Clinical trial results:
A Blinded, Placebo-Controlled Extension to Study TRCA-301 to Evaluate the Long-term Safety and Durability of Effect of TRC101 in Subjects with Chronic Kidney Disease and Metabolic Acidosis

Summary

EudraCT number	2017-002562-42
Trial protocol	BG HU SI HR
Global end of trial date	22 February 2019

Results information

Result version number	v1
This version publication date	01 August 2020
First version publication date	01 August 2020

Trial information

Trial identification

Sponsor protocol code	TRCA-301E

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03390842
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Tricida, Inc.
Sponsor organisation address	7000 Shoreline Ct, Suite 201, South San Francisco, CA, United States, 94080
Public contact	Clinical Operations, Tricida, Inc., 01 4159885120, ystasiv@tricida.com
Scientific contact	Clinical Operations, Tricida, Inc., 01 4159885120, ystasiv@tricida.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	01 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2019
Global end of trial reached?	Yes
Global end of trial date	22 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety of TRC101 in chronic kidney disease (CKD) patients with metabolic acidosis. The durability of effect of TRC101 in CKD patients with metabolic acidosis was also evaluated.

Protection of trial subjects:

The design and conduct of TRCA-301E included appropriate monitoring for safety and risk mitigation. The Medical Monitor was to review safety data on an ongoing basis to identify potential adverse safety trends. A Data Monitoring Committee (DMC), established for the parent study (TRCA-301), continued to review safety during this study. To avoid prolonged periods of serum bicarbonate above the normal range, serum bicarbonate levels were measured at every study visit and the study drug dose was to be interrupted if serum bicarbonate was confirmed to be > 30 mEq/L. In addition, the investigator and Medical Monitor were to discuss subjects whose serum bicarbonate decreased to < 12 mEq/L for possible causes of acute-on-chronic acidosis.
All Investigators participating in this study were governed under an appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC). The protocol, informed consent form (ICF) and any information provided to subjects was approved by the responsible IRB/IEC before enrollment of participants in the study at each investigational site. The Investigator was responsible for informing the IRBs/IECs of any reportable serious adverse events (SAEs) or other significant safety concerns, as well as the progress of the study, including completion or termination.
This study was conducted in accordance with United States (US) Food and Drug Administration (FDA) regulations, the International Council for Harmonisation (ICH) Guideline E6 (R2), Guideline for Good Clinical Practice (09 Nov 2016), the Declaration of Helsinki and IRB/IEC requirements. The study was also conducted in accordance with the European Union Clinical Trials Directive 2001/20/EC (EU CTD) for sites in the EU and all other applicable local and national laws and regulations governing the conduct of human clinical trials.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 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	Serbia: 1
Country: Number of subjects enrolled	Ukraine: 22
Country: Number of subjects enrolled	United States: 17
Country: Number of subjects enrolled	Georgia: 77
Country: Number of subjects enrolled	Slovenia: 3
Country: Number of subjects enrolled	Bulgaria: 68
Country: Number of subjects enrolled	Hungary: 8

Worldwide total number of subjects	196
EEA total number of subjects	79

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)	100
From 65 to 84 years	95
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects with non-dialysis-dependent CKD who completed the 12-week, randomized, double-blind, placebo-controlled parent study TRCA-301 and who had a serum bicarbonate value of ≥ 12 mEq/L at the TRCA-301 Week 12 Visit were eligible to continue into the 42-week extension study, TRCA-301E.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	TRC101 Treatment Arm

Arm description:

TRC101 was self-administered orally as an aqueous suspension, QD with food, at approximately the same time each day for 40 weeks. Subjects entered the study on the same blinded TRC101 dose they were receiving in the parent study, TRCA-301, as follows: 0, 3, 6 or 9 g TRC101 QD (0, 1, 2 or 3 packets, respectively). Subjects could have a blinded dose adjustment using these same doses in accordance with a protocol-specified titration algorithm.

Arm type	Experimental
Investigational medicinal product name	veverimer
Investigational medicinal product code	
Other name	TRC101
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

TRC101 was orally administered QD as a 3, 6 or 9 g dose (1, 2 or 3 packets, respectively) suspended in approximately 60 – 90 mL of water.

Arm title	Placebo Treatment Arm

Arm description:

Placebo was self-administered orally as an aqueous suspension, QD with food, at approximately the same time each day for 40 weeks. Subjects entered the study on the same blinded placebo dose they were receiving in the parent study, TRCA-301, as follows: 0, 1, 2 or 3 placebo packets QD. Subjects could have a blinded dose adjustment using these same doses in accordance with a protocol-specified titration algorithm.

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:

Placebo was supplied as a powder for oral suspension in packets. Placebo (1, 2, or 3 packets) was orally administered QD as a suspension in approximately 60 – 90 mL of water.

Number of subjects in period 1	TRC101 Treatment Arm	Placebo Treatment Arm
Started	114	82
Completed	111	74
Not completed	3	8
Adverse event, serious fatal	-	1
Consent withdrawn by subject	1	3
Adverse event, non-fatal	-	1
Lost to follow-up	2	2
Did not complete treatment period	-	1

Baseline characteristics

Reporting groups	
Reporting group title	TRC101 Treatment Arm
Reporting group description:	
TRC101 was self-administered orally as an aqueous suspension, QD with food, at approximately the same time each day for 40 weeks. Subjects entered the study on the same blinded TRC101 dose they were receiving in the parent study, TRCA-301, as follows: 0, 3, 6 or 9 g TRC101 QD (0, 1, 2 or 3 packets, respectively). Subjects could have a blinded dose adjustment using these same doses in accordance with a protocol-specified titration algorithm.	
Reporting group title	Placebo Treatment Arm
Reporting group description:	
Placebo was self-administered orally as an aqueous suspension, QD with food, at approximately the same time each day for 40 weeks. Subjects entered the study on the same blinded placebo dose they were receiving in the parent study, TRCA-301, as follows: 0, 1, 2 or 3 placebo packets QD. Subjects could have a blinded dose adjustment using these same doses in accordance with a protocol-specified titration algorithm.	

Reporting group values	TRC101 Treatment Arm	Placebo Treatment Arm	Total
Number of subjects	114	82	196
Age categorical			
Age (years) was calculated as the number of years between date of birth and date of informed consent, expressed as an integer.			
Units: Subjects			
< 65 years	56	44	100
≥ 65 years	58	38	96
Age continuous			
Age (years) was calculated as the number of years between date of birth and date of informed consent, expressed as an integer.			
Units: years			
arithmetic mean	62.9	61.7	
standard deviation	± 12.07	± 11.88	-
Gender categorical			
Units: Subjects			
Female	46	31	77
Male	68	51	119
History of Hypertension			
Units: Subjects			
Yes	110	79	189
No	4	3	7
History of Diabetes Mellitus			
Units: Subjects			
Yes	70	57	127
No	44	25	69
History of Congestive Heart Failure			
Units: Subjects			
Yes	34	28	62
No	80	54	134

Baseline eGFR			
Baseline eGFR is defined as the average of values of eGFR collected at the Screening 1 Visit, Screening 2 Visit, and Baseline Visit (i.e., Day 1 pre-dose) in the parent study TRCA-301, as measured by the central laboratory, based on serum creatinine values using the CKD-EPI formula.			
Units: mL/min/1.73m2			
arithmetic mean	29.4	27.9	
standard deviation	± 6.41	± 5.42	-
Baseline Bicarbonate			
Baseline Bicarbonate is defined as the average of the values of serum bicarbonate collected at the Screening 1 Visit, Screening 2 Visit, and Baseline Visit (i.e., Day 1 pre-dose) in the parent study TRCA-301, measured onsite using an i-STAT point-of-care device.			
Units: mEq/L			
arithmetic mean	17.21	17.13	
standard deviation	± 1.429	± 1.501	-

End points

End points reporting groups

Reporting group title	TRC101 Treatment Arm

Reporting group description:

TRC101 was self-administered orally as an aqueous suspension, QD with food, at approximately the same time each day for 40 weeks. Subjects entered the study on the same blinded TRC101 dose they were receiving in the parent study, TRCA-301, as follows: 0, 3, 6 or 9 g TRC101 QD (0, 1, 2 or 3 packets, respectively). Subjects could have a blinded dose adjustment using these same doses in accordance with a protocol-specified titration algorithm.

Reporting group title	Placebo Treatment Arm

Reporting group description:

Placebo was self-administered orally as an aqueous suspension, QD with food, at approximately the same time each day for 40 weeks. Subjects entered the study on the same blinded placebo dose they were receiving in the parent study, TRCA-301, as follows: 0, 1, 2 or 3 placebo packets QD. Subjects could have a blinded dose adjustment using these same doses in accordance with a protocol-specified titration algorithm.

Primary: Incidence of adverse events, serious adverse events and adverse events leading to withdrawal

End point title	Incidence of adverse events, serious adverse events and adverse events leading to withdrawal[1]

End point description:

The incidence of adverse events (AEs), serious adverse events (SAEs) and AEs leading to withdrawal. For incidence of AEs and SAEs, see Adverse Events Section. For incidence of AEs leading to withdrawal, see endpoint values below.

End point type	Primary

End point timeframe:

Week 12 Visit in the parent study, TRCA-301, to the Week 54 Visit in the extension study, TRCA-301E.

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: The protocol and statistical analysis plan did not prespecify any hypothesis testing.

End point values	TRC101 Treatment Arm	Placebo Treatment Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	81		
Units: percent				
number (not applicable)	0	1.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects with change from baseline in serum bicarbonate of ≥ 4 mEq/L or serum bicarbonate within the normal range

End point title	Subjects with change from baseline in serum bicarbonate of ≥ 4 mEq/L or serum bicarbonate within the normal range

End point description:	
Percent of subjects having a change from baseline in serum bicarbonate of at least 4 mEq/L or bicarbonate in the normal range (22 – 29 mEq/L) at the end of treatment (Week 52).	
End point type	Secondary
End point timeframe:	
Baseline in the parent study, TRCA-301, to the Week 52 Visit in the extension study, TRCA-301E.	

End point values	TRC101 Treatment Arm	Placebo Treatment Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	74		
Units: percent				
number (confidence interval 95%)	62.7 (53.0 to 71.8)	37.8 (26.8 to 49.9)		

Attachments (see zip file)	TRCA-301E_Secondary Endpoint 1 Chart.pdf

Statistical analyses

Statistical analysis title	% Subjects Who Met Endpoint: TRC101-Placebo
Comparison groups	Placebo Treatment Arm v TRC101 Treatment Arm
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015
Method	Fisher exact
Parameter estimate	Difference in % of subjects
Point estimate	24.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.2
upper limit	38.7

Statistical analysis title	% Subjects ≥4mEq/L Change from Baseline:TRC101-PBO
Comparison groups	TRC101 Treatment Arm v Placebo Treatment Arm
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0015
Method	Fisher exact
Parameter estimate	Treatment difference in % of subjects
Point estimate	24.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	9.7
upper limit	38.2

Statistical analysis title	% Subjects within Normal Range: TRC101-PBO
Comparison groups	TRC101 Treatment Arm v Placebo Treatment Arm
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Treatment difference in % of subjects
Point estimate	30.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.6
upper limit	43.7

Secondary: Change from baseline in serum bicarbonate at the end of treatment	
End point title	Change from baseline in serum bicarbonate at the end of treatment
End point description:	
Change from baseline in serum bicarbonate at the end of treatment (Week 52).	
End point type	Secondary
End point timeframe:	
Baseline in the parent study, TRCA-301, to the Week 52 Visit in the extension study, TRCA-301E.	

End point values	TRC101 Treatment Arm	Placebo Treatment Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	74		
Units: mEq/L				
arithmetic mean (standard deviation)	4.82 (± 3.868)	2.58 (± 3.811)		

Attachments (see zip file)	TRCA-301E_Secondary Endpoint 2 Chart.pdf

Statistical analyses

Statistical analysis title	Mean Change from Baseline: TRC101-Placebo
Comparison groups	TRC101 Treatment Arm v Placebo Treatment Arm
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Mixed-effect repeated measures model
Parameter estimate	Treatment difference in LS means
Point estimate	1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	3.03
Variability estimate	Standard error of the mean
Dispersion value	0.524

Secondary: Change from baseline in the total score of the KDQOL-PFD at the end of treatment

End point title	Change from baseline in the total score of the KDQOL-PFD at the end of treatment

End point description:

Change from baseline in the total score of the Kidney Disease Quality of Life Physical Function Domain (KDQOL-PFD) at the end of treatment. The KDQOL is a validated, kidney disease-specific measure of health-related quality of life. For study TRCA-301E, and parent study TRCA-301, the 10-question Item 3 of the KDQOL, also known as the SF-36 Physical Function subscale, was selected to measure physical functioning and is referenced herein as the KDQOL-PFD. The KDQOL-PFD was chosen as a patient-reported outcome measurement to evaluate the effects of TRC101 on daily activities that may be adversely affected by loss of muscle caused by metabolic acidosis. The minimum score for each of the 10 questions is 0 (physical activity highly limited) and the maximum is 100 (physical activity not limited). The total KDQOL-PFD score is calculated by adding the scores for all 10 questions, for a minimum and maximum possible total KDQOL-PFD score of 0 or 100, respectively.

End point type	Secondary

End point timeframe:

Baseline in the parent study, TRCA-301, to the Week 52 Visit in the extension study, TRCA-301E.

End point values	TRC101 Treatment Arm	Placebo Treatment Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	78		
Units: KDQOL-PFD total score				
arithmetic mean (standard error)	11.42 (± 2.201)	-0.71 (± 2.268)		

Attachments (see zip file)	TRCA-301E_Secondary Endpoint 3 Chart.pdf

Statistical analyses

Statistical analysis title	Mean Change from Baseline in KDQOL-PFD: TRC101-PBO
Comparison groups	TRC101 Treatment Arm v Placebo Treatment Arm
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	ANCOVA

Notes:

[2] - p-value based on analysis of covariance model with rank of change from baseline in total score as dependent variable; treatment (PBO or TRC101) as a fixed effect; and baseline total score, Baseline eGFR, Baseline Bicarbonate as continuous covariates.

Secondary: Change from baseline in the duration of repeated chair stand test at the end of treatment

End point title	Change from baseline in the duration of repeated chair stand test at the end of treatment

End point description:

Change from baseline in the duration of repeated chair stand test at the end of treatment (Week 52). The five-times repeated chair stand test was used as a measure of lower extremity muscle strength. In this test, the time it took for a subject to repeatedly stand from a chair five times was recorded. This test among the group of measures (gait speed, chair stand, and balance tests) comprising the Short Physical Performance Battery (SPPB), which has been used as a predictive tool for possible disability and for monitoring physical functioning in older people.

End point type	Secondary

End point timeframe:

Baseline in the parent study, TRCA-301, to the Week 52 Visit in the extension study, TRCA-301E.

End point values	TRC101 Treatment Arm	Placebo Treatment Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	77		
Units: seconds				
arithmetic mean (standard error)	-4.28 (± 1.240)	-1.42 (± 1.248)		

Attachments (see zip file)	TRCA-301E_Secondary Endpoint 4 Chart.pdf

Statistical analyses

Statistical analysis title	Change from Baseline for RCST: TRC101-Placebo

Statistical analysis description:

Change from Baseline in the Time to Complete the Repeated Chair Stand Test (RCST) at Week 52

Comparison groups	TRC101 Treatment Arm v Placebo Treatment Arm

Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 12 visit in the parent study, TRCA-301, to the Week 54 follow-up visit in the extension study, TRCA-301E.

Adverse event reporting additional description:

The TRCA-301E Safety Analysis Set included all subjects who received any amount of study drug (TRC101 or PBO) in TRCA-301E. Three subjects were excluded (2 TRC101, 1 PBO) because they entered TRCA-301E on a dose hold and remained on the dose hold for the duration of the study because their bicarbonate levels remained within the normal range.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	TRC101 Treatment Arm

Reporting group description:

TRC101 was self-administered orally as an aqueous suspension, QD with food, at approximately the same time each day for 40 weeks. Subjects entered the study on the same blinded TRC101 dose they were receiving in the parent study, TRCA-301, as follows: 0, 3, 6 or 9 g TRC101 QD (0, 1, 2 or 3 packets, respectively). Subjects could have a blinded dose adjustment using these same doses in accordance with a protocol-specified titration algorithm.

Reporting group title	Placebo Treatment Arm

Reporting group description:

Placebo was self-administered orally as an aqueous suspension, QD with food, at approximately the same time each day for 40 weeks. Subjects entered the study on the same blinded placebo dose they were receiving in the parent study, TRCA-301, as follows: 0, 1, 2 or 3 placebo packets QD. Subjects could have a blinded dose adjustment using these same doses in accordance with a protocol-specified titration algorithm.

Serious adverse events	TRC101 Treatment Arm	Placebo Treatment Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 112 (1.79%)	4 / 81 (4.94%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	2	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 112 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina unstable			
subjects affected / exposed	1 / 112 (0.89%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure			
subjects affected / exposed	1 / 112 (0.89%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 112 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 112 (0.89%)	0 / 81 (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			
Renal impairment			
subjects affected / exposed	0 / 112 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Azotaemia			
subjects affected / exposed	0 / 112 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic kidney disease			
subjects affected / exposed	1 / 112 (0.89%)	0 / 81 (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			
Pneumonia			
subjects affected / exposed	0 / 112 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Hyponatraemia			

subjects affected / exposed	0 / 112 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperkalaemia			
subjects affected / exposed	0 / 112 (0.00%)	1 / 81 (1.23%)	
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	TRC101 Treatment Arm	Placebo Treatment Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 112 (69.64%)	39 / 81 (48.15%)	
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 112 (15.18%)	20 / 81 (24.69%)	
occurrences (all)	19	22	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 112 (5.36%)	1 / 81 (1.23%)	
occurrences (all)	6	6	
Gastrointestinal disorders			
Flatulence			
subjects affected / exposed	8 / 112 (7.14%)	5 / 81 (6.17%)	
occurrences (all)	8	5	
Diarrhoea			
subjects affected / exposed	7 / 112 (6.25%)	5 / 81 (6.17%)	
occurrences (all)	8	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 112 (6.25%)	3 / 81 (3.70%)	
occurrences (all)	7	3	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	5 / 112 (4.46%)	7 / 81 (8.64%)	
occurrences (all)	5	8	

Infections and infestations Influenza subjects affected / exposed occurrences (all)	 12 / 112 (10.71%) 13	 6 / 81 (7.41%) 6	
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	 16 / 112 (14.29%) 20	 8 / 81 (9.88%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 December 2017	Original protocol. Note: 68 subjects were enrolled under the original protocol.
28 February 2018	Protocol Amendment 1: The protocol was amended to remove reference to the eligible age range for the parent study, TRCA-301, which was revised to increase the upper limit to 85 years. The amendment also clarified that the adverse event reporting period begins when subjects are enrolled in Study TRCA-301E. Adverse events with an onset time prior to enrollment in the extension study were reported in the parent study, TRCA-301. Note: 128 subjects were enrolled under Protocol Amendment 1.
05 July 2018	Protocol Amendment 2: The protocol was amended to add Kidney Disease and Quality of Life (KDQOL) questions and the repeated chair stand test to the tests and procedures performed at the Week 40 Visit. In addition, the study drug titration algorithm was simplified for subjects with blood bicarbonate in the normal range. Additional minor revisions were also made to correct typographical errors and provide updated administrative information. Note: All subjects had been enrolled in the trial when Protocol Amendment 2 was implemented.
08 November 2018	Protocol Amendment 3: The protocol was revised to add clarification regarding statistical methodology to be used for mixed-effect model repeated measures (MMRM) and analysis of covariance (ANCOVA) analyses of the durability of effect endpoints. In the event that the residuals from the MMRM or ANCOVA models were not normally distributed, alternative statistical analyses were to be used instead; these were to be specified in the Statistical Analysis Plan. Note: All subjects had been enrolled in the trial when Protocol Amendment 3 was implemented.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31248662