Clinical trial results:
Phase IV, Double-blind, Placebo-controlled, Randomised Withdrawal Trial Evaluating Sodium Zirconium Cyclosilicate (SZC) for the Management of Hyperkalaemia in Patients with Symptomatic Heart Failure with Reduced Ejection Fraction and Receiving Spironolactone (REALIZE-K)

Summary

EudraCT number	2020-003312-27
Trial protocol	HU ES
Global end of trial date	07 August 2024

Results information

Result version number	v1 (current)
This version publication date	26 April 2025
First version publication date	26 April 2025

Trial information

Trial identification

Sponsor protocol code	D9480C00018

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 8772409479, 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	07 August 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of SZC as compared with placebo in keeping potassium levels within the normal range (3.5-5.0 mEq/L) while on spironolactone ≥ 25 mg daily without assistance of rescue therapy for hyperkalaemia.

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 International Council for Harmonisation/Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 March 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 50
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Czechia: 16
Country: Number of subjects enrolled	Spain: 59
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Poland: 18
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	203
EEA total number of subjects	103

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	50
From 65 to 84 years	142
85 years and over	11

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study consisted of two phases, an open-label run-in phase and a placebo-controlled randomized-withdrawal phase (RWP).

Of the 366 participants enrolled in the open-label run-in phase, 203 participants entered into the RWP (102 received SZC treatment and 101 received placebo).

Period 1

Period 1 title	Randomized-withdrawal Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	SZC group

Arm description:

Participants continued on the SZC and spironolactone dose they were receiving at the end of the run-in phase.

Arm type	Experimental
Investigational medicinal product name	SZC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

10 g three times daily; then titrate between 5 g every other day and 5 g daily to 15 g daily

Arm title	Placebo group

Arm description:

Participants continued on the placebo and spironolactone dose they were receiving at the end of the run-in phase.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Titrate between 5 g every other day and 5 g daily to 15 g daily

Number of subjects in period 1	SZC group	Placebo group
Started	102	101
Completed	88	87
Not completed	14	14
Adverse event, serious fatal	1	2
Consent withdrawn by subject	2	2
Adverse event, non-fatal	5	5
Withdrawn as randomized in error	1	-
Withdrawn due to protocol deviation	1	-
Withdrawn due to not enough medication	-	1
Withdrawn due to stopping spironolactone	1	-
Lost to follow-up	1	-
Development of Study-specific Withdrawal Criteria	2	4

Baseline characteristics

Reporting groups	
Reporting group title	SZC group
Reporting group description:	
Participants continued on the SZC and spironolactone dose they were receiving at the end of the run-in phase.	
Reporting group title	Placebo group
Reporting group description:	
Participants continued on the placebo and spironolactone dose they were receiving at the end of the run-in phase.	

Reporting group values	SZC group	Placebo group	Total
Number of subjects	102	101	203
Age Categorical Units: Participants			
18-64 years	18	32	50
65-84 years	79	63	142
>=85 years	5	6	11
Age Continuous			
Age at Screening			
Units: Years			
arithmetic mean	72.5	69.2	
standard deviation	± 7.88	± 10.46	-
Sex: Female, Male Units: Participants			
Female	26	26	52
Male	76	75	151
Race/Ethnicity, Customized Units: Subjects			
White	91	94	185
Black or African American	5	5	10
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
American Indian or Alaskan Native	0	0	0
Other	6	2	8
Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	40	27	67
Not Hispanic or Latino	62	74	136
Unknown or Not Reported	0	0	0
Country Units: Subjects			
BRA	31	19	50
CAN	7	16	23
CZE	3	13	16
ESP	33	26	59
GBR	9	4	13

HUN	5	5	10
POL	8	10	18
USA	6	8	14
Type 2 diabetes at baseline			
Coded using baseline medical history			
Units: Subjects			
With type 2 diabetes at baseline	27	25	52
Without type 2 diabetes at baseline	75	76	151

End points

End points reporting groups

Reporting group title	SZC group
Reporting group description:	
Participants continued on the SZC and spironolactone dose they were receiving at the end of the run-in phase.	
Reporting group title	Placebo group
Reporting group description:	
Participants continued on the placebo and spironolactone dose they were receiving at the end of the run-in phase.	

Primary: Participants who achieved response, defined as serum potassium (sK+) within 3.5 to 5.0 mEq/L, spironolactone greater than or equal to 25 mg daily, no rescue therapy for hyperkalaemia

End point title	Participants who achieved response, defined as serum potassium (sK+) within 3.5 to 5.0 mEq/L, spironolactone greater than or equal to 25 mg daily, no rescue therapy for hyperkalaemia

End point description:

The median percentages of participants having a response are presented. Response means all three requirements were met. Non-response was indicated for participants lost to follow-up, including death.

The treatment effect was analysed using a generalised estimating equation (GEE) model with a binomial family and a log link, a dependent variable of response per visit, fixed independent variables of randomised treatment, subject recruitment country, a per visit indicator variable and open-label period cohort. The common odds ratio was derived together with two-sided 95% confidence intervals.

End point type	Primary

End point timeframe:

From Month 1 (Visit 9) to Month 6 (Visit 14), up to 6 months

End point values	SZC group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	101		
Units: Percentage of response				
number (not applicable)	72.1	35.7		

Statistical analyses

Statistical analysis title	SZC group vs Placebo group
Comparison groups	SZC group v Placebo group

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	4.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.89
upper limit	6.86

Secondary: Response defined as sK+ within 3.5-5.0 mEq/L, on the same dose of spironolactone as randomisation, no rescue therapy for hyperkalaemia

End point title	Response defined as sK+ within 3.5-5.0 mEq/L, on the same dose of spironolactone as randomisation, no rescue therapy for hyperkalaemia

End point description:

The median percentages of participants who achieved a response are presented. Response means all three requirements were met. Non-response was indicated for participants lost to follow-up, including death.

The analysis was performed using a GEE model with a binomial family and a log link, a dependent variable of response per visit, fixed independent variables of randomised treatment, subject recruitment country, a per visit indicator variable and open-label period cohort. The common odds ratio was derived together with two-sided 95% confidence intervals.

End point type	Secondary

End point timeframe:

From Month 1 (Visit 9) to Month 6 (Visit 14), up to 6 months

End point values	SZC group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	101		
Units: Percentage of responses				
number (not applicable)	58.2	22.9		

Statistical analyses

Statistical analysis title	SZC group vs Placebo group
Comparison groups	SZC group v Placebo group

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	4.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.78
upper limit	7.55

Secondary: Participant who achieved response, defined as spironolactone greater than or equal to 25 mg daily

End point title	Participant who achieved response, defined as spironolactone greater than or equal to 25 mg daily

End point description:

The median percentages of participants who achieved a response are presented. Response means that the requirement was met. Non-response was indicated for subjects lost to follow-up, including death.

The analysis was performed using a GEE model with a binomial family and a log link, a dependent variable of response per visit, fixed independent variables of randomised treatment, subject recruitment country, a per visit indicator variable and open-label period cohort. The common odds ratio was derived together with two-sided 95% confidence intervals.

End point type	Secondary

End point timeframe:

From Month 1 (Visit 9) to Month 6 (Visit 14), up to 6 months

End point values	SZC group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	101		
Units: Percentage of responses				
number (not applicable)	81.4	49.5		

Statistical analyses

Statistical analysis title	SZC group vs Placebo group
Comparison groups	SZC group v Placebo group
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	GEE model
Parameter estimate	Odds ratio (OR)
Point estimate	4.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	7.52

Secondary: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) at EOT

End point title	Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) at EOT

End point description:

The KCCQ is a 23-item instrument measuring, from the patients' perspectives, their heart failure-related symptoms, physical limitations, social limitations, self-efficacy, and health-related quality of life over the prior 2 weeks. All items are measured on a Likert scale with 5-7 response options. The KCCQ is scored by assigning each response an ordinal value, beginning with 1 for the response that implies the lowest level of functioning and 5-7 for the highest level of functioning. To calculate a score, the responses are summed within each domain and the average is taken. Scale scores are transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100. The CSS was calculated as the average of Physical Limitation Score and Total Symptom Score (TSS) and the TSS was calculated as the average of Symptom Frequency and Symptom Burden Scores.

End point type	Secondary

End point timeframe:

At EOT visit (approximately 6 months post-randomisation)

End point values	SZC group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	59		
Units: Score on a scale				
least squares mean (standard error)	71.27 (± 2.57)	72.27 (± 2.36)		

Statistical analyses

Statistical analysis title	SZC group vs Placebo group
Comparison groups	SZC group v Placebo group
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.724
Method	t-test, 2-sided
Parameter estimate	Least-squares Mean Difference
Point estimate	-1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.64
upper limit	4.63

Variability estimate	Standard error of the mean
Dispersion value	2.84

Secondary: Time to first hyperkalaemia (sK+ greater than 5.0mEq/L) episode

End point title	Time to first hyperkalaemia (sK+ greater than 5.0mEq/L) episode

End point description:

The time to first hyperkalaemia episode for participants on SZC compared to placebo during the randomised-withdrawal period, with hyperkalaemia defined as sK+ greater than 5.0 mEq/L as assessed by central laboratory, is presented in median time (days).

The analysis was performed using a Cox regression model including randomised treatment group and subject recruitment country, adjusted for the stratification factor (hyperkalaemia vs normokalaemia at study entry). Placebo group used as reference level in Cox model.

End point type	Secondary

End point timeframe:

From randomisation to the end of treatment (EOT) visit, up to 6 months

End point values	SZC group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	101		
Units: Days				
median (confidence interval 95%)	65.0 (35.00 to 98.00)	9.0 (8.00 to 13.00)		

Statistical analyses

Statistical analysis title	SZC group vs Placebo group
Comparison groups	SZC group v Placebo group
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.71

Secondary: Time to first instance of decrease or discontinuation of spironolactone

dose due to hyperkalaemia	
End point title	Time to first instance of decrease or discontinuation of spironolactone dose due to hyperkalaemia

End point description:

The time to first instance of decrease or discontinuation of spironolactone dose due to hyperkalaemia was determined.

The analysis was performed using a Cox regression model, adjusted for the stratification factor (hyperkalaemia vs normokalaemia at study entry).

000 = not applicable. Median time to first event could not be calculated due to the low number of events.

End point type	Secondary

End point timeframe:

From randomisation to the EOT visit, up to 6 months

End point values	SZC group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	101		
Units: Days				
median (confidence interval 95%)	000 (000 to 000)	000 (000 to 000)		

Statistical analyses

Statistical analysis title	SZC group vs Placebo group
Comparison groups	SZC group v Placebo group
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.73

Other pre-specified: Location and severity of peripheral oedema	
End point title	Location and severity of peripheral oedema

End point description:

The location and severity of peripheral oedema that occurred during the randomised-withdrawal phase are presented. Participants with multiple peripheral oedema events were counted only once. The location of oedema is not mutually exclusive so multiple locations may apply for each participant.

End point type	Other pre-specified

End point timeframe:

During the RWP and up to 14 days after discontinuation of SZC or placebo, up to 6.5 months

End point values	SZC group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	16		
Units: Participants				
Location of oedema: pedal oedema	13	10		
Location of oedema: ankle oedema	17	13		
Location of oedema: pretibial oedema	11	5		
Location of oedema: thigh oedema	1	0		
Severity of pedal oedema - right side: trace	4	3		
Severity of pedal oedema - right side: mild	1	5		
Severity of pedal oedema - right side: moderate	7	1		
Severity of pedal oedema - right side: severe	0	0		
Severity of pedal oedema - left side: trace	4	5		
Severity of pedal oedema - left side: mild	2	4		
Severity of pedal oedema - left side: moderate	7	1		
Severity of pedal oedema - left side: severe	0	0		
Severity of ankle oedema - right side: trace	4	4		
Severity of ankle oedema - right side: mild	5	6		
Severity of ankle oedema - right side: moderate	7	1		
Severity of ankle oedema - right side: severe	0	0		
Severity of ankle oedema - left side: trace	4	6		
Severity of ankle oedema - left side: mild	5	6		
Severity of ankle oedema - left side: moderate	8	1		
Severity of ankle oedema - left side: severe	0	0		
Severity of pretibial edema - right side: trace	2	1		
Severity of pretibial edema - right side: mild	4	2		
Severity of pretibial edema - right side: moderate	5	1		
Severity of pretibial edema - right side: severe	0	0		
Severity of pretibial edema - left side: trace	1	2		
Severity of pretibial edema - left side: mild	3	2		

Severity of pretibial edema - left side: moderate	7	1		
Severity of pretibial edema - left side: severe	0	0		
Severity of thigh edema - right side: trace	0	0		
Severity of thigh edema - right side: mild	0	0		
Severity of thigh edema - right side: moderate	1	0		
Severity of thigh edema - right side: severe	0	0		
Severity of thigh edema - left side: trace	0	0		
Severity of thigh edema - left side: mild	0	0		
Severity of thigh edema - left side: moderate	1	0		
Severity of thigh edema - left side: severe	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) that occurred during the RWP and up to 14 days after discontinuation of SZC/placebo and all AEs which occurred prior to first dose which worsened in severity following dosing during the RWP, up to 6.5 months, were included.

Adverse event reporting additional description:

Participants with multiple events in the same category were counted only once in that category. Participants with events in more than one category were counted once in each of those categories.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	SZC group

Reporting group description: -

Reporting group title	Placebo group

Reporting group description: -

Serious adverse events	SZC group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 101 (22.77%)	22 / 101 (21.78%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	2	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	1 / 101 (0.99%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 101 (0.99%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Toe amputation			
subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
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			
Sudden cardiac death			
subjects affected / exposed	1 / 101 (0.99%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Death			
subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 101 (0.99%)	0 / 101 (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	1 / 101 (0.99%)	0 / 101 (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			
Thoracic vertebral fracture			
subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Systolic dysfunction			
subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure			
subjects affected / exposed	12 / 101 (11.88%)	4 / 101 (3.96%)	
occurrences causally related to treatment / all	1 / 14	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 101 (0.99%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 101 (0.99%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Ureterolithiasis			

subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 101 (0.99%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 101 (0.00%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fasciitis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 101 (0.99%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	2 / 101 (1.98%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 101 (0.99%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 101 (0.99%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 101 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 101 (1.98%)	3 / 101 (2.97%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	1 / 101 (0.99%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SZC group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 101 (19.80%)	25 / 101 (24.75%)	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	6 / 101 (5.94%)	2 / 101 (1.98%)	
occurrences (all)	6	2	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	12 / 101 (11.88%)	23 / 101 (22.77%)	
occurrences (all)	16	34	
Hypokalaemia			
subjects affected / exposed	6 / 101 (5.94%)	0 / 101 (0.00%)	
occurrences (all)	6	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 June 2021	The overall rationale (one primary driver) for the changes implemented in the protocol amendment were minor clarifications and further descriptions (e.g., changes to individual inclusion/exclusion criteria).
03 August 2022	The overall rationale (one primary driver) for the changes implemented in protocol amendment 2 was the shortening of the randomised, double-blind, withdrawal phase from 8 to 6 months. Based on recent results from a similar study (DIAMOND study), shortening the duration by 2 months would not impact the results and may have alleviated the burden to the participants.
09 November 2023	Updates to the primary and secondary endpoint definitions with clarification and alignment updates on statistical analysis methods

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported