Clinical trial results:
A Phase 3 Multicenter, Multi-dose, Open-label Maintenance Study to Investigate the Long-term Safety and Efficacy of ZS (Sodium Zirconium Cyclosilicate), an Oral Sorbent, in Subjects with Hyperkalemia

Summary

EudraCT number	2014-004555-31
Trial protocol	DE GB NL RO
Global end of trial date	04 November 2016

Results information

Result version number	v1 (current)
This version publication date	02 May 2018
First version publication date	02 May 2018

Trial information

Trial identification

Sponsor protocol code	ZS-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02163499
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ZS Pharma Inc
Sponsor organisation address	508 Wrangler Drive, Suite 100, Coppell, United States, 75019
Public contact	Astra Clinical Study Information Center, ZS Pharma Inc, 1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Astra Clinical Study Information Center, ZS Pharma Inc, 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	09 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 November 2016
Global end of trial reached?	Yes
Global end of trial date	04 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To generate open-label, long-term (up to 12 months) safety and tolerability data for ZS in subjects with hyperkalemia (serum potassium [S-K] ≥ 5.1 mmol/L).

Protection of trial subjects:

Stopping rules If a subject develops excessive hypokalemia or hyperkalemia defined as i STAT potassium values < 3.0 mmol/L at any time during the study or > 6.5 mmol/L at any time during the Maintenance Phase of the main study or > 6.2 mmol/L at any time during the Randomized Withdrawal Study, the subject should immediately receive appropriate medical treatment and be discontinued from investigational product. In addition, a subject who develops any of the following cardiac events will be immediately discontinued from the study (independent of whether it occurs during the Acute Phase, Maintenance Phase, or Randomized Withdrawal Study): • Serious cardiac arrhythmias (ventricular tachycardia or ventricular fibrillation, new atrial fibrillation or atrial flutter, new paroxysmal supraventricular tachycardia [other than sinus tachycardia], new 2nd or 3rd degree atrioventricular block or significant bradycardia [heart rate < 40 bpm]) • Acute congestive heart failure • Significant increase in PR interval (> 250 msec in the absence of pre-existing atrioventricular block), widening of the QRS complex (> 140 msec in the absence of pre-existing bundle branch block) or peaked T-wave, or an increase in QTc > 30 msec to more than 500 msec, > 30 msec increase in QTc in a subject with a baseline QTc of > 500 msec, or an absolute increase in QTc of > 60 msec

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 May 2014
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	Germany: 18
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	South Africa: 31
Country: Number of subjects enrolled	Australia: 52
Country: Number of subjects enrolled	United States: 639
Country: Number of subjects enrolled	Netherlands: 1
Worldwide total number of subjects	751
EEA total number of subjects	29

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)	378
From 65 to 84 years	345
85 years and over	28

Subject disposition

Recruitment	
Recruitment details: -	
Pre-assignment	
Screening details: -	
Pre-assignment period milestones	
Number of subjects started	751
Number of subjects completed	751

Period 1	
Period 1 title	Acute Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Arm title	Sodium zirconium cyclosilicate
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Sodium zirconium cyclosilicate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

10 g TID

Number of subjects in period 1	Sodium zirconium cyclosilicate
Started	751
Completed	746
Not completed	5
Physician decision	1
Consent withdrawn by subject	1
Hypo- or hyperkalemia	1
Participant compliance	1
Protocol deviation	1

Period 2	
Period 2 title	Long term maintenance Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	Sodium zirconium cyclosilicate

Arm description:

Sodium zirconium cyclosilicate (ZS) 5 g once daily (5 g dose titrations)

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

Dosage and administration details:

5 g QD

Number of subjects in period 2	Sodium zirconium cyclosilicate
Started	746
Completed	466
Not completed	280
Adverse event, serious fatal	8
Consent withdrawn by subject	81
Physician decision	8
Hypo- or hyperkalemia	14
Adverse event, non-fatal	51
Met ECG withdrawal criteria	7
Various reasons	56
Participant compliance	17
Lost to follow-up	31
Sponsor decision	5
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	Acute Phase

Reporting group description: -

Reporting group values	Acute Phase	Total	
Number of subjects	751	751	
Age Categorical Units: Subjects			
Adults (18-64 years)	378	378	
From 65-84 years	345	345	
85 years and over	28	28	
Age Continuous Units: years			
median	64		
standard deviation	± 13.03	-	
Gender Categorical Units: Subjects			
Female	303	303	
Male	448	448	

