



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 m ² . 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: