Clinical trial results:
A phase 3b, multicenter, prospective, randomized, double blind, placebocontrolled study to reduce incidence of pre-dialysis hyperkalemia with Sodium Zirconium Cyclosilicate (DIALIZE)

Summary

EudraCT number	2017-003029-14
Trial protocol	GB
Global end of trial date	07 November 2018

Results information

Result version number	v1 (current)
This version publication date	27 November 2019
First version publication date	27 November 2019

Trial information

Trial identification

Sponsor protocol code	D9480C00006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03303521
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	151 85, Södertälje, Sweden,
Public contact	AstraZeneca Clinical, 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	07 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 November 2018
Global end of trial reached?	Yes
Global end of trial date	07 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of SZC in the treatment of hyperkalaemia in patients on haemodialysis.

Protection of trial subjects:

Patients given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2017
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	United Kingdom: 30
Country: Number of subjects enrolled	Japan: 56
Country: Number of subjects enrolled	Russian Federation: 66
Country: Number of subjects enrolled	United States: 44
Worldwide total number of subjects	196
EEA total number of subjects	30

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)	118
From 65 to 84 years	77
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening period ran for one week, beginning on a hemodialysis day following the Long Inter-Dialytic Interval (D -7) until the treatment period started on study day 1 (D1). Informed consent was obtained on study day -7 and patients were assessed to ensure they met the eligibility criteria during the screening period.

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, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Sodium Zirconium Cyclosilicate (SZC)

Arm description:

Suspension administered orally for a treatment period of eight weeks (4 weeks of dose adjustment, 4 weeks in stable dose). Single dose contains 1 to 3 sachets that should be suspended in 45 mL of water by patient and administered on non-dialysis days.

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

Dosage and administration details:

Powder for oral suspension in a sachet (5 g). Single dose contains 1 to 3 sachets that should be suspended in 45 mL of water by patient and administered on non-dialysis days

Arm title	Placebo

Arm description:

Suspension administered orally for a treatment period of eight weeks (4 weeks of dose adjustment, 4 weeks in stable dose). Single dose contains 1 to 3 sachets that should be suspended in 45 mL of water by patient and administered on non-dialysis days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder in sachet
Routes of administration	Oral use

Dosage and administration details:

Powder for oral suspension in a sachet. Single dose contains 1 to 3 sachets that should be suspended in 45 mL of water by patient and administered on non-dialysis days.

Number of subjects in period 1	Sodium Zirconium Cyclosilicate (SZC)	Placebo
Started	97	99
Completed	92	96
Not completed	5	3
Adverse event, serious fatal	1	-
Transferred to non-study dialysis center	1	-
Consent withdrawn by subject	2	-
Non-comliance to study protocol	-	1
Kidney transplantation	-	1
Adverse event, non-fatal	1	-
Investigational product discontinuation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Sodium Zirconium Cyclosilicate (SZC)
Reporting group description:	
Suspension administered orally for a treatment period of eight weeks (4 weeks of dose adjustment, 4 weeks in stable dose). Single dose contains 1 to 3 sachets that should be suspended in 45 mL of water by patient and administered on non-dialysis days.	
Reporting group title	Placebo
Reporting group description:	
Suspension administered orally for a treatment period of eight weeks (4 weeks of dose adjustment, 4 weeks in stable dose). Single dose contains 1 to 3 sachets that should be suspended in 45 mL of water by patient and administered on non-dialysis days.	

Reporting group values	Sodium Zirconium Cyclosilicate (SZC)	Placebo	Total
Number of subjects	97	99	196
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	65	53	118
From 65-84 years	32	45	77
85 years and over	0	1	1
Age Continuous Units: Years			
arithmetic mean	55.7	60.4	
standard deviation	± 13.84	± 13.2	-
Sex: Female, Male Units: Subjects			
Female	40	41	81
Male	57	58	115
Race/Ethnicity, Customized Units: Subjects			
White	50	52	102
Black Or African American	11	8	19
Asian	33	33	66
American Indian Or Alaska Native	1	2	3
Other	2	4	6

End points

End points reporting groups

Reporting group title	Sodium Zirconium Cyclosilicate (SZC)

Reporting group description:

Suspension administered orally for a treatment period of eight weeks (4 weeks of dose adjustment, 4 weeks in stable dose). Single dose contains 1 to 3 sachets that should be suspended in 45 mL of water by patient and administered on non-dialysis days.

Reporting group title	Placebo

Reporting group description:

Suspension administered orally for a treatment period of eight weeks (4 weeks of dose adjustment, 4 weeks in stable dose). Single dose contains 1 to 3 sachets that should be suspended in 45 mL of water by patient and administered on non-dialysis days.

Primary: Proportion of responders

End point title	Proportion of responders

End point description:

A subject was considered to be a responder if, during the evaluation period, they maintained a pre-dialysis serum potassium (S-K) between 4.0 and 5.0 mmol/L on at least 3 out of 4 dialysis treatments following the long inter-dialytic interval and did not receive rescue therapy. The S-K levels used for this analysis were based on the measurements obtained by the central laboratory.

End point type	Primary

End point timeframe:

Evaluation period runs over the last 4 weeks of the treatment period, starting after visit 11 and ending on visit 15, thus it comprises post-long inter-dialytic interval visits 12, 13, 14 and 15.

End point values	Sodium Zirconium Cyclosilicate (SZC)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	99		
Units: Percentage of participants				
number (not applicable)	41.2	1.0		

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

Proportion of responders

Comparison groups	Sodium Zirconium Cyclosilicate (SZC) v Placebo

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	68.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.85
upper limit	2810.85

Primary: Sensitivity analysis of the proportion of responders

End point title	Sensitivity analysis of the proportion of responders

End point description:

The sensitivity analysis assessed the impact of subjects classified as non-responders due to missing serum potassium (S-K) data. Missing values were imputed using available i-STAT measurements and last value carried forward approach. The Primary endpoint analysis was repeated on the imputed data.

End point type	Primary

End point timeframe:

Evaluation period runs over the last 4 weeks of the treatment period, comprising post-long inter-dialytic interval visits 12, 13, 14 and 15.

End point values	Sodium Zirconium Cyclosilicate (SZC)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	99		
Units: Percentage of participants				
number (not applicable)	42.3	2.0		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Sensitivity analysis of the proportion of responders

Comparison groups	Sodium Zirconium Cyclosilicate (SZC) v Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	35.51

Confidence interval	
level	95 %
sides	2-sided
lower limit	8.53
upper limit	309.48

Secondary: Proportion of patients needing rescue therapy

End point title	Proportion of patients needing rescue therapy

End point description:

Patients requiring any urgent intervention consistent with local practice patterns to reduce serum potassium (S-K) including insulin/glucose, beta-adrenergic agonists, sodium bicarbonate, K binders or any form of renal replacement therapy.

End point type	Secondary

End point timeframe:

An 8 week overall treatment period (a 4 week adjustment phase plus a 4 week evaluation phase).

End point values	Sodium Zirconium Cyclosilicate (SZC)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	99		
Units: Percentage of participants				
number (not applicable)	2.1	5.1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events will be collected from time of randomization throughout the treatment period and including the follow-up period (until Visit 16 or the last patient visit in the study). SAEs will be recorded from the time of informed consent.

Adverse event reporting additional description:

Safety Analysis Set (All randomized subjects who received at least 1 dose of investigational product, SZC or placebo. N=96 for SZC, N=99 for Placebo). Subjects excluded from the Safety Analysis Set (n=1 for SZC, n=0 Placebo) did not receive treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Suspension administered orally for a treatment period of eight weeks (4 weeks of dose adjustment, 4 weeks in stable dose). Single dose contains 1 to 3 sachets that should be suspended in 45 mL of water by patient and administered on non-dialysis days.

Reporting group title	Sodium Zirconium Cyclosilicate (SZC)

Reporting group description:

Suspension administered orally for a treatment period of eight weeks (4 weeks of dose adjustment, 4 weeks in stable dose). Single dose contains 1 to 3 sachets that should be suspended in 45 mL of water by patient and administered on non-dialysis days.

Serious adverse events	Placebo	Sodium Zirconium Cyclosilicate (SZC)	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 99 (8.08%)	7 / 96 (7.29%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Injury, poisoning and procedural complications			
Arteriovenous fistula occlusion			
subjects affected / exposed	0 / 99 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriovenous fistula site complication			
subjects affected / exposed	1 / 99 (1.01%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	1 / 99 (1.01%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 99 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 99 (0.00%)	2 / 96 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 99 (1.01%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 99 (1.01%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 99 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 99 (1.01%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			

subjects affected / exposed	0 / 99 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 99 (0.00%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 99 (1.01%)	0 / 96 (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			
Fluid overload			
subjects affected / exposed	2 / 99 (2.02%)	0 / 96 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	3 / 99 (3.03%)	1 / 96 (1.04%)	
occurrences causally related to treatment / all	0 / 3	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	Placebo	Sodium Zirconium Cyclosilicate (SZC)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 99 (11.11%)	7 / 96 (7.29%)	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 99 (6.06%)	4 / 96 (4.17%)	
occurrences (all)	6	5	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 99 (5.05%)	3 / 96 (3.13%)	
occurrences (all)	5	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2017	Stratification changed from site to country
11 September 2017	Cardiac monitoring/arrhythmia endpoint and related wording removed. Visit schedule updated (Visit 14 and 16 removed). Medications restrictions updated to reflect new information.
05 February 2018	Visit schedule updated (additional potassium sampling visits after Short InterDialytic Interval). EOT/EOS requirements updated for premature treatment discontinuation. Contraception and pregnancy restrictions updated to reflect EU guidelines. Outcome measure for primary objective updated. IDMC related wording added. Eligibility criteria updated (EC #2 removed; IC #9 added; IC #7 and EC #6 clarified). Patient dietary counseling and compliance with diet restrictions added. Dialysis adequacy and Interdialytic Weight Gain assessment clarified. Dosing instruction for Investigational Product updated. The list of pH-dependent drugs updated. EOS visit window updated. Study requirements for safety assessments and rescue treatment clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported