			
Units: Subjects			
White	64	65	64
Black or African American	0	0	0
Asian	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaskan Native	0	0	0

Other	0	0	0
Multiple	0	0	0
Not reported	4	3	4
Country Units: Subjects			
Belgium	0	2	0
Spain	57	60	57
France	4	2	4
United Kingdom	0	2	0
Italy	6	3	6
Netherlands	1	0	1

Reporting group values	Outpatient Period - Arm B: SoC (SSR)		
Number of subjects	68		
Age Categorical			
Age at Screening			
Units: Participants			
18-64 years	13		
65-84 years	47		
>=85 years	8		
Age Continuous			
Age at Screening			
Units: Years			
arithmetic mean	72.1		
standard deviation	± 10.99		
Sex: Female, Male Units: Participants			
Female	16		
Male	52		
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	10		
Not Hispanic or Latino	56		
Other category	2		
Race/Ethnicity, Customized Units: Subjects			
White	64		
Black or African American	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
American Indian or Alaskan Native	0		
Other	0		
Multiple	0		
Not reported	3		
Country Units: Subjects			
Belgium	2		
Spain	59		
France	2		
United Kingdom	2		

Italy	3		
Netherlands	0		

End points

End points reporting groups

Reporting group title	Outpatient Period - Arm A: SZC
Reporting group description:	
Participants discharged with SZC, as per local label, to manage hyperkalaemia (HK) until 7 days before the end of the study.	
Reporting group title	Outpatient Period - Arm B: Standard of Care (SoC)
Reporting group description:	
SZC was withdrawn and participants discharged with SoC, as per local practice, to manage HK until the end of study.	
Subject analysis set title	Outpatient Period - Arm A: SZC (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants were randomized and discharged with SZC, as per local label, to manage HK until 7 days before the end of the study.	
Subject analysis set title	Outpatient Period - Arm B: SoC (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants were randomized and had SZC withdrawn and were discharged with SoC, as per local practice, to manage HK until the end of study.	
Subject analysis set title	Outpatient Period - Arm A: SZC (SSR)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Set Randomized (SSR) includes all randomized participants who received at least 1 dose of SZC post-discharge. Participants in this arm were discharged with SZC, as per local label, to manage HK until 7 days before the end of the study.	
Subject analysis set title	Outpatient Period - Arm B: SoC (SSR)
Subject analysis set type	Safety analysis
Subject analysis set description:	
Includes all randomised participants who had SZC withdrawn and was discharged with SoC, as per local practice, to manage HK until the end of study.	

Primary: Occurrence (Yes/No) of NK (K+ between 3.5 and 5.0 mmol/L, inclusive) at 180 Days Post-discharge

End point title	Occurrence (Yes/No) of NK (K+ between 3.5 and 5.0 mmol/L, inclusive) at 180 Days Post-discharge
End point description:	
A response was defined as a participant having serum K+ within 3.5 and 5.0 mmol/L at 180 days post-discharge. No response was defined as a participant who: 1) used rescue therapy for hyperkalaemia (HK) during the outpatient period; 1) died prior to 180 days post-discharge; 3) were missing an assessment at visit 10; 4) were lost to follow-up prior to 180 days post-discharge; 5) down-titrated (or discontinued) RAASi. The number of participants who had a response/no response is presented.	
End point type	Primary
End point timeframe:	
At 180 days post-discharge (Visit 10)	

End point values	Outpatient Period - Arm A: SZC (FAS)	Outpatient Period - Arm B: SoC (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	69		
Units: Number of participants				
Response	21	25		
No response	47	44		

Statistical analyses

Statistical analysis title	Equivalence test
Comparison groups	Outpatient Period - Arm A: SZC (FAS) v Outpatient Period - Arm B: SoC (FAS)
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.558
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.66

Notes:

[1] - Equivalence margin is 0.29.

Sample size estimate:
• Two group χ^2 test
• Significance level: 5% (2-sided)
• Power: 80%
• Proportions with NK (K+ between 3.5 and 5.0 mmol/L, inclusive) at 180 days post-discharge:
- Arm A (SZC): 0.88
- Arm B (SoC): 0.59

Secondary: Time to First Occurrence of Any Component of All-cause Hospital Admissions or ED Visits with HK as a Contributing Factor, or All-cause Death, or Use of Rescue Therapy for HK at Any Time Post-discharge up to 180 Days

End point title	Time to First Occurrence of Any Component of All-cause Hospital Admissions or ED Visits with HK as a Contributing Factor, or All-cause Death, or Use of Rescue Therapy for HK at Any Time Post-discharge up to 180 Days

End point description:

The time to first occurrence of all-cause hospital admission, emergency department (ED) visits with HK as a contributing factor, all-cause death or use of rescue therapy for HK was calculated as date of first occurrence of (all-cause hospital admission, ED visits with HK as a contributing factor, all-cause death, use of rescue therapy for HK, date of loss to follow-up) – date of randomization + 1.

The median time to event (days) is presented. '9999' means 'Not Applicable' as no median time or confidence interval could be calculated due to fewer than 50% of participants experienced an event or there were too few events to estimate the confidence interval for the median, respectively.

End point type	Secondary

End point timeframe:

At any time post-discharge (from Visits 4 to 10), up to 180 days

End point values	Outpatient Period - Arm A: SZC (FAS)	Outpatient Period - Arm B: SoC (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	69		
Units: Days				
median (confidence interval 95%)	136 (60.00 to 9999)	9999 (63.00 to 9999)		

Statistical analyses

Statistical analysis title	Equivalence test
Comparison groups	Outpatient Period - Arm A: SZC (FAS) v Outpatient Period - Arm B: SoC (FAS)
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	equivalence[2]
P-value	= 0.743
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.51

Notes:

[2] - Equivalence margin is 0.262.

Sample size estimate:
• Log-Rank Test for Equality of Survival Curves
• Significance level: 5%
• Power: 80%
• Hazard ratio (HR; SZC/SoC): 0.329
• Proportions without the main secondary composite outcome (event-free) at 180 days post-discharge:
- Arm A (SZC): 83% (17% with the outcome/event of interest)
- Arm B (SoC): 56.8% (43.2% with the outcome/event of interest)

Secondary: Time to First Occurrence of Any Component of All-cause Hospital Admission or ED Visit with HK as a Contributing Factor at Any Time Post-discharge up to 180 Days

End point title	Time to First Occurrence of Any Component of All-cause Hospital Admission or ED Visit with HK as a Contributing Factor at Any Time Post-discharge up to 180 Days

End point description:

The time to first occurrence of any component of all-cause hospital admission or ED visit with HK as a contributing factor at any time post-discharge up to 180 days was calculated as the earliest date of (all-cause hospital admission, ED visits with HK as a contributing factor, all-cause death, use of rescue therapy for HK, date of loss to follow-up, date of 180 days post-discharge) – date of randomization + 1.

The median time to event (days) is presented. '9999' means 'Not Applicable' as no median time or

confidence interval could be calculated due to fewer than 50% of participants experienced an event or there were too few events to estimate the confidence interval for the median, respectively.

End point type	Secondary

End point timeframe:

At any time post-discharge (from Visits 4 to 10), up to 180 days

End point values	Outpatient Period - Arm A: SZC (FAS)	Outpatient Period - Arm B: SoC (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	69		
Units: Days				
median (confidence interval 95%)	9999 (116.00 to 9999)	9999 (123.00 to 9999)		

Statistical analyses

Statistical analysis title	Equivalence test
Comparison groups	Outpatient Period - Arm A: SZC (FAS) v Outpatient Period - Arm B: SoC (FAS)
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.951
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.79

Notes:

[3] - This outcome is unpowered.

Secondary: Number of All-cause Hospital Admissions or ED Visits with HK as a Contributing Factor at Any Time Post-discharge up to 180 Days

End point title	Number of All-cause Hospital Admissions or ED Visits with HK as a Contributing Factor at Any Time Post-discharge up to 180 Days

End point description:

The number of all-cause hospital admissions or ED visits with HK as a contributing factor at any time post-discharge up to 180 days is presented.

Participants who discontinued treatment, used rescue therapy for HK, experienced all-cause death or loss to follow-up prior to 180 days post-discharge or who down-titrated (including discontinued) RAASi were to have all available hospital admission data used irrespective of the intercurrent event (treatment policy strategy).

End point type	Secondary

End point timeframe:

At any time post-discharge (from Visits 4 to 10), up to 180 days

End point values	Outpatient Period - Arm A: SZC (FAS)	Outpatient Period - Arm B: SoC (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	69		
Units: Number of hospital admissions/ ED visits				
arithmetic mean (standard deviation)	0.7 (± 0.92)	0.6 (± 0.83)		

Statistical analyses

Statistical analysis title	Equivalence test
Comparison groups	Outpatient Period - Arm A: SZC (FAS) v Outpatient Period - Arm B: SoC (FAS)
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	equivalence[4]
P-value	= 0.152
Method	Negative binomial regression model
Parameter estimate	Incidence rate ratio
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	2.53
Variability estimate	Standard error of the mean
Dispersion value	0.4

Notes:

[4] - This outcome is unpowered.

Secondary: Time to First Occurrence of RAASi Down-titration (or Discontinuation) at Any Time Post-discharge up to 180 Days

End point title	Time to First Occurrence of RAASi Down-titration (or Discontinuation) at Any Time Post-discharge up to 180 Days

End point description:

The time to first occurrence of RAASi down-titration (or discontinuation) was calculated as date of first occurrence of (RAASi down-titration, all-cause death, date of loss to follow-up) – date of randomization + 1.

The median time to event (days) is presented. '9999' means 'Not Applicable' as no median time or confidence interval could be calculated due to fewer than 50% of participants experienced an event or there were too few events to estimate the confidence interval for the median, respectively.

End point type	Secondary

End point timeframe:

At any time post-discharge (from Visits 4 to 10), up to 180 days

End point values	Outpatient Period - Arm A: SZC (FAS)	Outpatient Period - Arm B: SoC (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	69		
Units: Days				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	Equivalence test
Comparison groups	Outpatient Period - Arm A: SZC (FAS) v Outpatient Period - Arm B: SoC (FAS)
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	= 0.515
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	4.35

Notes:

[5] - This outcome is unpowered.

Secondary: Time to First Occurrence of Hospital Admission or ED Visit, Both With HK as a Contributing Factor at Any Time Post-discharge up to 180 Days

End point title	Time to First Occurrence of Hospital Admission or ED Visit, Both With HK as a Contributing Factor at Any Time Post-discharge up to 180 Days

End point description:

The time to first occurrence of hospital admission or ED visit, both with HK as a contributing factor, was calculated as date of first occurrence of (Hospital admission or ED visit with HK as a contributing factor, all-cause death, use of rescue therapy for HK, date of loss to follow-up) – date of randomization + 1.

The median time to event (days) is presented. '9999' means 'Not Applicable' as no median time or confidence interval could be calculated due to fewer than 50% of participants experienced an event or there were too few events to estimate the confidence interval for the median, respectively.

End point type	Secondary

End point timeframe:

At any time post-discharge (from Visits 4 to 10), up to 180 days

End point values	Outpatient Period - Arm A: SZC (FAS)	Outpatient Period - Arm B: SoC (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	69		
Units: Days				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	Equivalence test
Comparison groups	Outpatient Period - Arm A: SZC (FAS) v Outpatient Period - Arm B: SoC (FAS)
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	equivalence[6]
P-value	= 0.258
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	1.83

Notes:

[6] - This outcome is unpowered.

Secondary: Number of Hospital Admissions or ED Visits with HK as a Contributing Factor, at Any Time Post-discharge up to 180 Days

End point title	Number of Hospital Admissions or ED Visits with HK as a Contributing Factor, at Any Time Post-discharge up to 180 Days

End point description:

The number of hospital admissions or ED visits with HK as a contributing factor, at any time post-discharge up to 180 days is presented.

Participants who discontinued treatment, used rescue therapy for HK, experienced all-cause death or loss to follow-up prior to 180 days post-discharge or who downtitrated (including discontinued) RAASi were to have all available hospital admission data used irrespective of the intercurrent event (treatment policy strategy).

End point type	Secondary

End point timeframe:

At any time post-discharge (from Visits 4 to 10), up to 180 days

End point values	Outpatient Period - Arm A: SZC (FAS)	Outpatient Period - Arm B: SoC (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	69		
Units: Number of hospital admissions/ ED visits				
arithmetic mean (standard deviation)	0.1 (± 0.24)	0.1 (± 0.26)		

Statistical analyses

Statistical analysis title	Equivalence test
Comparison groups	Outpatient Period - Arm A: SZC (FAS) v Outpatient Period - Arm B: SoC (FAS)
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	equivalence[7]
P-value	= 0.239
Method	Negative binomial regression model
Parameter estimate	Incidence risk ratio
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1.81
Variability estimate	Standard error of the mean
Dispersion value	0.31

Notes:

[7] - This outcome is unpowered.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from the start of the outpatient phase (OP) through 7 days post-last dose. AEs which occurred prior to first dose of investigational product that worsened after dosing during the OP were recorded; up to ~6 months

Adverse event reporting additional description:

AEs for the SSR are presented. Of the 137 participants randomised into the 2 arms (68 in Arm A: SZC and 69 in Arm B: SoC), there was 1 participant in the SoC who did not receive treatment during the OP and was excluded from the safety analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Outpatient Period - Arm B: SoC (SSR)
Reporting group description: -	
Reporting group title	Outpatient Period - Arm A: SZC (SSR)

Reporting group description: -

Serious adverse events	Outpatient Period - Arm B: SoC (SSR)	Outpatient Period - Arm A: SZC (SSR)	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 68 (30.88%)	29 / 68 (42.65%)	
number of deaths (all causes)	2	6	
number of deaths resulting from adverse events	2	6	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Male genital tract fistula			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 68 (0.00%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure chronic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	2 / 68 (2.94%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	

Pericarditis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis crisis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic stroke			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 68 (1.47%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease			

subjects affected / exposed	2 / 68 (2.94%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 68 (1.47%)	3 / 68 (4.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 68 (1.47%)	3 / 68 (4.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile abscess			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subcutaneous abscess			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 68 (1.47%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
COVID-19 pneumonia			

subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	0 / 68 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 68 (2.94%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Outpatient Period - Arm B: SoC (SSR)	Outpatient Period - Arm A: SZC (SSR)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 68 (44.12%)	22 / 68 (32.35%)	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	2 / 68 (2.94%)	4 / 68 (5.88%)	
occurrences (all)	2	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 68 (11.76%)	3 / 68 (4.41%)	
occurrences (all)	8	3	
Renal and urinary disorders			

Renal impairment subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 4	5 / 68 (7.35%) 5	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 8	1 / 68 (1.47%) 1	
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	17 / 68 (25.00%) 19	12 / 68 (17.65%) 14	
Metabolic acidosis subjects affected / exposed occurrences (all)	4 / 68 (5.88%) 4	3 / 68 (4.41%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 August 2021	Study intervention dispensation was added at visit 4 to allow for study intervention dispensation if dose needed to be adjusted.
07 July 2022	RAASi down-titration (including discontinuation) is now defined as non-response and included in the primary composite outcome as treatment failure due to its potential to normalise K levels. Objective #2 now assesses SZC's effect on reducing hospital admissions or ED visits with HK. Objective #3 focuses on SZC's effect on reducing hospital admissions or ED visits with HK. A new objective evaluates SZC's role in lowering the risk of RAASi down-titration. Objectives #4 to 10 were reclassified as exploratory to simplify endpoints. Inclusion criterion #4 now defines HK per site practice, with K >5.0 to ≤6.5 mmol/L. Exclusion criteria #3 and #14 were merged to exclude all kidney transplant recipients. Sensitivity analyses were updated to reflect SZC's benefit for mild versus moderate/severe HK. Re-screening was allowed (up to 2). Duration of inpatient stay was extended from 14 to 21 days post-baseline. Definition of overdose during SZC maintenance phase was modified from 15 g/day to 10 g/day.
16 October 2023	First secondary endpoint was revised to include all-cause hospital admissions or ED visits with HK as a contributing factor. The sample size was recalculated from 344 to 104 total evaluable participants. Inclusion criteria were expanded to allow participants with any stage of CKD or eGFR < 90 mL/min/1.73 m². Clarifications were made to inclusion criterion #4 regarding K levels at enrolment. Exclusion criteria were simplified to improve clarity and to exclude participants with a hospitalisation for an acute cardiovascular event within 12 weeks prior to screening. The planned interim analysis was cancelled due to the reduced sample size.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to high, imbalanced missing K data at Day 180 (51.5% SZC, 36.2% SoC), results are described with no conclusive statement and should be interpreted with caution.

Notes: