Clinical trial results:
A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate a Potassium Normalization Treatment Regimen Including Sodium Zirconium Cyclosilicate (ENERGIZE)

Summary

EudraCT number	2017-003955-50
Trial protocol	DK IT
Global end of trial date	21 December 2018

Results information

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

Trial information

Trial identification

Sponsor protocol code	D9480C00005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03337477
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	One Medimmune Way, Gaithersburg, United States, MD 20878
Public contact	Study Information Center, AstraZeneca Clinical, +1 877 240 9479, information.center@astrazeneca.com
Scientific contact	Study Information Center, AstraZeneca Clinical, +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	25 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2018
Global end of trial reached?	Yes
Global end of trial date	21 December 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The study is designed to determine if SZC 10g administered up to three times over 10h added to insulin and glucose in patients presenting with hyperkalaemia will prove tolerable and efficacious by performing a multicentre, international, randomized, double-blind, placebo-controlled, prospective, parallel-group study.

Protection of trial subjects:

Study monitors will perform ongoing source data verification and source data review to confirm that the safety and rights of subjects are being protected.

Background therapy:

insulin and glucose

Evidence for comparator: -

Actual start date of recruitment	13 February 2018
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	Denmark: 2
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	United States: 39
Worldwide total number of subjects	70
EEA total number of subjects	4

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)	46
From 65 to 84 years	22
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study in the United States, Russia, Denmark and Italy from 13 February 2018 to 21 December 2018.

Pre-assignment

Screening details:

Patients with S-K ≥5.8 mmol/L for whom treatment with insulin and glucose to manage hyperkalaemia has been determined medically appropriate by the Investigator. The study originally recruited patients with S-K ≥6.0 mmol/L; however, this inclusion criterion was updated during CSP Amendment to allow enrolment of patients with S-K ≥5.8 mmol/L.

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	Investigator, Monitor, Carer, Subject, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Sodium Zirconium Cyclosilicate (SZC) 10g

Arm description:

SZC will be administered in addition to insulin and glucose.

Arm type	Experimental
Investigational medicinal product name	Sodium Zirconium Cyclosilicate (SZC) 5g
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Powder for oral suspension in a sachet. Single dose contains two sachets that should be suspended in 45 mL of water by patient.

Arm title	Placebo

Arm description:

Placebo will be administered in addition to insulin and glucose.

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:

Powder for oral suspension in a sachet. Single dose contains two sachets that should be suspended in 45 mL of water by patient.

Number of subjects in period 1	Sodium Zirconium Cyclosilicate (SZC) 10g	Placebo
Started	33	37
Completed	22	24
Not completed	11	13
Adverse event, serious fatal	-	1
Consent withdrawn by subject	-	1
Lost to follow-up	-	2
varying reasons	11	9

Baseline characteristics

Reporting groups	
Reporting group title	Sodium Zirconium Cyclosilicate (SZC) 10g
Reporting group description: SZC will be administered in addition to insulin and glucose.	
Reporting group title	Placebo
Reporting group description: Placebo will be administered in addition to insulin and glucose.	

Reporting group values	Sodium Zirconium Cyclosilicate (SZC) 10g	Placebo	Total
Number of subjects	33	37	70
Age, Customized Units: Subjects			
<50 years	6	11	17
>=50 - <65 years	11	18	29
>=65 years	16	8	24
Age Continuous Units: years			
arithmetic mean	62.0	56.4	
standard deviation	± 12.7	± 14.4	-
Sex: Female, Male Units: Subjects			
Female	16	19	35
Male	17	18	35
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	11	9	20
White	22	26	48
More than one race	0	0	0
Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	10	16
Not Hispanic or Latino	27	27	54
Unknown or Not Reported	0	0	0
Region of Enrollment			
Country			
Units: Subjects			
Denmark	0	2	2
Italy	1	1	2
Russia	13	14	27
United States	19	20	39

End points

End points reporting groups

Reporting group title	Sodium Zirconium Cyclosilicate (SZC) 10g
Reporting group description: SZC will be administered in addition to insulin and glucose.	
Reporting group title	Placebo
Reporting group description: Placebo will be administered in addition to insulin and glucose.	

Primary: Mean absolute change in S-K from baseline until 4h after start of dosing with SZC/placebo

End point title	Mean absolute change in S-K from baseline until 4h after start of dosing with SZC/placebo
End point description: The least squares means (LS-means) are derived from a linear regression model of absolute change in S-K at 4h with the following covariates: treatment group; baseline S-K; time from the start of dosing insulin to the start of dosing SZC/placebo and the dose (units/kg) of the first course of insulin. The 95% CI is associated with LS-Means.	
End point type	Primary
End point timeframe: Baseline to 4h potassium measurements.	

End point values	Sodium Zirconium Cyclosilicate (SZC) 10g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	36		
Units: mmol/L				
least squares mean (confidence interval 95%)	-0.41 (-0.63 to -0.19)	-0.27 (-0.48 to -0.07)		

Statistical analyses

Statistical analysis title	Comparison with Placebo
Statistical analysis description: Difference in LS-means	
Comparison groups	Sodium Zirconium Cyclosilicate (SZC) 10g v Placebo
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	0.17
Variability estimate	Standard deviation
Dispersion value	0.15

Secondary: Fraction of patients responding to therapy defined as: S-K <6.0mmol/L between 1 and 4h and S-K <5.0mmol/L at 4h; and no additional potassium lowering therapy from 0 to 4h with exception of the initial insulin treatment

End point title	Fraction of patients responding to therapy defined as: S-K <6.0mmol/L between 1 and 4h and S-K <5.0mmol/L at 4h; and no additional potassium lowering therapy from 0 to 4h with exception of the initial insulin treatment

End point description:

Additional therapies for hyperkalaemia are 2nd dose of insulin, Beta-agonists, Diuretics, Dialysis, Sodium bicarbonate and Potassium binders when administered with the expressed intent to lower S-K. Patients with any missing potassium value from 1h to 4h inclusive will be treated as non-responders.

End point type	Secondary

End point timeframe:

Baseline to 4h potassium meansurements.

End point values	Sodium Zirconium Cyclosilicate (SZC) 10g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	36		
Units: Proportion of participants				
number (not applicable)	0.063	0.056		

Statistical analyses

No statistical analyses for this end point

Secondary: The fraction of patients achieving normokalaemia 1, 2 and 4h after start of dosing with SZC/placebo

End point title	The fraction of patients achieving normokalaemia 1, 2 and 4h after start of dosing with SZC/placebo

End point description:

Proportion of patients achieving normokalaemia, S-K 3.5-5.0 mmol/L, at 1, 2 and 4h after start of dosing

End point type	Secondary

End point timeframe:

Baseline to 4h potassium meansurements.

End point values	Sodium Zirconium Cyclosilicate (SZC) 10g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	36		
Units: Proportion of participants				
number (not applicable)				
1h	0.156	0.139		
2h	0.125	0.056		
4h	0.063	0.056		

Statistical analyses

No statistical analyses for this end point

Secondary: The fraction of patients achieving S-K <5.5mmol/l 1, 2, and 4h after start of dosing with SZC/placebo

End point title	The fraction of patients achieving S-K <5.5mmol/l 1, 2, and 4h after start of dosing with SZC/placebo

End point description:

End point type	Secondary

End point timeframe:

Baseline to 4h potassium meansurements.

End point values	Sodium Zirconium Cyclosilicate (SZC) 10g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	36		
Units: Proportion of paticipants				
number (not applicable)				
1h	0.313	0.306		
2h	0.375	0.167		
4h	0.156	0.139		

Statistical analyses

No statistical analyses for this end point

Secondary: The fraction of patients achieving S-K <6.0mmol/l 1, 2, and 4h after start of dosing with SZC/placebo

End point title	The fraction of patients achieving S-K <6.0mmol/l 1, 2, and 4h after start of dosing with SZC/placebo

End point description:

End point type	Secondary

End point timeframe:

Baseline to 4h potassium meansurements.

End point values	Sodium Zirconium Cyclosilicate (SZC) 10g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	36		
Units: Proportion of paticipants				
number (not applicable)				
1h	0.656	0.611		
2h	0.625	0.472		
4h	0.469	0.361		

Statistical analyses

No statistical analyses for this end point

Secondary: The fraction of patients administered additional potassium lowering therapy due to hyperkalaemia from 0 to 4h.

End point title	The fraction of patients administered additional potassium lowering therapy due to hyperkalaemia from 0 to 4h.

End point description:

Additional therapies for hyperkalaemia are 2nd dose of insulin, Beta-agonists, Diuretics, Dialysis, Sodium bicarbonate and Potassium binders when administered with the expressed intent to lower S-K.

End point type	Secondary

End point timeframe:

Baseline to 4h potassium meansurements.

End point values	Sodium Zirconium Cyclosilicate (SZC) 10g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	36		
Units: Proportion of participants				
number (not applicable)	0.156	0.306		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean absolute change in S-K from baseline to 1h and 2h after start of dosing with SZC/placebo

End point title	Mean absolute change in S-K from baseline to 1h and 2h after start of dosing with SZC/placebo

End point description:

The least squares means (LS-means) are derived from a linear regression model of absolute change in S-K at 1h and 2h with the following covariates: treatment group; baseline S-K; time from the start of dosing insulin to the start of dosing SZC/placebo and the dose (units/kg) of the first course of insulin. The 95% CI is associated with LS-Means.

End point type	Secondary

End point timeframe:

Baseline to 2h potassium measurements.

End point values	Sodium Zirconium Cyclosilicate (SZC) 10g	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	36		
Units: mmol/L				
least squares mean (confidence interval 95%)				
1h	-0.67 (-0.90 to -0.44)	-0.67 (-0.89 to -0.45)		
2h	-0.72 (-0.96 to -0.48)	-0.36 (-0.59 to -0.14)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (including SAEs) were collected from time of signature of informed consent form throughout the treatment period and including the follow-up period (Visit 2 or last contact).

Adverse event reporting additional description:

AEs occurring between 0h to 24h and after 24h were summarised separately. AEs occurring between 0h to 24h are reported in EudraCT Results Form.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Sodium Zirconium Cyclosilicate (SZC) 10g

Reporting group description:

SZC will be administered in addition to insulin and glucose.

Reporting group title	Placebo

Reporting group description:

Placebo will be administered in addition to insulin and glucose.

Serious adverse events	Sodium Zirconium Cyclosilicate (SZC) 10g	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 29 (3.45%)	2 / 33 (6.06%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 29 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Clonic convulsion			
subjects affected / exposed	0 / 29 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 29 (3.45%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 29 (0.00%)	1 / 33 (3.03%)	
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	Sodium Zirconium Cyclosilicate (SZC) 10g	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 29 (20.69%)	8 / 33 (24.24%)	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 29 (3.45%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	4 / 29 (13.79%)	3 / 33 (9.09%)	
occurrences (all)	5	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 June 2018	The primary purpose of the protocol amendment was to allow the study to integrate better with standard of care, while minimizing the impact on the scientific integrity of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Recruitment was stopped at 70 patients randomized instead of 132, as initially planned.

Notes: