# 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 | v2 (current) |
| This version publication date | 11 January 2022 |
| First version publication date | 01 August 2020 |
| Version creation reason | • Correction of full data set<br>Make minor corrections |

## 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 | Slovenia: 3 |
| Country: Number of subjects enrolled | Ukraine: 22 |
| Country: Number of subjects enrolled | United States: 17 |
| Country: Number of subjects enrolled | Bulgaria: 68 |
| Country: Number of subjects enrolled | Georgia: 77 |
| Country: Number of subjects enrolled | Hungary: 8 |
| Country: Number of subjects enrolled | Serbia: 1 |

| | |
|---|---|
| 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 | 114 | 82 | | |
| Units: mEq/L | | | | |
| least squares mean (standard error) | 4.70 (± 0.335) | 2.71 (± 0.403) | | |

| **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 | 196 |
| 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 | 1 | |
| 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 | 7 | |

| | | | |
|---|---|---|---|
| Infections and infestations<br>Influenza<br>subjects affected / exposed<br>occurrences (all) | <br><br>12 / 112 (10.71%)<br>13 | <br><br>6 / 81 (7.41%)<br>6 | |
| Metabolism and nutrition disorders<br>Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all) | <br><br>16 / 112 (14.29%)<br>19 | <br><br>8 / 81 (9.88%)<br>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.<br>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.<br>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.<br>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