Clinical trial results:
A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TRC101 in Subjects with Chronic Kidney Disease and Metabolic Acidosis

Summary

EudraCT number	2016-003825-41
Trial protocol	HU BG SI HR
Global end of trial date	15 May 2018

Results information

Result version number	v1
This version publication date	10 July 2020
First version publication date	10 July 2020

Trial information

Trial identification

Sponsor protocol code	TRCA-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03317444
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	11 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2018
Global end of trial reached?	Yes
Global end of trial date	15 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the efficacy of TRC101 in chronic kidney disease (CKD) patients with metabolic acidosis (serum bicarbonate 12 – 20 mEq/L).
The secondary objective of the study was to evaluate the safety of administration of TRC101 in CKD patients with metabolic acidosis (serum bicarbonate 12 – 20 mEq/L).

Protection of trial subjects:

The design and conduct of TRCA-301 included appropriate monitoring for safety and risk mitigation. The Medical Monitor reviewed blinded safety data on an ongoing basis to identify potential adverse safety trends. Central laboratory reports contained flags that alerted investigators and Tricida personnel to abnormal, critical, and exclusionary laboratory values, and the Medical Monitor routinely reviewed these results as well as adverse events on an ongoing basis. Electrolytes and serum bicarbonate levels were monitored at every study visit. An Independent Data Monitoring Committee reviewed unblinded safety data during the study on a regular basis.
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 on Harmonisation (ICH) guideline E6 (R2), Guideline for Good Clinical Practice (9 November 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	26 September 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	9 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovenia: 3
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Bulgaria: 68
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Serbia: 3

Country: Number of subjects enrolled	Ukraine: 25
Country: Number of subjects enrolled	United States: 27
Country: Number of subjects enrolled	Georgia: 80
Worldwide total number of subjects	217
EEA total number of subjects	82

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)	103
From 65 to 84 years	113
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

After potential subjects provided informed consent, their eligibility was to be evaluated based on laboratory values, medical history, concomitant medications, vital signs, pregnancy test (if applicable) and physical examination. Subjects were 18 – 85 years of age with CKD (eGFR of 20 – 40 mL/min/1.73m^2) and low serum bicarbonate (12 – 20 mEq/L).

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	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	TRC101 Treatment Arm

Arm description:

The first dose of blinded study drug (2 packets for a total of 6 g TRC101) was given at the study site on Day 1 in the morning with food. For the remainder of the Treatment Period, TRC101 was self-administered orally as an aqueous suspension, QD with lunch, for 12 weeks. Beginning at the Week 4 Visit, subjects could have a blinded dose adjustment to 0, 3 or 9 g (0, 1 or 3 packets, respectively) of TRC101 QD in accordance with a protocol-specified titration algorithm. The last dose of study drug was to be taken the day before the Week 12 Visit, unless the subject was enrolled in the extension Study TRCA-301E.

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:

The first dose of blinded study drug (2 packets of placebo) was given at the study site on Day 1 in the morning with food. For the remainder of the Treatment Period, placebo was self-administered orally as an aqueous suspension, QD with lunch, for 12 weeks. Beginning at the Week 4 Visit, subjects could have a blinded dose adjustment to 0, 1 or 3 packets of placebo QD in accordance with a protocol-specified titration algorithm. The last dose of study drug was to be taken the day before the Week 12 Visit, unless the subject was enrolled in the extension Study TRCA-301E.

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	124	93
Completed	119	89
Not completed	5	4
Adverse event, serious fatal	-	2
Consent withdrawn by subject	2	1
Need for dialysis	1	-
Adverse event, non-fatal	1	1
Subject unable to attend visits due to rehab	1	-

Baseline characteristics

Reporting groups	
Reporting group title	TRC101 Treatment Arm

Reporting group description:

The first dose of blinded study drug (2 packets for a total of 6 g TRC101) was given at the study site on Day 1 in the morning with food. For the remainder of the Treatment Period, TRC101 was self-administered orally as an aqueous suspension, QD with lunch, for 12 weeks. Beginning at the Week 4 Visit, subjects could have a blinded dose adjustment to 0, 3 or 9 g (0, 1 or 3 packets, respectively) of TRC101 QD in accordance with a protocol-specified titration algorithm. The last dose of study drug was to be taken the day before the Week 12 Visit, unless the subject was enrolled in the extension Study TRCA-301E.

Reporting group title	Placebo Treatment Arm

Reporting group description:

The first dose of blinded study drug (2 packets of placebo) was given at the study site on Day 1 in the morning with food. For the remainder of the Treatment Period, placebo was self-administered orally as an aqueous suspension, QD with lunch, for 12 weeks. Beginning at the Week 4 Visit, subjects could have a blinded dose adjustment to 0, 1 or 3 packets of placebo QD in accordance with a protocol-specified titration algorithm. The last dose of study drug was to be taken the day before the Week 12 Visit, unless the subject was enrolled in the extension Study TRCA-301E.

Reporting group values	TRC101 Treatment Arm	Placebo Treatment Arm	Total
Number of subjects	124	93	217
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	58	45	103
≥ 65 years	66	48	114
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	63.3	
standard deviation	± 12.64	± 12.08	-
Gender categorical			
Units: Subjects			
Female	50	33	83
Male	74	60	134
History of Hypertension			
Units: Subjects			
Yes	120	90	210
No	4	3	7
History of Diabetes Mellitus			
Units: Subjects			
Yes	76	65	141
No	48	28	76
History of Congestive Heart Failure			
Units: Subjects			
Yes	36	31	67
No	88	62	150

Baseline eGFR			
Baseline eGFR was defined as the average of the values of eGFR collected at the Screening 1 Visit, Screening 2 Visit, and Baseline Visit (i.e., Day 1 pre-dose), based on serum creatinine values measured by the central laboratory and using the CKD-EPI formula.			
Units: mL/min/1.73m^2			
arithmetic mean	29.2	27.8	
standard deviation	± 6.29	± 5.45	-
Baseline Bicarbonate			
Baseline Bicarbonate was 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), measured onsite using an i-STAT point-of-care device.			
Units: mEq/L			
arithmetic mean	17.27	17.30	
standard deviation	± 1.429	± 1.504	-

End points

End points reporting groups

Reporting group title	TRC101 Treatment Arm

Reporting group description:

The first dose of blinded study drug (2 packets for a total of 6 g TRC101) was given at the study site on Day 1 in the morning with food. For the remainder of the Treatment Period, TRC101 was self-administered orally as an aqueous suspension, QD with lunch, for 12 weeks. Beginning at the Week 4 Visit, subjects could have a blinded dose adjustment to 0, 3 or 9 g (0, 1 or 3 packets, respectively) of TRC101 QD in accordance with a protocol-specified titration algorithm. The last dose of study drug was to be taken the day before the Week 12 Visit, unless the subject was enrolled in the extension Study TRCA-301E.

Reporting group title	Placebo Treatment Arm

Reporting group description:

The first dose of blinded study drug (2 packets of placebo) was given at the study site on Day 1 in the morning with food. For the remainder of the Treatment Period, placebo was self-administered orally as an aqueous suspension, QD with lunch, for 12 weeks. Beginning at the Week 4 Visit, subjects could have a blinded dose adjustment to 0, 1 or 3 packets of placebo QD in accordance with a protocol-specified titration algorithm. The last dose of study drug was to be taken the day before the Week 12 Visit, unless the subject was enrolled in the extension Study TRCA-301E.

Primary: 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:

Percentage of subjects having a change from baseline in serum bicarbonate ≥ 4 mEq/L or having serum bicarbonate in the normal range (22 – 29 mEq/L) at the end of treatment (Week 12 Visit).

End point type	Primary

End point timeframe:

Baseline to Week 12

End point values	TRC101 Treatment Arm	Placebo Treatment Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	89		
Units: percent				
number (confidence interval 95%)	59.2 (49.8 to 68.0)	22.5 (14.3 to 32.6)		

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

Statistical analyses

Statistical analysis title	% Subjects Who Met Endpoint: TRC101-Placebo
Comparison groups	TRC101 Treatment Arm v Placebo Treatment Arm

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Treatment difference in % of subjects
Point estimate	36.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.5
upper limit	48.9

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	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Treatment difference in % of subjects
Point estimate	34.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.2
upper limit	46.8

Statistical analysis title	% Subjects within Normal Range: TRC101-PBO
Comparison groups	TRC101 Treatment Arm v Placebo Treatment Arm
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Treatment difference in % of subjects
Point estimate	33.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.7
upper limit	45.6

Secondary: Change from baseline to end of treatment in serum bicarbonate

End point title	Change from baseline to end of treatment in serum bicarbonate
End point description: Mean change from baseline to end of treatment (Week 12 Visit) in serum bicarbonate	
End point type	Secondary
End point timeframe: Baseline to Week 12	

End point values	TRC101 Treatment Arm	Placebo Treatment Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	89		
Units: mEq/L				
least squares mean (confidence interval 95%)	4.42 (3.85 to 4.98)	1.78 (1.13 to 2.44)		

Attachments (see zip file)	TRCA-301_Secondary Endpoint 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	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed-effect repeated measures model
Parameter estimate	Treatment difference in LS means
Point estimate	2.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.77
upper limit	3.5
Variability estimate	Standard error of the mean
Dispersion value	0.44

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Data are the number of patients with adverse events occurring on or after the date of the first dose of TRC101 or placebo.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Active Treatment Arm

Reporting group description:

The first dose of blinded study drug (2 packets of TRC101 [6 g]) was given at the study site on Day 1 in the morning with food. For the remainder of the Treatment Period, TRC101 was self-administered orally as an aqueous suspension, QD with lunch, for 12 weeks. Beginning at the Week 4 Visit, subjects could have a blinded dose adjustment to 0, 3 or 9 g (0, 1 or 3 packets, respectively) of TRC101 QD in accordance with a protocol-specified titration algorithm. The last dose of study drug was to be taken the day before the Week 12 Visit, unless the subject was enrolled in the extension Study TRCA-301E.

Reporting group title	Placebo Treatment Arm

Reporting group description:

The first dose of blinded study drug (2 packets of placebo) was given at the study site on Day 1 in the morning with food. For the remainder of the Treatment Period, placebo was self-administered orally as an aqueous suspension, QD with lunch, for 12 weeks. Beginning at the Week 4 Visit, subjects could have a blinded dose adjustment to 0, 1 or 3 packets of placebo QD in accordance with a protocol-specified titration algorithm. The last dose of study drug was to be taken the day before the Week 12 Visit, unless the subject was enrolled in the extension Study TRCA-301E.

Serious adverse events	Active Treatment Arm	Placebo Treatment Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 124 (2.42%)	2 / 93 (2.15%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	2	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 124 (0.81%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 124 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute left ventricular failure			

subjects affected / exposed	1 / 124 (0.81%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 124 (0.81%)	0 / 93 (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			
Diabetic hyperglycaemic coma			
subjects affected / exposed	0 / 124 (0.00%)	1 / 93 (1.08%)	
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	1 / 124 (0.81%)	0 / 93 (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			
Acute kidney injury			
subjects affected / exposed	1 / 124 (0.81%)	0 / 93 (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 / 124 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Active Treatment Arm	Placebo Treatment Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 124 (25.00%)	13 / 93 (13.98%)	
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	7 / 124 (5.65%) 7	4 / 93 (4.30%) 5	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	11 / 124 (8.87%) 20	3 / 93 (3.23%) 6	
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	13 / 124 (10.48%) 16	6 / 93 (6.45%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2017	Original Protocol. Note: No subjects were enrolled under the original protocol.
31 July 2017	Protocol Amendment 1: The primary endpoint was revised to be based on a responder analysis, in order to assess the magnitude of the treatment effect of TRC101 on blood bicarbonate, for the purpose of powering future investigational studies of TRC101. The restrictions on management of common underlying comorbidities with concomitant medications were relaxed, while minimizing potential impact on blood bicarbonate by changes in concomitant medications, to align the management of concomitant medications with future investigational studies of TRC101. The inclusion and exclusion criteria were revised to ensure that study population reflects the population to be enrolled in future investigational studies of TRC101. Note: No subjects were enrolled under protocol amendment 1.
01 September 2017	Protocol Amendment 2: The design of the extension study, TRCA-301E, conducted under a separate study protocol but mentioned in the parent study (TRCA-301), was changed from an open-label study to a blinded, placebo-controlled study, therefore references to the extension study in the TRCA-301 protocol as an open-label study required revision. In addition, revisions were made to the description of the efficacy endpoint analyses for consistency with the Statistical Analysis Plan and for clarification.
15 January 2018	Protocol Amendment 3: The upper limit of age eligibility was increased from 80 to 85 years in the inclusion criterion #2. This change was made to better reflect the age range of the TRC101 target population; enrollment of subjects between the ages of 80 and 85 years is consistent with other recent studies in the CKD stage 3/4 patient population.

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/30857647