Clinical trial results:
A Phase II, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, Multicentre, Three Month Duration Potassium Reduction Initiative to Optimise RAAS Inhibition Therapy with Sodium Zirconium Cyclosilicate in Heart Failure (PRIORITIZE HF)

Summary

EudraCT number	2018-000175-33
Trial protocol	HU SK PL BG
Global end of trial date	22 May 2020

Results information

Result version number	v1 (current)
This version publication date	05 June 2021
First version publication date	05 June 2021

Trial information

Trial identification

Sponsor protocol code	D9484C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03532009
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Södertälje, Södertälje, Sweden, SE-151 85
Public contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, 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	22 May 2020

Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to determine if there was a difference between sodium zirconium cyclosilicate (SZC) and placebo in renin-angiotensin aldosterone system (RAAS) blockade treatment.

Protection of trial subjects:

This study was conducted in accordance with the protocol and with the following:
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines;
- Applicable International Conference on Harmonisation Good Clinical Practice Guidelines;
- Applicable laws and regulations.

Background therapy:

Patients continued to receive their RAAS inhibition (RAASi) therapy as before randomisation, but additional monitoring of their local lab serum-potassium (S-K) allowed up-titration of their RAASi therapy to a target dose.

Evidence for comparator:

Placebo was used as comparator in PRIORITIZE HF as the primary efficacy endpoints could have been affected by treating physicians knowing the treatment allocation of individual patients, and as there is no other drug currently approved or widely used to allow up-titration of RAASi in patients at high risk of hyperkalaemia. Hence placebo was a necessary and appropriate comparator.

Actual start date of recruitment	26 June 2018
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: 22
Country: Number of subjects enrolled	Bulgaria: 16
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Hungary: 31
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Russian Federation: 63
Country: Number of subjects enrolled	Slovakia: 16
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	182
EEA total number of subjects	80

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	33
From 65 to 84 years	134
85 years and over	15

Subject disposition

Recruitment

Recruitment details:

This study was performed at 64 sites in 9 countries (Brazil, Bulgaria, Canada, Hungary, Poland, Romania, Russia, Slovakia, and the United States of America) between 26 June 2018 and 22 May 2020.

Pre-assignment

Screening details:

Patients were randomised in a 1:1 ratio to receive SZC or placebo for 3 months while titrating RAASi therapies. The study was prematurely terminated due to the COVID-19 pandemic resulting in a reduced sample size (182 randomised patients as opposed to the planned 280 patients).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Sodium zirconium cyclosilicate

Arm description:

Patients with S-K concentration > 5.0 millimole/litre (mmol/L) at the last assessment before randomisation received SZC 10 grams (g) orally 3 times daily (tid) for 2 days followed by SZC 5 g once daily (qd) for 3 months. Patients with S-K concentration ≤ 5.0 mmol/L at the last assessment before randomisation received SZC 5 g orally qd for 3 months. SZC was up- or down- titrated depending on local laboratory S-K concentration at every study visit.

Arm type	Experimental
Investigational medicinal product name	Sodium zirconium cyclosilicate
Investigational medicinal product code	AZD7270
Other name	SZC
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Patients with S-K concentration > 5.0 mmol/L at the last assessment before randomisation received SZC 10 g orally 3 tid for 2 days followed by SZC 5 g qd for 3 months. Patients with S-K concentration ≤ 5.0 mmol/L at the last assessment before randomisation received SZC 5 g orally qd for 3 months. SZC was up- or down- titrated depending on local laboratory S-K concentration at every study visit.

Arm title	Placebo

Arm description:

Patients with S-K concentration > 5.0 mmol/L at the last assessment before randomisation received placebo orally tid for 2 days followed by placebo qd for 3 months. Patients with S-K concentration ≤ 5.0 mmol/L at the last assessment before randomisation received placebo orally qd for 3 months. Placebo was up- or down- titrated depending on local laboratory S-K concentration at every study visit.

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:

Patients with S-K concentration > 5.0 mmol/L at the last assessment before randomisation received placebo orally tid for 2 days followed by placebo qd for 3 months. Patients with S-K concentration ≤ 5.0 mmol/L at the last assessment before randomisation received placebo orally qd for 3 months. Placebo

was up- or down- titrated depending on local laboratory S-K concentration at every study visit.

Number of subjects in period 1	Sodium zirconium cyclosilicate	Placebo
Started	92	90
Received treatment	91	90
Completed	90	86
Not completed	2	4
Withdrawal by Patient	-	2
Not specified	1	1
Adverse event, serious fatal	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Sodium zirconium cyclosilicate
Reporting group description:	
Patients with S-K concentration > 5.0 millimole/litre (mmol/L) at the last assessment before randomisation received SZC 10 grams (g) orally 3 times daily (tid) for 2 days followed by SZC 5 g once daily (qd) for 3 months. Patients with S-K concentration ≤ 5.0 mmol/L at the last assessment before randomisation received SZC 5 g orally qd for 3 months. SZC was up- or down- titrated depending on local laboratory S-K concentration at every study visit.	
Reporting group title	Placebo
Reporting group description:	
Patients with S-K concentration > 5.0 mmol/L at the last assessment before randomisation received placebo orally tid for 2 days followed by placebo qd for 3 months. Patients with S-K concentration ≤ 5.0 mmol/L at the last assessment before randomisation received placebo orally qd for 3 months. Placebo was up- or down- titrated depending on local laboratory S-K concentration at every study visit.	

Reporting group values	Sodium zirconium cyclosilicate	Placebo	Total
Number of subjects	92	90	182
Age Categorical Units: Patients			
≤ 17 years	0	0	0
18 - 64 years	17	16	33
65 - 84 years	65	69	134
≥ 85 years	10	5	15
Age Continuous Units: years			
arithmetic mean	72.9	71.0	
standard deviation	± 8.8	± 8.1	-
Sex: Female, Male Units: Patients			
Female	41	33	74
Male	51	57	108
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	90	89	179
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	15	14	29
Not Hispanic or Latino	77	76	153
Unknown or Not Reported	0	0	0
S-K Concentration			
The patient's baseline S-K concentration was measured using the site's local laboratory or an i-STAT device at the last assessment before randomisation.			

Units: Subjects			
≤ 5.0 mmol/L	65	67	132
> 5.0 mmol/L	27	23	50
New York Heart Association (NYHA) Functional Classification			
The Investigator evaluated NYHA using the following classifications: Class I: No limitation of physical activity; Class II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea; Class III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea; Class IV: Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.			
Units: Subjects			
Class I	0	0	0
Class II	61	57	118
Class III	31	33	64
Class IV	0	0	0
Left Ventricular Ejection Fraction (LVEF)			
Measured using echocardiography, multiple gate acquisition scan, computer tomography scanning, magnetic resonance imaging or ventricular angiography.			
Units: LVEF Percentage			
arithmetic mean	33.8	33.9	
standard deviation	± 5.8	± 6.1	-
Estimated Glomerular Filtration Rate (eGFR)			
eGFR was calculated using the chronic kidney disease epidemiology collaboration equation.			
Units: Millilitre/minute/1.73 metre^2			
arithmetic mean	40.0	42.7	
standard deviation	± 11.0	± 11.5	-

End points

End points reporting groups

Reporting group title	Sodium zirconium cyclosilicate

Reporting group description:

Patients with S-K concentration > 5.0 millimole/litre (mmol/L) at the last assessment before randomisation received SZC 10 grams (g) orally 3 times daily (tid) for 2 days followed by SZC 5 g once daily (qd) for 3 months. Patients with S-K concentration ≤ 5.0 mmol/L at the last assessment before randomisation received SZC 5 g orally qd for 3 months. SZC was up- or down- titrated depending on local laboratory S-K concentration at every study visit.

Reporting group title	Placebo

Reporting group description:

Patients with S-K concentration > 5.0 mmol/L at the last assessment before randomisation received placebo orally tid for 2 days followed by placebo qd for 3 months. Patients with S-K concentration ≤ 5.0 mmol/L at the last assessment before randomisation received placebo orally qd for 3 months. Placebo was up- or down- titrated depending on local laboratory S-K concentration at every study visit.

Primary: Percentage of Patients Receiving Different Categories of RAASi Treatments at Month 3

End point title	Percentage of Patients Receiving Different Categories of RAASi Treatments at Month 3

End point description:

RAASi treatment categories:
- No, or less than target dose, angiotensin converting enzyme inhibitors (ACEi)/ angiotensin receptor blockers (ARB)/ angiotensin receptor/ neprolysin inhibitors (ARNI) and no mineralocorticoid receptor antagonist (MRA);
- ACEi/ARB/ARNI at target dose and no MRA;
- MRA at less than target dose;
- MRA at target dose.

Missing values at 3 months were imputed using a multiple imputation approach with 10000 imputations. The imputation model included RAASi category at 3 months as the outcome variable and the following covariates: RAASi category, local lab-K, eGFR and systolic blood pressure measured at the last visit before the 3 months (starting with the randomisation visit) when all the covariates' data were available.

All randomised patients with a non-missing value for the RAASi treatment category (after imputation) were included.

End point type	Primary

End point timeframe:

At the end of the treatment visit (Month 3)

End point values	Sodium zirconium cyclosilicate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	87		
Units: Percentage of Patients				
number (not applicable)				
No, or less than target dose ACEi/ARB/ARNI, no MRA	14.7	13.5		
ACEi/ARB/ARNI at target dose and no MRA	14.7	15.1		
MRA at less than target dose	14.2	24.5		

MRA at target dose	56.4	47.0		

Statistical analyses

Statistical analysis title	SZC versus (vs) Placebo

Statistical analysis description:

The p-value was obtained by pooling the p-values from Chi-square tests performed on individual data sets using the F-distribution and reflects a global test of no difference in distribution of patients in the respective categories between SZC and placebo groups. The null hypothesis was that there is no difference between SZC and placebo in the distribution of percentage of patients in the 4 RAASi treatment categories. The hypothesis was tested at a significance level of 5%.

Comparison groups	Sodium zirconium cyclosilicate v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.426
Method	F-test

Other pre-specified: Number of Patients who Experienced Adverse Events (AEs) During the Study

End point title	Number of Patients who Experienced Adverse Events (AEs) During the Study

End point description:

An AE is the development of any untoward medical occurrence in a patient or clinical study patient administered an investigational product (IP) and which does not necessarily have a causal relationship with the IP. An AE can be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of an IP.

A serious adverse event (SAE) is an AE occurring during any study phase, that fulfils one or more of the following criteria:
- Results in death;
- Is immediately life-threatening;
- Requires in-patient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above.

The Safety analysis set included all patients randomly assigned to study treatment and who took at least one dose of study drug.

End point type	Other pre-specified

End point timeframe:

From Day 1 of treatment up to the end of the follow-up period (Week 17)

End point values	Sodium zirconium cyclosilicate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	90		
Units: Patients				
Any SAE	14	10		
Any AE leading to discontinuation of IP	5	2		
Any AE	43	47		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Patients who Experienced Clinically Important Abnormalities in Clinical Laboratory Parameters

End point title	Number of Patients who Experienced Clinically Important Abnormalities in Clinical Laboratory Parameters

End point description:

The number of patients who experienced clinically important abnormalities in clinical laboratory assessments as assessed by the Investigator are presented. Clinically important abnormalities in clinical laboratory parameters were reported as AEs. Clinical laboratory assessments included clinical chemistry, haematology and urinalysis performed at the central laboratory.

The Safety analysis set included all patients randomly assigned to study treatment and who took at least one dose of study drug.

End point type	Other pre-specified

End point timeframe:

From Day 1 of treatment up to the end of the follow-up period (Week 17)

End point values	Sodium zirconium cyclosilicate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	90		
Units: Patients				
Anaemia	1	1		
Iron deficiency anaemia	1	0		
Hypoglycaemia	1	1		
Hypertriglyceridaemia	0	1		
Hyponatraemia	0	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Patients who Experienced Clinically Important

Abnormalities in Vital Signs Measurements

End point title	Number of Patients who Experienced Clinically Important Abnormalities in Vital Signs Measurements

End point description:

The number of patients who experienced clinically important abnormalities in vital signs assessments as assessed by the Investigator are presented. Clinically important abnormalities in vital signs measurements were reported as AEs. Vital signs assessments included weight, pulse, and systolic and diastolic blood pressure measurements.

The Safety analysis set included all patients randomly assigned to study treatment and who took at least one dose of study drug.

End point type	Other pre-specified

End point timeframe:

From Day 1 of treatment up to the end of the follow-up period (Week 17)

End point values	Sodium zirconium cyclosilicate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	90		
Units: Patients				
Hypotension	4	1		
Hypertension	2	0		
Hypertensive crisis	1	1		
Blood pressure inadequately controlled	0	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Patients who Experienced Clinically Significant Changes in Electrocardiogram (ECG) Measurements

End point title	Number of Patients who Experienced Clinically Significant Changes in Electrocardiogram (ECG) Measurements

End point description:

The number of patients who experienced clinically significant changes in ECG measurements as assessed by the Investigator are presented. Clinically important abnormalities in ECG measurements were reported as AEs. 12-lead ECGs were obtained using a digital ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT (using QT interval corrected by Fredericia's algorithm) intervals.

The Safety analysis set included all patients randomly assigned to study treatment and who took at least one dose of study drug.

End point type	Other pre-specified

End point timeframe:

From Day 1 of treatment up to the end of the follow-up period (Week 17)

End point values	Sodium zirconium cyclosilicate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	90		
Units: Patients	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Patients who Experienced Low and High S-K Levels

End point title	Number of Patients who Experienced Low and High S-K Levels

End point description:

The S-K levels used for this analysis were based on the measurements obtained by the central laboratory. Patients with S-K levels < 3.5 mmol/L were considered to have low S-K levels. Patients with S-K levels > 5.0 mmol/L were considered to have high S-K levels.

The Safety analysis set included all patients randomly assigned to study treatment and who took at least one dose of study drug.

End point type	Other pre-specified

End point timeframe:

From Day 1 of treatment up to the end of the follow-up period (Week 17)

End point values	Sodium zirconium cyclosilicate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	90		
Units: Patients				
S-K < 3.0 mmol/L	0	0		
S-K < 3.5 mmol/L	7	0		
S-K > 5.5 mmol/L	23	32		
S-K > 6.0 mmol/L	3	4		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Events of Low and High S-K Levels

End point title	Number of Events of Low and High S-K Levels

End point description:

The S-K levels used for this analysis were based on the measurements obtained by the central laboratory. Patients with S-K levels < 3.5 mmol/L were considered to have had an event of low S-K levels. Patients with S-K levels > 5.0 mmol/L were considered to have had an event of high S-K levels.

The Safety analysis set included all patients randomly assigned to study treatment and who took at least one dose of study drug.

End point type	Other pre-specified

End point timeframe:

From Day 1 of treatment up to the end of the follow-up period (Week 17)

End point values	Sodium zirconium cyclosilicate	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	90		
Units: Events				
S-K < 3.0 mmol/L	0	0		
S-K < 3.5 mmol/L	12	0		
S-K > 5.5 mmol/L	37	59		
S-K > 6.0 mmol/L	3	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 of treatment up to the end of the follow-up period (Week 17)

Adverse event reporting additional description:

All non-serious adverse event results including totals include non-serious adverse events over the 5% frequency threshold only. The Safety analysis set included all patients randomly assigned to study treatment and who took at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Patients with S-K concentration > 5.0 mmol/L at the last assessment before randomisation received placebo orally tid for 2 days followed by placebo qd for 3 months. Patients with S-K concentration ≤ 5.0 mmol/L at the last assessment before randomisation received placebo orally qd for 3 months. Placebo was up- or down- titrated depending on local laboratory S-K concentration at every study visit.

Reporting group title	Sodium zirconium cyclosilicate

Reporting group description:

Patients with S-K concentration > 5.0 mmol/L at the last assessment before randomisation received SZC 10 g orally tid for 2 days followed by SZC 5 g qd for 3 months. Patients with S-K concentration ≤ 5.0 mmol/L at the last assessment before randomisation received SZC 5 g orally qd for 3 months. SZC was up- or down- titrated depending on local laboratory S-K concentration at every study visit.

Serious adverse events	Placebo	Sodium zirconium cyclosilicate	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 90 (11.11%)	14 / 91 (15.38%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 90 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 90 (1.11%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina unstable			

subjects affected / exposed	1 / 90 (1.11%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 90 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 90 (1.11%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	2 / 90 (2.22%)	2 / 91 (2.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial fibrosis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 90 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 90 (0.00%)	1 / 91 (1.10%)	
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 / 90 (1.11%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	0 / 90 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	1 / 90 (1.11%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 90 (1.11%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 90 (1.11%)	0 / 91 (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			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 90 (1.11%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 90 (1.11%)	0 / 91 (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			
Bronchitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diverticulitis			
subjects affected / exposed	0 / 90 (0.00%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 90 (1.11%)	0 / 91 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 90 (1.11%)	1 / 91 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Sodium zirconium cyclosilicate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 90 (7.78%)	16 / 91 (17.58%)	
Cardiac disorders			
Cardiac failure chronic			
subjects affected / exposed	2 / 90 (2.22%)	7 / 91 (7.69%)	
occurrences (all)	2	7	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	3 / 90 (3.33%)	5 / 91 (5.49%)	
occurrences (all)	3	5	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 90 (3.33%)	6 / 91 (6.59%)	
occurrences (all)	3	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2018	The amendment included: - Updates to the Schedule of Activities. - Wording added to clarify which S-K measurement was to be used to determine if patients have S-K > 5.0 mmol/L. - A new section was added describing the process for study and site closure. - A recommendation to perform the Visit 2 i-STAT assessment before other Visit 2 assessments (except Kansas City Cardiomyopathy Questionnaire) was added.
27 February 2019	The amendment included: - Updates to the Schedule of Activities. - Updates to the objectives. - Beta blocker language clarified. - Added clarifications of RAASi titration. - Updates to the inclusion and exclusion criteria. - Modified wording to allow a patient to only be rescreened once. - Wording for the requirement if a previous temporary discontinuation became permanent. - Modified procedure for blood pressure measurements. - Modified efficacy analyses to be based on the Full analysis set as opposed to the intent-to-treat principle using the Full analysis set. - Added that missing data at 3 months will be imputed for the primary variable and changed the laboratory data shift tables to present baseline to the most extreme value during treatment. - Method for multiplicity control was deleted.
12 June 2019	The amendment included: - The entire document was updated to use local laboratories for rapid ascertainment of S-K and creatinine for enrolment and randomisation purposes and for dose titration decisions rather than using the i-STAT device and to remove the requirement for an unblinded Investigator at the end of the study to manage patient RAASi treatment decisions. - Updates to the laboratory assessments. - New wording that patients treated with low dose of MRA at baseline, who did not have MRA increased specifically due to prior hyperkalaemia, were eligible for the study. - New wording to define that up titration of study drug should be considered before down-titration RAASi if local lab-K > 5.0 and ≤ 6.0 mmol/L. - Specified order of RAASi medication titration (first MRA, then ACEi/ARB/ARNI). - Changed target dose of spironolactone from a range of 25-50 mg to 50 mg. - Modified wording to clarify that patients should continue to complete all subsequent visits after study drug discontinuation.
22 May 2020	The amendment (dated 26-May-2020) included: - Updates to the eligibility criteria (patients with low dose baseline MRA could be enrolled into the study, and patients with lower baseline S-K were also eligible). - An order shift in CSP RAASi up-titration guidance (to add/up-titrate MRA first, followed by ACEi/ARB/ARNI). - General design updates.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
28 March 2019	The study was paused from March to September 2019 to undergo a major protocol amendment. During the study interruption patients were called to attend the end of trial visit (Visit 8) prematurely.	23 September 2019

Notes:

Limitations and caveats

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

The study was prematurely terminated due to the COVID-19 pandemic resulting in a reduced sample size and a high premature treatment discontinuation rate.

Notes: