A Phase 3b, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of TRC101 in Delaying Chronic Kidney Disease Progression in Subjects with Metabolic Acidosis

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OBJECTIVES:To evaluate the effect of TRC101 on the progression of chronic kidney disease and to evaluate the safety profile of TRC101 in CKD patients with metabolic acidosis.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON55510

Source
ToetsingOnline

Brief title
TRCA-303

Condition

- Renal disorders (excl nephropathies)

Synonym
chronic kidney disease, increased levels of acid in blood

Research involving
Human

Sponsors and support

Primary sponsor: Tricida Inc.
Source(s) of monetary or material Support: Tricida;Inc.

Intervention

Keyword: Chronic Kidney Disease, Phase 3b, TRC101, VALOR

Outcome measures

Primary outcome

The primary efficacy endpoint of the study is progression of chronic kidney disease, defined by the time to first occurrence of any event in the composite endpoint as adjudicated by the independent blinded CEAC:

• A confirmed >= 40% reduction in eGFR

• ESRD

• Renal death

Secondary outcome

Secondary Efficacy Endpoints

1. Time to first occurrence of any event in the composite of death (all-cause), ESRD, or a confirmed >= 50% reduction in eGFR

2. Change from the A1 Visit (predose) to Month 12 in the total score of the KDQOL-PFD

3. Change from the A1 Visit (predose) to Month 12 in the time to complete the repeated chair stand test

4. Time to ESRD or renal death

5. Time to first occurrence of the primary composite endpoint or cardiovascular (CV) death

6. Time to first occurrence of a confirmed doubling of serum creatinine

7. Time to first occurrence of a confirmed >= 50% reduction in eGFR

8. Time to first occurrence of a confirmed >= 40% reduction in eGFR

9. Frequency of all-cause hospitalization

10. Time to CV death

11. Time to all-cause mortality

With the exception of endpoints #2, #3, #6 and #9, all secondary endpoint

events will be adjudicated by the CEAC.

Study description

Background summary

Patients with chronic kidney disease (CKD) continue to generate acid from their diet and metabolism but have a reduced ability to excrete acid via the kidneys. As a result, metabolic acidosis, characterized by a reduced serum bicarbonate concentration (i.e., below 22 mEq/L),
can develop in advanced stages of CKD. Metabolic acidosis affects 9 - 32% of patients with CKD Stages 3 - 5. If metabolic acidosis is left untreated, the consequences include increased mortality, progression of CKD, acceleration of muscle breakdown, and the
development or exacerbation of bone disease.

Clinical outcomes for CKD patients with bicarbonate levels below the normal range are significantly worse compared to patients with normal bicarbonate (i.e., 22 - 29 mEq/L) as demonstrated in multiple large retrospective cohort studies. As described in these reports, the relationship between decreasing bicarbonate levels and clinical outcomes is believed to be a continuum (i.e., as bicarbonate decreases from normal levels the risk of adverse outcomes, such as progression of CKD and death, progressively increases). Furthermore, the risk of deleterious clinical outcomes for patients with bicarbonate levels in the range required for subjects in this study (i.e., 12 - 20 mEq/L) is significantly greater than for patients with bicarbonate levels indicative of more mild metabolic acidosis (i.e., > 20 to 22 mEq/L). Correction of low bicarbonate levels in patients with CKD (i.e., with oral alkali supplementation or consumption of a less acidic diet) has been shown to result in slowing of progression of renal disease in several small single-center studies.

Oral alkali supplements (e.g., oral sodium bicarbonate and sodium citrate) are variably used in clinical practice to treat metabolic acidosis in patients with CKD. However, use of these agents is often limited to use in CKD patients with mild metabolic acidosis due to concerns
about sodium overload in patients who often have one or more conditions for which sodium restriction is indicated. The daily doses of sodium bicarbonate required to increase serum bicarbonate levels by 3 - 4 mEq/L in patients with metabolic acidosis can be prohibitively high (6 - 8 g per day introducing 1.7 - 2.2 g of sodium for an 80 kg patient. Combined with the sodium intake from diet, the sodium intake from therapeutic doses of oral sodium bicarbonate would result in a total daily sodium load exceeding the guideline-recommended limit of 2 g/day for CKD patients (Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group 2012) independent of underlying comorbidities. Furthermore, common conditions accompanying CKD (e.g., hypertension, heart failure, and edema) may be aggravated, and efficacy of diuretics negated, by the sodium load that sodium-containing alkali therapies deliver. In addition, potassiumcontaining alkali treatments can cause or aggravate hyperkalemia in CKD patients whose ability to excrete potassium loads is reduced. Given these considerations, there is a clear unmet medical need for new treatments with demonstrated efficacy and safety to treat metabolic acidosis.

TRC101 is being developed as a first-in-class, orally administered, counterion-free, insoluble, non-absorbed hydrochloric acid binder for the treatment of metabolic acidosis associated with CKD. The mechanism of action of TRC101 involves binding of proton (H+) and chloride (Cl-), resulting in a net reduction and removal of hydrochloric acid (HCl) from the gastrointestinal (GI) tract, which results in an increase in serum bicarbonate levels. TRC101 has both high H+ and Cl- binding capacity and Cl- binding selectivity. The high amine content of the polymer is responsible for the high H+ and Cl- binding capacity of TRC101; the polymer*s extensive crosslinking leads to insolubility of the polymer and
provides size exclusion properties and high selectivity over other competing anions, such as phosphate, citrate, bile acids and short-chain and long-chain fatty acids present in the GI tract.

This study will explore whether treatment of metabolic acidosis with TRC101 results in slowing of progression of kidney disease in patients with CKD.

Study objective

OBJECTIVES:
To evaluate the effect of TRC101 on the progression of chronic kidney disease and to evaluate the safety profile of TRC101 in CKD patients with metabolic acidosis.

Study design

This is a randomized, double-blind, placebo-controlled trial. Eligible subjects will be randomized in a 1:1 ratio to TRC101 or placebo. The primary endpoint of the study will be progression of renal disease, defined by time to first occurrence of any event in the composite endpoint consisting of a confirmed >= 40% reduction in eGFR, end-stage renal disease (ESRD), and renal death. The study will terminate when the independent blinded Clinical Endpoint Adjudication Committee has positively adjudicated the targeted number of primary efficacy endpoint events. The maximum duration of follow-up for a randomized subject is anticipated to be 6 years in Part B of the study.

Intervention

Part A
At the A1 Visit, subjects will receive study drug QD for 4-8 weeks.

Part B
Approximately 1,600 subjects will be randomized in a 1:1 ratio to study drug.

Study drug will be self-administered orally as an aqueous suspension, QD with food.

Study burden and risks

See attached document 'D6. Risk-Benefit Statement - 18Aug2018'.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Have provided written informed consent prior to participation in the study.
2. Male or female subjects 18 to 85 years of age, inclusive, at Screening 1 Visit.
3. The mean of two Screening eGFR measurements, drawn at least 2 weeks apart and both within 6 weeks of the first day of Part A, is 20 to 40 mL/min/1.73m2, inclusive, calculated using the CKD-EPI equation as reported by the central laboratory.
• Note: If more than two eGFR values were measured at the central laboratory during the Screening Period, the Screening eGFR will be based on the most recent two values that are at least 2 weeks apart and within 6 weeks of the first day of Part A.
Enrollment of subjects with Screening eGFR in the range 15 to < 20 mL/min/1.73m2 may be allowed in the future with notification to the sites by Tricida and will not require a protocol amendment. Subjects with a Screening eGFR value in the range of 15 to < 20 mL/min/1.73m2 may not be enrolled until Tricida has authorized this change in writing.
4. Have stable renal function as defined by eGFR Screening values that are not different by > 20% (the higher of the two Screening eGFR values will be used as the denominator to calculate the 20% allowable difference).
• Note: If more than two eGFR values were measured at the central laboratory during the Screening Period, the first and last values must be used for calculation of the allowable eGFR difference.
5. Based on onsite measurement using an i STAT point of care device, have three serum bicarbonate values, each >= 2 weeks apart from each other and all within 6 weeks of the A1 Visit, in the range from 12 to 20 mEq/L, inclusive. One of these three values must be from the A1 Visit, pre-dose.
One retest (which can be performed on the same day as the test being repeated) using the i-STAT point of care device is allowed from Screening 1 Visit through the A1 Visit.
Subjects with Baseline Bicarbonate (defined as the average of the serum bicarbonate values at Screening 1, Screening 2 and the A1 Visit [predose]) values of 12 to 18 mEq/L are eligible without restriction. Once approximately

half of study subjects have been randomized with Baseline Bicarbonate > 18 to 20 mEq/L, randomization may be closed to additional subjects with Baseline Bicarbonate in this range.
6. Mean systolic and diastolic blood pressure (determined as the average of three replicates) must be < 160/92 mmHg at the Screening 2 Visit.
7. Receiving treatment with an ACE inhibitor and/or ARB at the maximum tolerated (for the individual subject) dose within the country-specific labeled dose range, without adjustments, for >= 4 weeks prior to the Screening 1 Visit and during the Screening Period. The maximum tolerated dose for an individual subject may be less than the maximum labeled dose or may be zero if the medical reason is documented.
Subjects not treated with an ACE inhibitor or ARB must be approved by the Medical Monitor following a review of the medical justification.
Non-diabetic subjects with urine ACR < 30 mg/g (< 3.39 mg/mmol) are not required to be receiving treatment with an ACE inhibitor and/or ARB.
8. If receiving an oral alkali supplement, the dose must be stable for >= 2 weeks prior to Screening 1 Visit and during the Screening Period.
If not receiving alkali treatment, there must be no such treatment within the 2 weeks prior to Screening 1 Visit or during the Screening Period.
9. Have a hemoglobin A1c (HbA1c) value of <= 11.0% (0.11 fraction; 97 mmol/mol) at the Screening 1 Visit (based on central laboratory measurement).
10. Have adequate peripheral venous access for blood draws.
11. Women who are of childbearing potential must have negative pregnancy tests at the Screening 1 and Part B Day 1 Visits and be willing to use an acceptable method of birth control from the Screening 1 Visit until 1 week after study drug completion. Acceptable methods include hormonal contraception (oral contraceptives, patch, implant, and injection), intrauterine devices, double barrier methods (e.g., vaginal diaphragm, vaginal sponge, condom, spermicidal jelly), sexual abstinence or a vasectomized partner. Women who are surgically sterile with documentation of such, or who are at least 1-year post-last menstrual period and > 55 years of age, are considered not to be of childbearing potential.

Exclusion criteria

1. Have any level of low serum bicarbonate at either Screening Visit that, in the opinion of the Investigator, requires emergency intervention or evaluation for an acute acidotic process.
2. Have had anuria, dialysis, or acute kidney injury/acute renal failure in the 3 months prior to the Screening 1 Visit.
3. Have chronic obstructive pulmonary disease (COPD) that is treated with chronic oral steroids, that requires the subject to be on oxygen, or that required hospitalization within the previous 6 months.
4. Had heart failure with maximum New York Heart Association (NYHA) Class IV symptoms (see Appendix 5) during the 3 months prior to the Screening 1 Visit.

5. Had a heart, liver or kidney transplant.
Note: Subjects on the cadaveric transplant list or being evaluated for a future living donor transplant may be enrolled.
6. Have planned initiation of renal replacement (RRT) therapy (dialysis or transplantation) within 6 months following randomization.
7. Have had a stroke or transient ischemic attack within the 6 months prior to Screening 1 Visit.
8. Have had a cardiac event within 3 months prior to Screening 1 Visit, including: myocardial infarction, acute coronary syndrome, coronary bypass grafting, percutaneous coronary intervention, valve procedure, inpatient or outpatient treatment for acute decompensated heart failure.
9. Have been hospitalized for any reason during the 2 months prior to the Screening 1 Visit, other than for pre-planned diagnostic or minor invasive procedures (e.g., placement of dialysis access).
Note 1: Subjects who had major cardiovascular procedures or percutaneous cardiac interventional or therapeutic procedures during this time frame are excluded, even if the procedures were pre-planned.
Note 2: Subjects hospitalized during this time frame for < 48 hours or for self-limited conditions (e.g., hypoglycemia, hyperkalemia, nausea) may be enrolled with approval of the Medical Monitor.
10. Have liver enzyme (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) or total bilirubin values > 3× the upper limit of normal (ULN) at the Screening 2 Visit based on central laboratory measurements.
11. Have a corrected serum calcium < 8.0 mg/dL (80 mg/L; 2 mmol/L) at the Screening 1 Visit, based on central laboratory measurement.
12. Have active cancer during the 1 year prior to Screening 1 Visit or cancer that is currently being treated or will be treated during the study, other than non-melanoma skin cancer or low-grade cervical carcinoma. Subjects with cancers that are being treated with hormonal therapy only may be permitted with approval of the Medical Monitor.
13. Have received any investigational drug during the last month (28 days or >= 5 half-lives [if known], whichever is longer) preceding the Screening 1 Visit or during the Screening Period.
14. Have a known allergy to placebo (microcrystalline cellulose).
15. Have an inability to consume the study drug or otherwise comply with the protocol.
16. Has received cytotoxic therapy, immunosuppressive therapy, or other immunotherapy for renal disease within 6 months prior to the Screening 1 Visit or during the Screening Period.
Note: Glucocorticoid use is allowed.
17. Have a history of alcoholism or drug/chemical abuse, as defined by The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), within 6 months prior to the Screening 1 Visit.
18. Have, in the opinion of the Investigator, any medical condition, uncontrolled systemic disease or serious concurrent illness that would significantly decrease study compliance or jeopardize the safety of the subject or affect the interpretability of the subject*s data.

19. Participated (i.e., was randomized) in Study TRCA-301.
20. Are pregnant or currently breastfeeding.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-05-2019
Enrollment:	36
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	veverimer

Ethics review

Approved WMO

Date:	30-10-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	21-03-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-11-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	03710291
EudraCT	EUCTR2018-001303-36-NL
CCMO	NL66767.042.18