End points

End points reporting groups

Reporting group title	Sodium zirconium cyclosilicate
Reporting group description: -	
Reporting group title	Sodium zirconium cyclosilicate
Reporting group description:	
Sodium zirconium cyclosilicate (ZS) 5 g once daily (5 g dose titrations)	

Primary: Restoration of normal serum potassium (S-K) values (3.5 to 5.0 mmol/L, inclusive) at the end of the Acute Phase

End point title	Restoration of normal serum potassium (S-K) values (3.5 to 5.0 mmol/L, inclusive) at the end of the Acute Phase[1]
End point description:	
Percentage of subjects with S-K values between 3.5 and 5.0 mmol/L, inclusive at the end of the Acute Phase - ITT Population	
End point type	Primary
End point timeframe:	
72 Hours	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No extra statistical Analysis,other than confidence interval, needed as no comparison between treatment groups are being carried out

End point values	Sodium zirconium cyclosilicate			
Subject group type	Reporting group			
Number of subjects analysed	748			
Units: Percentage				
number (confidence interval 77.9%)				
Percentage	77.9 (74.8 to 80.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Maintenance of normokalemia for subjects across Extended Dosing Phase Days 85 to 365

End point title	Maintenance of normokalemia for subjects across Extended Dosing Phase Days 85 to 365[2]
End point description:	
Percentage of subjects with mean S-K values ≤ 5.1 mmol/L during Extended Dosing Phase - ITT Population	
End point type	Primary
End point timeframe:	
Study Days 85 to 365	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No extra statistical analysis required as no hypothesis being considered and you have percentage of subjects that remained Normokalemia, for the extended dosing period, togehter with a confidence interval

End point values	Sodium zirconium cyclosilicate			
Subject group type	Reporting group			
Number of subjects analysed	646			
Units: Percentage				
number (confidence interval 88.4%)				
Percentage	88.4 (85.7 to 90.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean S-K levels Study Days 85 to End of Study

End point title	Mean S-K levels Study Days 85 to End of Study
End point description:	
Mean S-K levels months 3 to 12(EP Days 85, 113, 141, 176, 211, 239, 267, 295, 330, 365 and EOS),months 6 to 9, and months 9 to 12.	
End point type	Secondary
End point timeframe:	
12 months and 7 days	

End point values	Sodium zirconium cyclosilicate			
Subject group type	Reporting group			
Number of subjects analysed	734			
Units: mmol/L				
arithmetic mean (standard deviation)				
Acute Phase Baseline	5.59 (± 0.425)			
Extended Dosing Days 85 to 365/End of Study	4.66 (± 0.379)			
Extended Dosing Days 211 to 267	4.68 (± 0.404)			
Extended Dosing Days 295 to 365	4.62 (± 0.401)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from start of first study drug medication to end of study visit which occurred +/- 7 days after last dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Induction Phase
Reporting group description: -	
Reporting group title	Long term maintenance phase

Reporting group description: -

Serious adverse events	Induction Phase	Long term maintenance phase	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 751 (0.13%)	162 / 746 (21.72%)	
number of deaths (all causes)	0	8	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast canver			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metasases to lung			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 751 (0.00%)	4 / 746 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension crisis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occulsive disease			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Leg amputation			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
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			
Asthenia			
subjects affected / exposed	0 / 751 (0.00%)	2 / 746 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest pain			
subjects affected / exposed	0 / 751 (0.00%)	11 / 746 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalized oedema			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Local swelling			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrosis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Dependence enabling machine or device			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
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			
Acute respiratory failure			
subjects affected / exposed	0 / 751 (0.00%)	5 / 746 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 751 (0.00%)	3 / 746 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysponea			
subjects affected / exposed	0 / 751 (0.00%)	5 / 746 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypercapnia			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Interstitial lung disease			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary oedema			
subjects affected / exposed	0 / 751 (0.00%)	3 / 746 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 751 (0.00%)	3 / 746 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram abnormal			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Troponin increased			
subjects affected / exposed	0 / 751 (0.00%)	2 / 746 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted fracture			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug dose omission			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lower limb fracture			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 751 (0.00%)	6 / 746 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 751 (0.00%)	3 / 746 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrilliation			

subjects affected / exposed	0 / 751 (0.00%)	3 / 746 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bundle branch block right			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
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	0 / 751 (0.00%)	11 / 746 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 751 (0.00%)	11 / 746 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			

subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart injury			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 751 (0.00%)	3 / 746 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocarditis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis uraemic			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
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 / 751 (0.00%)	2 / 746 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerbrovascular accident			

subjects affected / exposed	0 / 751 (0.00%)	3 / 746 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 751 (0.00%)	2 / 746 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemia attac			
subjects affected / exposed	0 / 751 (0.00%)	2 / 746 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 751 (0.00%)	2 / 746 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Ascites			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorhage			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	0 / 751 (0.00%)	2 / 746 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	0 / 751 (0.00%)	2 / 746 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 751 (0.00%)	2 / 746 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 751 (0.00%)	2 / 746 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 751 (0.00%)	4 / 746 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematuria			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hydronephrosis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 751 (0.00%)	8 / 746 (1.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
subjects affected / exposed	0 / 751 (0.00%)	4 / 746 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neuropathic arthropathy			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
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 / 751 (0.00%)	3 / 746 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 751 (0.00%)	7 / 746 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			

subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gas gangrene			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic airways disease			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 751 (0.00%)	3 / 746 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 751 (0.00%)	8 / 746 (1.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis acute			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 751 (0.00%)	14 / 746 (1.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia cryptococcal			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			

subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 751 (0.00%)	3 / 746 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 751 (0.13%)	4 / 746 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 751 (0.00%)	2 / 746 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 751 (0.00%)	3 / 746 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			

subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 751 (0.00%)	4 / 746 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 751 (0.00%)	4 / 746 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 751 (0.00%)	1 / 746 (0.13%)	
occurrences causally related to treatment / all	0 / 0	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	Induction Phase	Long term maintenance phase	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 751 (1.73%)	354 / 746 (47.45%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 751 (0.13%)	78 / 746 (10.46%)	
occurrences (all)	1	94	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 751 (0.13%)	72 / 746 (9.65%)	
occurrences (all)	1	84	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 751 (0.00%)	42 / 746 (5.63%)	
occurrences (all)	0	45	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 751 (0.53%)	56 / 746 (7.51%)	
occurrences (all)	4	67	
Constipation			
subjects affected / exposed	2 / 751 (0.27%)	46 / 746 (6.17%)	
occurrences (all)	2	53	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 751 (0.40%)	55 / 746 (7.37%)	
occurrences (all)	3	79	
Upper respiratory tract infection			
subjects affected / exposed	0 / 751 (0.00%)	37 / 746 (4.96%)	
occurrences (all)	0	38	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2014	Changed the description of ZS to sodium zirconium cyclosilicate. Increased the number of subjects in the randomized withdrawal study from 120 to 200 subjects due to a US FDA request for a less sensitive power analysis. Removed the testing for fasting plasma glucose since fasting serum glucose was collected at the same time points. Modified the dose stopping rule to include the Acute Phase and changed the upper limit of the i-STAT potassium value that required discontinuation of study drug from 6.4 to 7.0 mmol/L to mirror the upper limit that was used in the recently completed Phase 3 study, ZS-003. Added details regarding the analysis of data from the randomized withdrawal study.
16 October 2014	Reduced the i-STAT potassium value requiring a dose increase of ZS to 5 g QD or 10 gQD from 5.6 to 7.0 mmol/L to 5.1 to 7.0 mmol/L. Reduced the i-STAT potassium value that required discontinuation of study drug in the randomized withdrawal study from > 7.0 mmol/L to > 6.2 mmol/L, which was consistent with the completed study, ZS-004, which had a placebo arm. Limited participation in the randomized withdrawal study to selected sites in North America rather than all study sites. Clarified that the site was to contact the Medical Monitor for dosing directions in the rare case that the i-STAT potassium value was between 3.0 to 3.4 mmol/L during the Acute Phase. Updated animal toxicity data from a 9-month oral toxicity study in dogs to support dosing in man beyond 9 months. Removed the requirement that a person who was reading a consent form to a vision-impaired non-English speaking subject be a member of the research team who was fluent in the language of the subject since it was not always possible to have members of the research team fluent in multiple languages. In most cases, study sites had access to individuals who were not members of the study team who could read the consent to the subject in the subject's primary language and translate information between the subject and the investigator. Clarified that only sexually active women of childbearing potential were to use 2 forms of medically acceptable contraception with at least 1 being a barrier method. Removed the lower limit for room temperature storage of study drug based on ongoing stability data.

22 December 2014	Reduced the i-STAT potassium value that required a subject to stop dosing in the Extended Dosing Phase from > 7.0 mmol/L to > 6.5 mmol/L for increased safety during long-term dosing. Required subjects to return to the site 7 (± 1) days later if a RAAS inhibitor or diuretic dose was adjusted or initiated during the Extended Dosing Phase or randomized withdrawal study to measure potassium since changes in either of these medications may have altered the level of blood potassium. The i-STAT potassium value was to be evaluated, and the dose of ZS was adjusted or stopped based on the rules in the protocol. Clarified that all Extended Dosing Phase visits from Day 8 onwards may have taken place either 1 day early or 1 day late to provide greater flexibility with scheduling. Removed the requirement for the randomized withdrawal study to start when the first subject on Extended Dosing Phase Day 176 met the criteria for entry in the randomized withdrawal study. Changed the lower limit of age of an eligible subject from 19 to 18 years of age. Added the collection of blood samples for analysis of zirconium at baseline and on the morning of Acute Phase Day 2 as recommended by the US FDA at selected study sites in North America. Added additional sampling time points for the collection of blood for aldosterone and renin on Extended Dosing Phase Days 29 and 267. Modified secondary and exploratory endpoints and a secondary objective. Removed information from nonclinical studies that was available in the Investigator's Brochure. Deleted the collection of urine for p-cresol and indole at all time points and deleted the collection of blood for BNP and galectin-3 at all time points except baseline (Acute Phase Day 1)
18 February 2015	Increased the enrollment in the Extended Dosing Phase from 500 to 750 subjects to allow sites in Europe sufficient opportunity to enroll subjects in the study. Allowed the Medical Monitor to request a dose adjustment based on the central laboratory potassium value and not the i-STAT value if there was a significant discrepancy between the values. This was to be determined on a case-by-case basis by the Medical Monitor. Dose escalation was still only requested if central laboratory S-K value was > 5.0 mmol/L (increase from 5 g QOD to 5 g QD or increase from 5 to 10 g QD) or > 5.5 mmol/L (increase from 10 to 15 g QD). Defined medically acceptable contraception as requested by the Clinical Trials Facilitation Group in the European Union as part of the Voluntary Harmonization Procedure assessment.
11 March 2015	Added clarification of medically acceptable contraception methods to Inclusion Criterion 5.

29 April 2015	Incorporated the use of a lower volume of water (40 mL with no mandatory rinses) to deliver the study drug for subjects who enrolled in the trial under this amendment at selected sites in the US. All other subjects were to continue to use 180 mL plus 2 mandatory rinses of 30 mL each to deliver the study drug. This allowed for the collection of safety and tolerability data of the study drug using a lower volume of water. Subjects who enrolled in the study under this amendment at selected sites in the US received a dosing card that provided detailed written directions for proper preparation of study drug doses. If a subject who should have consumed ZS using 40 mL of water with no mandatory rinses mistakenly used 180 mL of water followed by two 30 mL rinses, this was to be recorded on the subject's dosing card and in EDC as a deviation and accounted for during data analysis. Added 2 new secondary endpoints and modified an exploratory endpoint. Incorporated all country-specific wording, thereby eliminating the need for any country-specific amendments. Specified that expected progression of CKD requiring dialysis, transplant or other treatment resulting in study discontinuation was not to be reported as an adverse event in this trial. The event was to be reported on the End of Study eCRF in EDC. Removed the requirement that the independent Data Monitoring Committee (iDMC). review data on an ongoing basis for this study. The ZS Pharma Medical Monitor continued to monitor safety data throughout the study.
02 February 2016	Removed the randomized withdrawal study from the trial. Emerging data from ZS-005 consistently showed that once treatment was stopped (on Day 365), S-K values returned into the hyperkalemic range. In addition, interim data from Study ZS-005 very clearly demonstrated that ZS maintained normokalemia in 90 to 100% of the subjects with a mean S-K value of 4.6 mmol/L. Changed the title of the protocol due to removal of the randomized withdrawal study from the trial. Clarified that subjects who had a history of heart failure were classified according to the New York Heart Association functional classification system. Clarified that adverse events were collected for 7 (± 1) days after the last dose of study drug which corresponded with the acceptable time frame of the End of Study visit. Clarified that expected progression of CKD requiring dialysis, transplant, or other treatment resulting in study discontinuation not related to ZS was not to be reported as an adverse event or serious adverse event.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported