Protocol for Study TRCA-301

Official Study Title:

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

ClinicalTrials.gov Identifier:

NCT03317444

Document Date:

November 27, 2017

CLINICAL STUDY PROTOCOL

Study Title:	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
Study Number:	TRCA-301
Investigational Drug:	TRC101
IND Number:	125,832
Indication:	Treatment of metabolic acidosis associated with chronic kidney disease
Investigators:	Multicenter
EudraCT Number:	2016-003825-41
Sponsor:	Tricida, Inc. 7000 Shoreline Court, Suite 201 South San Francisco, CA 94080, U.S.A.
Lead Medical Monitor:	[redacted], MD, FASN Telephone: [redacted] Fax: [redacted] Email: [redacted]
Regional Medical Monitor (Europe):	[redacted], MD, PhD Telephone: [redacted] Fax: [redacted] Email: [redacted]
Original Protocol Date:	March 02, 2017
Amendment 1:	June 05, 2017
Amendment 2:	August 03, 2017
Amendment 3:	November 27, 2017

Sponsor Clinical Study Protocol Approval

Study Title:	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
Study Number:	TRCA-301
Final Date:	November 27, 2017

This clinical study protocol was subject to critical review and has been approved by Tricida, Inc.

Signed: _____ Date: 27-Nov-2017

[redacted], PhD

[redacted], Clinical Operations

Tricida, Inc.

Principal Investigator's Signature

Study Title:	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
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I agree to conduct the study as detailed herein and in compliance with this Protocol, ICH Guidelines for Good Clinical Practice, the Declaration of Helsinki, all applicable U.S. regulations (including Parts 11, 50, 54, 56, 312 and 314), the EU Clinical Trials Directive and all other applicable local and/or national laws, regulations and requirements.

Signed:_____ Date:_____

Name: _____
Title: _____
Institution Address: _____
_____
_____
_____

TRCA-301 PROTOCOL AMENDMENT #3
Summary and Rationale for Changes

The following is a summary of the changes made in this protocol amendment, the sections affected, and the rationale for each change.

No.	Section(s)	Description of Changes	Rationale
1.	All, Table 2	**Global:** • Updated title page, signature pages, headers and text to reflect amended protocol version and date.	Administrative.
2.	Synopsis, Sections 4.1, 4.2	**Study Population/Inclusion Criteria:** • Increased upper limit of age eligibility from 80 to 85 years in the inclusion criterion #2.	To better reflect the age range of the target population.

SYNOPSIS

TITLE:

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

PROTOCOL NUMBER:

TRCA-301

INVESTIGATIONAL PRODUCT:

TRC101

INDICATION:

Treatment of metabolic acidosis associated with chronic kidney disease (CKD)

OBJECTIVES:

Efficacy: To evaluate the efficacy of TRC101 in CKD patients with metabolic acidosis (blood bicarbonate 12 to 20 mEq/L)

Safety: To evaluate the safety of administration of TRC101 in CKD patients with metabolic acidosis (blood bicarbonate 12 to 20 mEq/L)

POPULATION:

This study will enroll approximately 210 male and female subjects, 18 to 85 years of age with CKD (an estimated glomerular filtration rate [eGFR] of 20 to 40 mL/min/1.73m^2) and low blood bicarbonate (12 to 20 mEq/L). At least half of the subjects enrolled will have a blood bicarbonate level of 12 to 18 mEq/L.

STUDY DESIGN AND DURATION:

This is a double-blind, placebo-controlled, parallel-design, 2-arm study. Approximately 210 subjects will be randomized in a 4:3 ratio into one of the two arms (6 g TRC101 or placebo administered once daily [QD] with lunch).

Study periods are the following:

- Screening Period (up to 2 weeks).
- Treatment Period (12 weeks) starting with Baseline Visit (Day 1). At the end of 12-week Treatment Period eligible subjects may enroll into a 40-week extension study.
- Follow-up Period (2 weeks after discontinuation of treatment, whether subject completes treatment or discontinues early) for subjects who do not enroll in the extension study.

After providing informed consent, the eligibility of potential subjects will be evaluated based on laboratory values, medical history, concomitant medications, vital signs, pregnancy test (if applicable), and physical examination. Three qualifying fasting blood bicarbonate values (obtained at Screening 1, Screening 2, and Baseline Visits based on onsite measurement using an i-STAT point-of-care device) are required to establish subject's eligibility. Both Screening blood bicarbonate values and the average of two Screening and Day 1 values (i.e., baseline bicarbonate) must be within the range 12 to 20 mEq/L. Two qualifying eGFR values of 20 to 40 mL/min/1.73m^2 at the Screening 1 and Screening 2 Visits are required to establish subject's eligibility. The Screening 1 and Screening 2 Visits must be at least 5 days apart.

Qualified subjects will be randomized on the morning of the Baseline Visit (Day 1), which is the first day of the 12-week Treatment Period. A collection of baseline venous blood and urine samples will be performed in a fasting state pre-dose. Following randomization, designated unblinded site staff will assist the subject in administering the first dose of study drug, which will be taken onsite in the morning with food (light meal or snack) after collection of baseline laboratory specimens. Subjects will be given a dosing diary in which to record the time of study drug dosing.

Subjects will continue dosing on an out-patient basis for the subsequent 12 weeks (Treatment Period). Dosing of oral concomitant medications and study drug will be separated by at least 4 hours. The study drug dose will be fixed during the first 4 weeks of the Treatment Period, except for subjects with blood

bicarbonate ≥ 27 mEq/L. Subjects with a blood bicarbonate level of 27 to 30 mEq/L will have their dose of study drug decreased per the titration algorithm (see Appendix 2). Subjects with a confirmed blood bicarbonate level > 30 mEq/L, will undergo an interruption of the study drug dose in accordance with the titration algorithm (see Appendix 2). Beginning at the Week 4 Visit, subjects with a blood bicarbonate level below the normal range (< 22 mEq/L) will have a blinded adjustment of the study drug dose in accordance with the titration algorithm (see Appendix 2). At any time during the study, subjects with a confirmed blood bicarbonate level < 12 mEq/L will be evaluated by the Investigator for new acute acidotic processes and discussed with the Medical Monitor. The Medical Monitor will determine whether the subject may continue in the study. During the 12-week Treatment Period, subjects will attend eight study visits (Day 1, Weeks 1, 2, 4, 6, 8, 10, and 12) for efficacy and safety assessments.

Subjects who complete the Treatment Period will be offered participation in a 40-week extension study (TRCA-301E). Subjects who are not willing to participate in the extension study or who are not eligible will enter the 2-week Follow-up Period and return to the study site for two visits: Follow-up 1 (Week 13) and Follow-up 2 (Week 14), for adverse event (AE) collection, fasting blood draws and safety assessments as outlined in the Schedule of Events (see Appendix 1). Subjects who withdraw from the study prematurely (i.e., prior to the Week 12 Visit) will undergo an Early Termination (ET) Visit, during which all Week 12 Visit assessments will be performed, followed by Follow-up 1 and 2 Visits in 1 and 2 weeks, respectively. Blood draws for bicarbonate measurements will be done when subjects are in a fasted state (at least 4 hours) and at approximately the same time of day for each subject.

The maximum study duration is anticipated to be 16 weeks per subject, including the Screening Period (up to 2 weeks), 12-week Treatment Period, and 2-week Follow-up Period. The maximum TRCA-301 study duration for subjects who continue into the extension Study TRCA-301E will be 14 weeks (excluding the 2-week Follow-up Period).

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 at Screening 1 Visit.
3. Have a blood bicarbonate value of 12 to 20 mEq/L at Screening 1 and Screening 2 Visits AND an average value for Screening 1, Screening 2, and Baseline Visits (i.e., baseline blood bicarbonate) within the range 12 to 20 mEq/L based on onsite measurement using an i-STAT point of care device.

   Screening 1 and Screening 2 Visits must be at least 5 days apart.

   Note: Subjects with baseline blood bicarbonate values of 12 to 18 mEq/L are eligible without restriction. Once 105 subjects with baseline blood bicarbonate values of > 18 to 20 mEq/L have been enrolled, randomization may be closed to additional subjects with baseline blood bicarbonate in this range.
4. At both Screening Visits have an eGFR value of 20 to 40 mL/min/1.73m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as reported by the central laboratory. If a central laboratory eGFR value from Screening 2 Visit is not available, eGFR can be calculated using CKD-EPI equation based on onsite serum creatinine measurement at the Baseline Visit to establish subject's eligibility.

   Screening 1 and Screening 2 Visits must be at least 5 days apart.
5. Have stable renal function as defined by eGFR values at both Screening Visits that are not different by more than 20% (the higher of the two Screening eGFR values will be used as the denominator to calculate the 20% allowable difference).
6. At both Screening Visits have systolic blood pressure < 170 mmHg (all three replicates).
7. Have a hemoglobin A1c (HbA1c) value of ≤ 9.0% at the Screening 1 Visit based on central laboratory measurement.
8. Have adequate peripheral venous access for blood draws.
9. Women who are of childbearing potential must have negative pregnancy tests at the Screening 1 Visit and Day 1 and be willing to use an acceptable method of birth control from the Screening

1 Visit until 1 month after study 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 blood 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, acute kidney injury, history of acute renal insufficiency or known ≥ 30% increase in serum creatinine or known ≥ 30% acute or chronic decrease in eGFR 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, or that required hospitalization with a primary cause of heart failure, during the preceding 6 months (see Appendix 3).
5. Have had a heart or kidney transplant.

   Note: Patients on the cadaveric transplant list or being evaluated for a future living donor transplant may be enrolled.
6. Planned initiation of renal replacement therapy (dialysis or transplantation) within 12 weeks following randomization.
7. Have had a stroke or transient ischemic attack (TIA) within the 6 months prior to randomization.
8. Have had a cardiac event within 12 weeks prior to randomization, 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.

   Note: Subjects who had major cardiovascular procedures or percutaneous cardiac procedures during this time frame are excluded, even if the procedures were pre-planned.
10. Have a history or current diagnosis of clinically significant diabetic gastroparesis (based on Investigator's judgment) or a history of bariatric surgery.
11. Have a history or current diagnosis of bowel obstruction, swallowing disorders, severe gastrointestinal (GI) disorders, inflammatory bowel disease, major GI surgery, frequent diarrhea or active gastric/duodenal ulcers.
12. Have liver enzyme (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) or total bilirubin values > 3 × the upper limit of normal (ULN) at Screening based on central laboratory measurements.
13. Have a serum calcium ≤ 8.0 mg/dL at the Screening 1 Visit based on central laboratory measurement.
14. Have a serum potassium value < 3.8 mEq/L or > 5.9 mEq/L at the Screening 1 or Screening 2 Visit.
15. Have active cancer during the 1 year prior to Screening, other than non-melanoma skin cancer, or cancer that is currently being treated or will be treated during the study. Subjects with cancers that are being treated with hormonal therapy only may be permitted with approval of the Medical Monitor.

16. Have received any investigational medication during the last month (28 days or ≥ 5 half-lives [if known], whichever is longer) preceding the Screening 1 Visit.
17. Have used any of the following in the 14 days prior to the Screening 1 Visit: lanthanum carbonate, colesevelam, cholestyramine, sodium or calcium polystyrene sulfonate, calcium acetate, sevelamer, bixalomer, patiromer, and other polymeric binder drugs.
18. Have had a change in doses (including starting or stopping treatment) in the 2 weeks prior to the Screening 1 Visit or during Screening Period to the following: calcium-containing supplements, such as calcium carbonate and calcium citrate; antacids; H2-blockers; proton pump inhibitors. See Section 5.9 for examples of specific drugs.
19. Have had a change in doses (including starting or stopping treatment) in the 4 weeks prior to the Screening 1 Visit or during Screening Period to the following: sodium bicarbonate, potassium citrate, sodium citrate or other alkali therapy; diuretics; renin-angiotensin-aldosterone system [RAAS] inhbitors, such as angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], aldosterone antagonists [AAs], mineralocorticoid receptor antagonists [MRAs]; non-ophthalmic carbonic anhydrase inhibitors. See Section 5.9 for examples of specific drugs.

    Note: For diuretics, dose changes of up to ± 50% relative to the average dose during the Screening Period are considered "stable", and a dose change up to ± 50% between the Screening 1 Visit and the Baseline Visit is considered "stable".
20. Have a known allergy to placebo [redacted]
21. Inability to consume the study drug or otherwise comply with the protocol.
22. 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 validity of the study results.
23. Have participated in a previous clinical study of TRC101.
24. Currently breastfeeding.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Investigational product: TRC101.

Placebo: [redacted], NF Grade.

Approximately 210 subjects will be randomized in a 4:3 ratio to one of the following treatments:

- 6 g TRC101 QD (n~120)
- Placebo (n~90)

TRC101 or placebo will be administered orally as an aqueous suspension, QD with lunch, for 12 weeks. Concomitant oral medications must be taken at least 4 hours before or after study drug administration. The first dose of study drug will be given at the study site on Day 1 in the morning with food. The last dose of study drug will be taken the day before the Week 12 Visit unless the subject is enrolled in the extension Study TRCA-301E.

MAIN EFFICACY ASSESSMENT:

Efficacy will be assessed by blood bicarbonate values.

SAFETY ASSESSMENTS:

Safety assessments will include AEs, vital signs, physical examination (including body weight), safety laboratory measurements, coagulation (for subjects on vitamin K antagonists or factor Xa inhibitors only), spot urine, urinalysis, and electrocardiograms (ECGs).

ENDPOINTS:

Primary Efficacy:

Having a change from baseline (CFB) in blood bicarbonate ≥ 4 mEq/L or having blood bicarbonate in the normal range (22 to 29 mEq/L) at the end of treatment (Week 12 Visit).

Secondary Efficacy:

CFB in blood bicarbonate at the end of treatment (Week 12 Visit).

Exploratory Efficacy:

1. CFB in the total score of the Kidney Disease and Quality of Life (KDQOL) Question 3 items (daily activities) at the end of treatment (Week 12 Visit).
2. CFB in repeated chair stand test duration at the end of treatment (Week 12 Visit).

Safety:

1. AEs, SAEs and withdrawal of study treatment due to AE.
2. Having met the high bicarbonate dose interruption criterion (confirmed > 30 mEq/L) at any time during the Treatment Period.

STATISTICAL ANALYSES:

This is a double-blind, placebo-controlled, parallel-design, 2-arm, study. Subjects will be randomized in a 4:3 ratio into one of the two arms (6 g TRC101 or placebo administered QD with lunch). Randomization will be stratified by baseline blood bicarbonate (≤ 18 mEq/L vs. > 18 mEq/L) and screening eGFR (< 30 mL/min/1.73m^2 vs. ≥ 30 mL/min/1.73m^2), which represents an average of two eGFR values obtained at Screening 1 and Screening 2 Visits.

Two populations will be analyzed in this study:

1. Modified intent-to-treat (MITT) analysis set: All randomized subjects who had baseline and at least one post-baseline bicarbonate values.
2. Safety analysis set: All subjects who received any amount of study drug (TRC101 or placebo).

Frequencies and percentages will be presented for the categorical variables and descriptive statistics will be presented for continuous variables.

Efficacy: Efficacy data will be summarized by treatment group for subjects in the MITT analysis set based on the randomized treatment group assignment. The bicarbonate results read from the i-STAT device will be the basis for efficacy evaluations.

The primary efficacy analysis will compare TRC101 and placebo with respect to the proportions of subjects who are responders at the end of treatment (Week 12 Visit). Responders are defined as having a CFB in blood bicarbonate ≥ 4 mEq/L or having blood bicarbonate in the normal range (22 to 29 mEq/L) at the end of treatment (Week 12 Visit). The primary endpoint analysis will include:

1. The difference in proportion (between TRC101 and placebo subjects) and its exact (Clopper-Pearson) 95% CI, as well as the p-value from Fisher's exact test comparing the TRC101 group and the placebo group will be reported by time point; and
2. The proportion of subjects in each group who are responders, along with their exact (Clopper-Pearson) 95% CIs, will be summarized by treatment group and time point.

The secondary efficacy analysis will compare the least squares (LS) means CFB in bicarbonate level between the TRC101 group and placebo group at the end of treatment (Week 12 Visit). The secondary endpoint will be assessed using a longitudinal mixed model for repeated measures (MMRM).

Exploratory efficacy analyses will be specified in the statistical analysis plan (SAP).

Statistical significance will be declared with a two-sided test at the 0.05 level. In order to control family-wise error rate, statistical testing for the primary and secondary efficacy endpoints will be performed sequentially. At the Week 12 Visit, Fisher's exact test will be used to compare the group proportions. If this formal test is statistically significant, a second formal test for the proportion of TRC101 responders at Week 12 will be conducted. Only when the primary efficacy result is statistically significant will a formal

test for the secondary efficacy endpoint (CFB in blood bicarbonate at Week 12 Visit) be performed.

Safety: Safety will be summarized by treatment group for subjects in the safety analysis set. Number and percentage of subjects with treatment-emergent AEs (TEAEs) classified by system organ class (SOC) and preferred term (PT); number (%) of subjects experiencing TEAEs by severity, causality, seriousness and action taken with regard to study drug will be summarized by treatment group. Number (%) of subjects with TEAEs leading to discontinuation of study treatment will also be summarized by treatment group. Clinical laboratory test results, vital signs and ECG findings will be summarized using descriptive statistics by treatment group and time point. The primary analysis for change in eGFR will be based on serum creatinine (a supportive analysis will use serum cystatin C, due to the potential for changes in muscle mass related to bicarbonate correction). Categorical display methods (e.g., frequencies, shift tables) and plots of laboratory values over time may also be used, as appropriate. Newly observed, clinically significant physical examination findings will be listed.

Other Analyses: Demographic and baseline characteristics will be summarized by treatment group. Exposure to study drug, dosing compliance, and concomitant medications will be summarized by treatment group. The number and percentage of subjects who used prior and/or concomitant medications will be summarized by Anatomic Therapeutic Chemical (ATC) classification levels and treatment group.

SAMPLE SIZE DETERMINATION:

Primary efficacy endpoint: A sample size of 120 subjects in the TRC101 group and 90 subjects in the placebo group will have high power to detect differences between the TRC101- and placebo-treated groups. The sample size calculation is based on the data from the Phase 1/2 Study TRCA-101, where 3% of placebo and 46% of TRC101 treated subjects had an increase in blood bicarbonate of ≥ 4 mEq/L or had blood bicarbonate in the normal range at Week 2. We assume the full TRC101 treatment effect had not been reached during this short treatment period. In Study TRCA-301, we expect to observe that 50 to 55% of TRC101-treated and 10% of placebo-treated subjects will have an increase of ≥ 4 mEq/L or have blood bicarbonate in the normal range at the end of treatment (Week 12 Visit). A Fisher's exact test with a 0.05 two-sided significance level will have over 99% power to detect this difference when 90 placebo subjects and 120 TRC101 subjects are enrolled. If the true proportion of TRC101 subjects who respond at the Week 12 Visit is indeed between 50% and 55% and if no more than 5% of subjects have missing data at Week 12, the study will have roughly 90% power to result in a 95% confidence limit with a lower bound of at least 35% and 40%, respectively.

The sample size calculation for the secondary efficacy endpoint will be documented in the SAP.

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LIST OF ABBREVIATIONS AND ACRONYMS

AA	aldosterone antagonist
ACE	angiotensin-converting enzyme
ADME	absorption, distribution, metabolism, excretion
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
β–HCG	beta human chorionic gonadotropin
BE	base excess
BID	twice daily
BUN	blood urea nitrogen
CFB	change from baseline
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CK	creatine kinase
CRO	contract research organization
CV	cardiovascular
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ET	early termination
EU	European Union
EUCTD	European Union Clinical Trials Directive

FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GI	gastrointestinal
HbA1c	hemoglobin A1c
HCO_3^-	bicarbonate
HDL	high density lipoprotein
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ISF	Investigative Site File
KDQOL	Kidney Disease and Quality of Life
LDL	low density lipoprotein
LLN	lower limit of normal
LS	least square
MCH	mean corpuscular hemoglobin
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MRA	mineralocorticoid receptor antagonist
NF	National Formulary
NOAEL	no observed adverse effect level
NYHA	New York Heart Association
pCO_2	partial pressure of carbon dioxide

pO_2	partial pressure of oxygen
PT	preferred term
PTH	parathyroid hormone
QD	once daily
RAAS	renin-angiotensin-aldosterone system
RBC	red blood cell
RDW	red cell distribution width
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SO_2	oxygen saturation
SOC	system organ class
SUSAR(s)	suspected unexpected serious adverse reaction(s)
TCO_2	total carbon dioxide
TEAE(s)	treatment emergent adverse event(s)
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1 INTRODUCTION

1.1 Disease Background

Patients with chronic kidney disease (CKD) continue to generate acid from metabolism but have a reduced ability to excrete acid via the kidney. As a result, metabolic acidosis, characterized by a reduced blood bicarbonate concentration (i.e., below 22 mEq/L), can develop in advanced stages of CKD. Chronic metabolic acidosis affects 13 – 39% of CKD Stage 3 – 5 patients (Eustace, 2004; Raphael, 2014; Moranne, 2009). If chronic metabolic acidosis is left untreated, the consequences include increased mortality, acceleration of kidney disease, acceleration of muscle breakdown, and the development or exacerbation of bone disease (Dobre, 2015).

Clinical outcomes for CKD patients with bicarbonate levels that are below normal (i.e., < 22 mEq/L) are significantly worse compared to patients with normal bicarbonate (i.e., 22 – 29 mEq/L); this has been demonstrated in multiple large retrospective database analyses reported in the literature (Shah 2009; Dobre 2013; Raphael 2011; Tangri 2011; Kovesdy 2009; Navaneethan 2011; Raphael 2016). 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 death, progression of CKD and hospitalization, progressively increases). Hazard ratios for patients with bicarbonate levels in the range required for subjects in this study (i.e., 12 to 20 mEq/L) are significantly worse 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 (de Brito-Ashurst 2009; Phisitkul 2010; Mahajan 2010; Goraya 2013; Goraya 2014; Garneata 2016), improvements in muscle mass/function (de Brito-Ashurst 2009; Abramowitz 2013) and improvement in bone health (Domrongkitchaiporn 2002).

Currently, no approved therapies are available for controlling bicarbonate in patients who have chronic metabolic acidosis. Use of unapproved oral alkali supplements (e.g., food additives such as oral sodium bicarbonate and off-label use of potassium citrate) is general clinical practice, however these agents have been studied only in patients with mild metabolic acidosis. Most prospective trials limited doses of oral sodium bicarbonate to < 2 g per day resulting in modest increases in blood bicarbonate of 2 – 3 mEq/L. The daily doses of sodium bicarbonate required to increase blood bicarbonate levels by 3 – 4 mEq/L in patients with metabolic acidosis are prohibitively high (6 – 8 g per day introducing 1.6 – 2.2 g of sodium; Abramowitz 2013). Combined with the sodium intake from diet, this would result in a total daily sodium load exceeding the guideline-recommended limit of 2.4 g/day for CKD patients (KDOQI, 2002) independent of underlying comorbidities. Furthermore, common conditions accompanying CKD (e.g., hypertension, heart failure, edema) may be aggravated by the sodium load that alkali therapies deliver and efficacy of diuretics reduced. As such, there is a clear unmet medical need for new treatments with demonstrated efficacy and safety to treat chronic metabolic acidosis.

1.2 Description of Investigational Product

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 in patients with CKD. It is a free-flowing powder composed of low-swelling, spherical beads approximately 100 micrometers in diameter. The TRC101 bead size is carefully controlled in order to restrict absorption of particles from the gastrointestinal (GI) tract, consistent with several literature reports that show particles larger than 0.5 micrometers are not systemically absorbed (Jung, 2000). Nonclinical studies with radiolabeled TRC101 conducted in rats and dogs confirmed the lack of systemic absorption of TRC101.

TRC101 is insoluble in aqueous and nonaqueous solvents. 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 and the polymer's extensive crosslinking provides size exclusion properties and selectivity for binding Cl^- over other potential interfering anions. The TRC101 mechanism of action involves binding of H^+ and Cl^-, resulting in a net reduction and removal of hydrochloric acid from the GI tract which results in an increase in serum bicarbonate levels. Binding Cl^- in addition to H^+ reduces exchange of Cl^- with bicarbonate in the GI lumen, preventing a subsequent decrease in serum bicarbonate.

The TRC101 drug substance is packaged in individual-dose packets without addition of any excipients to create the clinical study material (i.e., drug product), a powder for oral suspension also called TRC101.

1.3 Relevant Nonclinical Background

1.3.1 Nonclinical Pharmacology

Nonclinical in vitro and in vivo studies have demonstrated robust proton and chloride binding and removal by the TRC101 polyamine polymer. In vitro studies have demonstrated that TRC101 selectively binds and retains HCl under conditions that mimic the pH, exposure times, and ionic content of various compartments of the GI tract. The marked binding capacity and selectivity for HCl observed with TRC101 in vitro translates into in vivo pharmacological effects. When TRC101 was packaged in nylon sachets, fed to a single pig, and then recovered from collected feces, analysis of the anions bound to the recovered polymer revealed an in vivo binding of 2.6 mEq of chloride per gram of TRC101. Furthermore, removal of HCl by TRC101 results in a dose-dependent increase in mean serum bicarbonate, as observed in rats with adenine-induced nephropathy and metabolic acidosis compared to untreated controls.

1.3.2 Safety Pharmacology

The nonclinical Good Laboratory Practice (GLP) safety program for TRC101 includes three studies assessing safety pharmacology. These assessments of the central nervous system

(CNS), respiratory, cardiovascular (CV), and GI systems did not identify any TRC101-related adverse effects in rats up to 2 g/kg/day (GI) or up to 4 g/kg/day (CNS, respiratory) and in dogs up to 2 g/kg/day (CV).

1.3.3 Nonclinical ADME

TRC101 is insoluble in both aqueous and organic solvents. Due to its insolubility, stability, and size (averaging 100 micrometers in diameter), the polymer is not anticipated to be absorbed from the lumen of the GI tract. To confirm lack of absorption following oral administration, the absorption, distribution, metabolism and excretion (ADME) of radiolabeled TRC101, in both rats and dogs, were characterized after a single oral dose of [^{14}C]-TRC101. The studies demonstrated no radioactivity in tissues or organs other than the GI tract, no detectable radiolabel in the plasma, approximately 95 – 99% of the radioactive dose excreted in the feces with most recovered within the first 48 hours after dosing, and ≤ 0.02% of radiolabel excreted in the urine of dogs and rats. The level of radioactivity excreted in urine was consistent with the level of unincorporated radiolabel measured in a water extraction of the radiolabeled polymer, [^{14}C]-TRC101. Therefore, it can be concluded that TRC101 is not systemically absorbed following oral administration in rats and dogs.

1.3.4 Nonclinical Toxicology

Nonclinical toxicology studies of TRC101 to date include non-Good Laboratory Practice (GLP) 7-day repeat dose toxicology studies in rats and dogs; a GLP 33-day repeat dose toxicology study with a 2-week recovery in rats; a GLP 28-day repeat dose toxicology study with a 2-week recovery in dogs; GLP 13-week repeat dose toxicology interim analyses in the rat and the dog as part of the chronic toxicology studies, a screening non-GLP in vitro genotoxicity study (bacterial reverse mutation [Ames] assay), and two GLP in vitro genotoxicity studies (Ames assay and chromosomal aberration assay in human peripheral blood lymphocytes); non-GLP pilot embryo-fetal development (EFD) studies in the rat and the rabbit; no single dose studies were conducted. The oral route of exposure was selected for the repeat dose toxicology and EFD studies in rats, rabbits, and/or dogs because this is the intended route of human exposure. These studies demonstrate that TRC101 has a very low order of toxicity; the genotoxicity studies demonstrate that TRC101 is neither mutagenic nor clastogenic; the pilot EFD studies suggest that there are no adverse TRC101-related effects on maternal reproductive function or embryo-fetal parameters. There were no effects on male or female reproductive organs in the GLP repeat dose toxicology studies in rat and dog. The no observed adverse effect levels (NOAELs) for the 13-week repeat dose toxicology interim analyses were the highest doses tested, i.e., 2 g/kg/day in rats and dogs, providing support for up to 12 weeks of dosing in humans with TRC101 doses up to 9 g/day. In the same studies, local tolerance was assessed, and histopathological evaluation of the GI tract indicated that TRC101 was generally well tolerated. Tricida has received a waiver from the Food and Drug Administration (FDA) for the conduct of the in vivo micronucleous assay, the male and female fertility and early embryonic development study in rats, and the peri- and post-natal developmental study in rats. No carcinogenicity studies of TRC101 have been conducted.

1.4 Relevant Clinical Background

For a summary of the known and potential risks and benefits of TRC101 to human subjects, see the TRC101 Investigator's Brochure.

1.4.1 Study TRCA-101

To date, TRC101 has been studied in one Phase 1/2 clinical trial, Study TRCA-101, in subjects with CKD Stage 3 – 4 (estimated glomerular filtration rate [eGFR] 20 to < 60 mL/min/1.73m^2) and baseline serum bicarbonate levels of 12 to 20 mEq/L. Study TRCA-101 was a double-blind, placebo-controlled, parallel-design, 6-arm, fixed dose study, evaluating the safety and efficacy of three doses of TRC101 (3, 6 and 9 g/day) and two dosing regimens (once daily [QD] and twice daily [BID]) versus placebo. Subjects enrolled in Study TRCA-101 were treated for 2 weeks while in residence at the clinical research units, after which they were discharged and followed for up to an additional 2 weeks (off treatment). While in residence during the treatment period, subjects ate a standardized study diet controlled for protein and caloric content, as well as anions, cations and fiber, in accordance with dietary recommendations for CKD patients (KDOQI, 2002). Care was taken to ensure the diet was neither acidic nor basic. The specific foods selected for the menus were chosen to closely approximated the regions' typical diet. The primary objective of the study was to assess the safety and tolerability of TRC101. The main efficacy endpoint was change from baseline (CFB) to end-of-treatment in serum bicarbonate level.

The study population comprised 135 subjects (86 male and 49 female), with a mean age of 60.3 years (range of 30 to 79 years), a mean baseline eGFR of 34.8 mL/min/1.73m^2 (range of 19 to 66 mL/min/1.73m^2; 44.4% with CKD Stage 4) and a mean baseline serum bicarbonate level of 17.7 mEq/L (range of 14.1 – 20.4 mEq/L). Subjects had baseline comorbidities common in CKD patients, including hypertension (93.3%), diabetes (69.6%), left ventricular hypertrophy (28.9%), and congestive heart failure (21.5%). As would be expected in a CKD Stage 3 – 4 population, nearly all study subjects had indications for sodium restriction: hypertension (93.3%), congestive heart failure (21.5%), peripheral edema (14.1%) and use of diuretics (42.2%). Because TRC101 does not result in sodium load as discussed in Section 1.2, enrollment of such subjects was appropriate.

1.4.1.1 Safety

A 14-day treatment with TRC101, at doses of 1.5, 3 or 4.5 g BID, or 6 g QD, appeared to be safe and generally well tolerated. In the 135 subjects who participated (104 subjects in the TRC101 combined group and 31 subjects in the placebo group), there were no deaths, adverse events resulting in treatment discontinuation, or serious adverse events (SAEs). The overall incidence of treatment-emergent adverse events (TEAEs) was 53.8% in the TRC101 combined group (26.9% assessed as related to study drug) of and 45.2% in the placebo group (12.9% assessed as related to study drug). The majority of reported TEAEs were mild in severity: 44.2% in the TRC101 combined group (26.0% assessed as related to study drug)

and 35.5% in the placebo group (12.9% assessed as related to study drug). Fewer TEAEs were reported as moderate: 9.6% in the TRC101 combined group (1.0% assessed as related to study drug) and 9.7% in the placebo group (none assessed as related). No severe or SAEs were reported in either treatment group.

The most common adverse events (≥ 5% incidence) in the TRC101-treated subjects were diarrhoea (20.2%), headache (7.7%), constipation (6.7%), and hyperglycaemia (6.7%). The most common adverse events in the placebo-treated subjects were diarrhoea (12.9%), glomerular filtration rate decreased (6.5%), blood glucose increased (6.5%), and hypoglycaemia (6.5%). No event appeared to be dose-related.

Gastrointestinal (GI) adverse events were the most commonly reported in TRC101-treated subjects, which is consistent with a non-absorbed drug acting primarily within the GI tract, and all were mild or moderate in severity. Diarrhoea was the most common adverse event; all events were mild, self-limited, of short duration, often resolving while study treatment was ongoing, and none required treatment or resulted in discontinuation of study drug or early withdrawal from the study. Diarrhoea events exhibited no apparent dose response, occurring in 36.0%, 12.0%, 23.1% of subjects in the 1.5, 3, and 4.5 g BID TRC101 dose groups, respectively, and in 10.7% of subjects in the 6 g QD TRC101 group. In the pooled placebo group diarrhoea occurred in 12.9% of subjects. Given the small numbers, there is likely no difference between the groups.

No trends suggested an off-target effect of TRC101 on other electrolytes (i.e., sodium, potassium, magnesium, calcium or phosphate). No treatment-related effect on serum chloride levels or any effect on urine electrolytes was observed. No subject experienced increases in serum bicarbonate that resulted in metabolic alkalosis (i.e., serum bicarbonate > 29 mEq/L). There were also no trends suggesting an effect of TRC101 on renal function, liver function, lipids, vital signs or ECG intervals.

For additional details regarding the safety data from Study TRCA-101, see the TRC101 Investigator's Brochure.

1.4.1.2 Efficacy

Over a 2-week treatment period, TRC101 significantly increased serum bicarbonate levels in the study population of CKD patients with baseline serum bicarbonate levels ranging from 14.1 to 20.4 mEq/L. TRC101 had a rapid onset of action (i.e., statistically significant increase in mean within group CFB in serum bicarbonate; $p < 0.0001$) within the first 24 – 48 hours following the initiation of treatment for all TRC101 dose groups combined. The onset of action for between-group differences (active vs. placebo) appeared to occur between 48 – 72 hours after the initiation of treatment with TRC101. At Day 4 (72 hours after the first dose of TRC101), the mean increase in serum bicarbonate from baseline for each TRC101 group was 1 – 2 mEq/L: 1.5 g BID ($p = 0.0011$); 3 g BID ($p = 0.0001$); 6 g QD ($p = 0.0003$); 4.5 g BID ($p < 0.0001$).

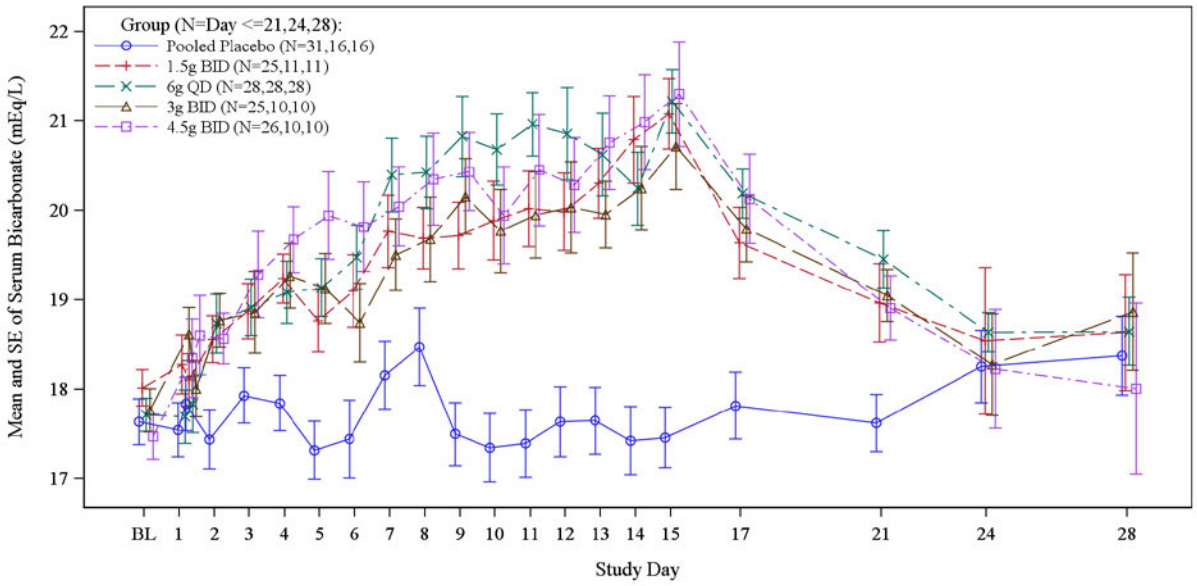
At Day 15, all active doses/dosing regimens evaluated (1.5, 3 and 4.5 g TRC101 BID and 6 g TRC101 QD) showed statistically significantly ($p < 0.0001$) increased mean serum bicarbonate levels from baseline by approximately 3 – 4 mEq/L and each dose increased serum bicarbonate levels to a significantly ($p < 0.0001$) greater extent than placebo. The observed increase in serum bicarbonate in each TRC101 dose group did not appear to be dose- or dosing regimen-dependent, except for potentially earlier onset of action in the highest TRC101 group, 4.5 g BID.

After 2 weeks of treatment, the TRC101 6 g QD dose group demonstrated a similar increase from baseline in serum bicarbonate compared to the TRC101 3 g BID dose group (3.51 mEq/L versus 2.98 mEq/L, respectively), and the difference between the QD and BID dosing regimens was not statistically significant ($p = 0.3408$).

Figure 1 illustrates the steady increase in mean serum bicarbonate observed in all TRC101 dose groups during the 14-day treatment period with a mean increase at the end of treatment of approximately 3 to 4 mEq/L across all active dose groups. The slope of serum bicarbonate increase remained constant in all TRC101 dose groups, with no evidence of serum bicarbonate reaching a plateau at the end of 2-week treatment. Therefore, the maximal effect of each TRC101 dose tested in Study TRCA-101 has not yet been determined. Serum bicarbonate levels in the placebo group remained essentially unchanged throughout the study, suggesting that the diet with a controlled protein (0.66 g/kg/day on average) and cation/anion content administered in the clinical research unit matched well with what the subjects ate at home and, therefore, had no significant impact on their serum bicarbonate values.

The 2-week treatment period in study TRCA-101 was followed by a 2-week follow-up period during which subjects were off treatment. Following discontinuation of TRC101, serum bicarbonate levels decreased within 2 days and were near their baseline values within 9 days (Figure 1). These results underscore the rapid reversibility of TRC101 effect. In addition, the data demonstrate that chronic nature of the underlying metabolic acidosis in these CKD patients and suggest that continued treatment with TRC101 would be needed to maintain elevated serum bicarbonate level.

Figure 1 Mean Change in Serum Bicarbonate by Treatment Group Over Time



BID = twice daily; BL = baseline; QD = once daily; SE = standard error

For additional details regarding the efficacy data from Study TRCA-101, see the TRC101 Investigator's Brochure.

1.5 Description and Justification for Route of Administration, Dosage, Dosage Regimen and Treatment Period

In this study, TRC101 will be administered orally, as a powder suspended in water, QD with food. TRC101 is a high molecular weight, nonabsorbed polymer with a site of action in the GI tract; thus, oral administration is the appropriate route. A dose of 6 g QD TRC101 was chosen as the starting dose for this study since it was shown to be safe, well tolerated, and efficacious in Study TRCA-101 (along with the 1.5 g BID, 3 g BID and 4.5 g BID TRC101 doses). A starting dose of 6 g provides the option of bidirectional dose adjustment (i.e., up or down titration), thus potentially allowing greater flexibility in controlling blood bicarbonate levels compared to a 3 g or 9 g starting dose. A QD dosing regimen is more convenient for study subjects than a BID dosing regimen and therefore may result in greater compliance during a 12-week treatment period. Placebo QD will be used as a comparator. Additional details on the rationale for the doses, dosing regimen and treatment period are provided in Section 3.2.

1.6 Description of Population to be Studied

In the completed Study TRCA-101, the allowable ranges for eGFR and blood bicarbonate were 20 to < 60 mL/min/1.73m^2 and 12 to 20 mEq/L, respectively. The population studied in this clinical study is CKD patients with chronic metabolic acidosis who have eGFR from 20

to 40 mL/min/1.73m^2 and blood bicarbonate levels from 12 to 20 mEq/L. At least half of the subjects enrolled will have blood bicarbonate level of 12 to 18 mEq/L.

This study is designed to provide significant overlap with the population investigated in Study TRCA-101 and in future investigational studies of TRC101.

The lower limit of the bicarbonate range is intended to exclude patients who are acutely acidotic as their management is largely aimed at rapid treatment of the underlying etiology of the acidosis. Whereas clinical practice guidelines also recommend treating milder acidosis (serum bicarbonate > 20 to 22 mEq/L) (KDIGO 2013; KDOQI 2003), the population for the current study will include only those with blood bicarbonate 12 to 20 mEq/L. This is to ensure that all subjects have significant metabolic acidosis.

To make the study more generalizable to the intended target population of CKD patients, this study will be conducted in outpatients whose dietary intake is not mandated by the study protocol, unlike the in-unit TRCA-101 study which used a controlled diet. Additionally, compared with the TRCA-101 study, exclusions for common concomitant medications such as H2 blockers and proton pump inhibitors have been removed from this protocol, and subjects with more severe heart failure (i.e., NYHA Class III) may be enrolled (see Appendix 3).

This protocol allows the use of "background" medications that can affect eGFR and blood bicarbonate (e.g., oral alkali, calcium supplements, diuretics, renin angiotensin aldosterone system [RAAS] inhibitors) with some restrictions. Doses of alkali medications may not be changed and new oral alkali therapies must not be initiated during the study. If a subject requires treatment for sustained, clinically-significant worsening of metabolic acidosis during the study in the judgment of the Investigator, diet counseling (i.e., reduced protein intake, vegetarian/vegan protein sources) may be implemented as clinically appropriate and in agreement with the Medical Monitor. Subjects with confirmed blood bicarbonate decrease < 12 mEq/L should be investigated for possible causes of acute-on-chronic acidosis and the Investigator should discuss these cases with the Medical Monitor. The rationale for allowance of alkali treatment is to avoid significantly worsening acidosis among the placebo subjects; however, maintaining a stable dose of such treatments is necessary to avoid confounding of the primary efficacy measurement. Subjects may be, but are not required to be, on RAAS inhibitor(s) at Baseline. Investigators will be advised to avoid changing RAAS inhibitor doses during the study, when possible, but dose changes necessary for the management of comorbidities or acute events (e.g., hyperkalemia/worsening hyperkalemia) are not prohibited. Investigators will be advised to avoid changing diuretic doses when possible, but dose changes necessary for the management of comorbidities or acute events (e.g., heart failure, acute kidney injury) are not prohibited.

The rationale for the above restriction on background concomitant medications that may affect eGFR in this study is to gain experience with this aspect of the study design which may be used in a future study evaluating the rate of eGFR decline.

1.7 Description of Assay Methodology for Measurement of Blood/Serum Bicarbonate Concentration

Bicarbonate concentrations in venous blood will be assessed in this study using the i-STAT System (handheld blood analyzer with G3+ cartridge manufactured by Abbott Point of Care, Princeton, NJ) in all subjects. In addition, either a clinical chemistry analyzer performing enzymatic measurement of bicarbonate in serum or a benchtop venous blood gas analyzer for measuring bicarbonate will be used consistently for each subject. These assays (with the i-STAT assay and one of two other assays being mandatory) will be conducted at the local laboratory or at the study site.

All efficacy analyses will be conducted using bicarbonate concentrations collected from the i-STAT devices. The i-STAT measurements of blood bicarbonate levels will be the basis of study drug dose adjustment decisions. Data from the other assay methodology (either enzymatic or venous blood gas bicarbonate analysis) will be evaluated in an exploratory manner.

The two blood gas analysis methods (benchtop and i-STAT) provide a calculated bicarbonate concentration from measurement of pH and pCO_2 in a whole blood sample. The enzymatic assay method used in most clinical laboratories directly measures the total CO_2 (bicarbonate + dissolved CO_2) concentration in a serum sample using an assay that relies upon the conversion of dissolved CO_2 to HCO_3^- with base, followed by a series of enzymatic reactions resulting in a decrease in the 380/410 nm absorbance of the reaction mixture.

2 STUDY OBJECTIVES

2.1 Efficacy

This study is intended to evaluate the efficacy of TRC101 in CKD patients with metabolic acidosis (blood bicarbonate 12 to 20 mEq/L).

2.2 Safety

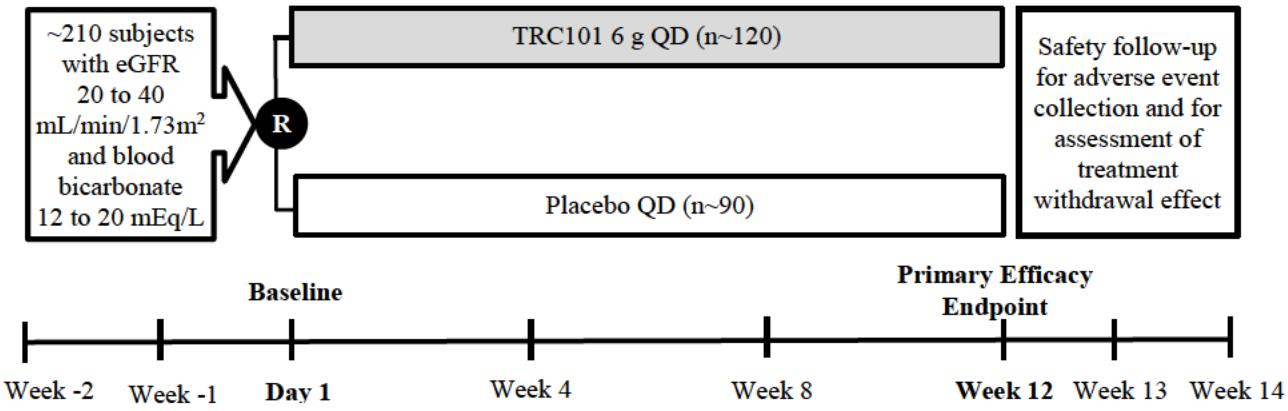
This study is intended to evaluate the safety of administration of TRC101 in CKD patients with metabolic acidosis (blood bicarbonate 12 to 20 mEq/L).

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a double-blind, placebo-controlled, parallel-design, 2-arm study. Approximately 210 subjects will be randomized in a 4:3 ratio into one of the two arms (6 g TRC101 or placebo administered QD with lunch) (Figure 2).

Figure 2 Study TRCA-301 Study Design Schematic



eGFR = estimated glomerular filtration rate; QD = once daily; R = randomization

Study periods are the following:

- Screening Period (up to 2 weeks).
- Treatment Period (12 weeks) starting with Baseline Visit (Day 1). At the end of the 12-week Treatment Period eligible subjects may enroll in a 40-week extension study.
- Follow-up Period (2 weeks after discontinuation of treatment, whether subject completes treatment or discontinues early) for subjects who do not enroll in the extension study.

After potential subjects provide informed consent, their eligibility will be evaluated based on laboratory values, medical history, concomitant medications, vital signs, pregnancy test (if applicable), and physical examination. Three qualifying fasting blood bicarbonate values (obtained at Screening 1, Screening 2, and Baseline Visits based on onsite measurement using an i-STAT point-of-care device) are required to establish subject's eligibility. Both Screening blood bicarbonate values and the average of two Screening and Day 1 values (i.e., baseline bicarbonate) must be within the 12 to 20 mEq/L range. Two qualifying eGFR values of 20 to 40 mL/min/1.73m^2 obtained at the Screening 1 and Screening 2 Visits that are not different by more than 20% are required to establish subject's eligibility. The higher of the two Screening eGFR values will be used as the denominator to calculate the 20% allowable difference. The Screening 1 and Screening 2 Visits must be at least 5 days apart.

Qualified subjects will be randomized on the morning of the Baseline Visit (Day 1), which is the first day of the 12-week Treatment Period. A collection of baseline venous blood and

urine samples will be performed in a fasting state pre-dose. Following randomization, designated unblinded site staff will assist the subject in administering the first dose of study drug, which will be taken onsite in the morning with food (light meal or snack) after collection of baseline laboratory specimens. Subjects will be given a dosing diary in which to record the time of study drug dosing.

Subjects will continue dosing on an out-patient basis for the subsequent 12 weeks (Treatment Period). Dosing of oral concomitant medications and study drug will be separated by at least 4 hours. The study drug dose will be fixed during the first 4 weeks of the Treatment Period, except for subjects with blood bicarbonate ≥ 27 mEq/L. Subjects with a blood bicarbonate level of 27 to 30 mEq/L will have their dose of study drug decreased per the blinded titration algorithm (see Appendix 2). Subjects with a confirmed blood bicarbonate level of > 30 mEq/L will undergo an interruption of the study drug dose in accordance with the titration algorithm (see Appendix 2). Beginning at the Week 4 Visit, subjects with a blood bicarbonate level below the normal range (< 22 mEq/L) will have a blinded adjustment of the study drug dose in accordance with the titration algorithm (see Appendix 2). At any time during the study, subjects with confirmed blood bicarbonate level < 12 mEq/L will be evaluated by the Investigator for new acute acidotic processes and discussed with the Medical Monitor. The Medical Monitor will determine whether the subject may continue in the study.

During the 12-week Treatment Period, subjects will attend eight study visits (Day 1, Weeks 1, 2, 4, 6, 8, 10, and 12) for efficacy and safety assessments. Subjects will be fasted (other than water) for at least 4 hours prior to blood draws. Assessments will be performed at the time points indicated in the Schedule of Events (Appendix 1). Safety assessments will include: adverse events (AEs), vital signs (blood pressure, heart rate, temperature and respiratory rate); physical examination (including body weight); clinical laboratory testing (Table 2), and 12-lead ECGs. Efficacy will be assessed by examining changes in blood bicarbonate.

Subjects who complete the Treatment Period will be offered participation in a 40-week extension study (TRCA-301E). Subjects who are not willing to participate in the extension study or who are not eligible will enter the 2-week Follow-up Period and return to the study site for two visits: Follow-up 1 (Week 13) and Follow-up 2 (Week 14), for adverse event collection, fasting blood draws and safety assessments as outlined in the Schedule of Events (Appendix 1). Subjects who withdraw from the study prematurely (i.e., prior to the Week 12 Visit) will undergo an Early Termination (ET) Visit during which all Week 12 Visit assessments will be performed, followed by Follow-up 1 and 2 Visits in 1 and 2 weeks, respectively. Blood draws for bicarbonate measurements will be done when subjects are in a fasted state and at approximately the same time of day for each subject.

See Appendix 1, Schedule of Events, for further information on the conduct of the study.

3.2 Rationale for Study Design and Control Group

3.2.1 Study Design

This study is randomized to reduce bias. Because no approved treatment is available for chronic metabolic acidosis, placebo was chosen as the comparator. Furthermore, a comparison to placebo allows for better characterization of the efficacy and safety of new chemical entities. However, due to the chronicity and severity of the baseline metabolic acidosis in this 12-week study, subjects receiving oral alkali treatment at baseline will be allowed to continue on this treatment at stable doses to avoid significant worsening of acidosis in the placebo-treated subjects.

The Investigators, site personnel (except for designated unblinded staff responsible for study drug dispensing and accountability), subjects, Tricida, contract research organization (CRO) personnel (except for those responsible for unblinded monitoring) will be blinded to reduce bias. The data monitoring committee (DMC) members and the statisticians responsible for reporting to the DMC will be unblinded during the study. A blinding plan will describe the specific requirements for maintaining the blind at the site and sites will be trained on these requirements.

In the completed Study TRCA-101, treatment with TRC101 for 2 weeks resulted in a significant increase in serum bicarbonate in all three doses studied (3, 6 and 9 g/day) (Section 1.4.1.2); however, the maximum effect of each of these fixed doses was not determined. At the end of 2 weeks, all three BID dosing regimens (1.5 g, 3 g, and 4.5 g) as well as the QD dosing regimen (6 g) appeared to be similarly effective based on mean changes from baseline in serum bicarbonate after 2 weeks. However, a greater proportion of subjects receiving 3 g BID and 4.5 g BID achieved larger increases in blood bicarbonate (e.g., $\geq$ 4 mEq/L) than the lowest 1.5 g BID dose. Based on these findings, the mid-dose (i.e., 6 g QD) was selected as the starting dose for this study. The subjects whose blood bicarbonate is below the normal range after 4 weeks of fixed-dose treatment will have their dose up-titrated to 9 g QD while the blind is maintained. Given that no dose-related adverse events occurred in Study TRCA-301, this dosing regimen was chosen to optimize efficacy while examining the plateau effect of 6 g QD TRC101 over 4 weeks, the sustained efficacy of TRC101 over 12 weeks, and the effects of dose adjustment.

A QD dosing regimen was selected to simplify administration of concomitant medications and to enhance compliance and convenience. Study drug will be administered in the middle of the day, with lunch, so as to facilitate maintaining at least a 4-hour interval between dosing with study drug and oral concomitant medications.

3.2.2 Safety Monitoring

The design and conduct of TRCA-301 includes appropriate monitoring for safety and risk mitigation. The Medical Monitor will review blinded safety data on an ongoing basis to identify potential adverse safety trends. Central laboratory reports will contain flags that will

alert investigators and Tricida personnel to abnormal, critical, and exclusionary laboratory values, and the Medical Monitor will routinely review these results on an ongoing basis.

A DMC, which will be established for this study, will review safety during the study. The DMC will comprise, at a minimum, one biostatistician and two clinicians, at least one of whom is a nephrologist. The responsibilities of the DMC will be defined in a written charter, which will include the meeting schedule, format and structure, and the use of treatment codes. Study enrollment and study activities will continue during DMC safety reviews. The Chairperson of the DMC will be a nephrologist.

The DMC will be supported by an independent statistical group which will prepare unblinded analyses for the DMC and will have no role in the SAP after the study has started enrolling subjects. A separate, blinded statistical group (i.e., not associated with the DMC) will be responsible for producing and finalizing the SAP and executing final data analysis of the study.

TRC101 is a high molecular weight, counterion-free polymer. It is not absorbed and does not circulate systemically. Experience in Study TRCA-101 has shown that the anticipated risks of treatment with TRC101 are non-serious, mild to moderate, short-lived diarrhea or constipation, that generally resolves while treatment is ongoing. Adverse events will be monitored throughout the study.

Risks of TRC101 effects on non-target substances (e.g., serum potassium, magnesium, calcium, phosphate, lipids) were not evident in the clinical data from Study TRCA-101; nevertheless, close attention will be paid to electrolyte levels, which will be assessed at every study visit.

No cases of alkalosis (i.e., serum bicarbonate > 29 mEq/L) were observed in Study TRCA-101. However, an exaggerated pharmacological effect of TRC101 is theoretically possible, given the longer duration of treatment in this study. While kidneys are generally efficient at excreting excess bicarbonate, the rapidity with which this can happen is impaired at low levels of renal function. To avoid prolonged periods of blood bicarbonate above the normal range, blood bicarbonate levels will be measured at every study visit and study drug dose will be blindly decreased if blood bicarbonate level is 27 to 30 mEq/L and interrupted if blood bicarbonate is confirmed to be > 30 mEq/L. It is known from Study TRCA-101 that the effects of TRC101 are rapidly reversible, with the majority of the effect lost within approximately 1 week of treatment discontinuation and with serum bicarbonate returning essentially back to baseline within approximately 2 weeks of treatment discontinuation. In addition, patients with higher risk of inhibition of respiratory response to metabolic acidosis (i.e., 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) will be excluded from this study.

Among subjects randomized to placebo, in particular, a decrease in bicarbonate during the 12-week Treatment Period is a possibility, particularly if dietary acid load increases or renal function deteriorates. This protocol requires that the Investigator evaluate subjects whose blood bicarbonate decreases to < 12 mEq/L for possible causes of acute-on-chronic acidosis and discuss these cases with the Medical Monitor regarding continuation of the subject in the study.

3.3 Study Duration

The maximum study duration is anticipated to be up to 16 weeks per subject, including the Screening Period (up to 2 weeks), 12-week Treatment Period, and 2-week Follow-up Period. The maximum TRCA-301 study duration for subjects who continue into the extension Study TRCA-301E will be 14 weeks (excluding 2-week Follow-up Period).

4 STUDY POPULATION SELECTION AND WITHDRAWAL

4.1 Study Population

This study will enroll approximately 210 male and female subjects, 18 to 85 years of age with CKD (eGFR of 20 to 40 mL/min/1.73 m^2) and low blood bicarbonate (12 to 20 mEq/L). At least half of the subjects enrolled will have a blood bicarbonate level of 12 to 18 mEq/L.

4.2 Inclusion Criteria

Each subject must meet ALL of the following criteria to be enrolled in this study.

1. Have provided written informed consent prior to participation in the study.

2. Male or female subjects 18 to 85 years of age at the Screening 1 Visit.

3. Have a blood bicarbonate value of 12 to 20 mEq/L at Screening 1 and Screening 2 Visits AND an average value for Screening 1, Screening 2, and Baseline Visits (i.e., baseline blood bicarbonate) within the range 12 to 20 mEq/L based on onsite measurement using an i-STAT point of care device.

   Screening 1 and Screening 2 Visits must be at least 5 days apart.

   Note: Subjects with baseline blood bicarbonate values of 12 to 18 mEq/L are eligible without restriction. Once 105 subjects with baseline blood bicarbonate values of > 18 to 20 mEq/L have been enrolled, randomization may be closed to additional subjects with baseline blood bicarbonate in this range.

4. At both Screening Visits have an eGFR value of 20 to 40 mL/min/1.73m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as reported by the central laboratory. If a central laboratory eGFR value at Screening 2 Visit is not available, eGFR can be calculated using CKD-EPI equation based on onsite serum creatinine measurement at the Baseline Visit to establish subject's eligibility.

Screening 1 and Screening 2 Visits must be at least 5 days apart.

5. Have stable renal function as defined by eGFR values at both Screening Visits that are not different by more than 20% (the higher of the two Screening eGFR values will be used as the denominator to calculate the 20% allowable difference).
6. At both Screening Visits have systolic blood pressure < 170 mmHg (all three replicates).
7. Have a hemoglobin A1c (HbA1c) value of ≤ 9.0% at the Screening 1 Visit based on central laboratory measurement.
8. Have adequate peripheral venous access for blood draws.
9. Women who are of childbearing potential must have negative pregnancy tests at the Screening 1 Visit and Day 1 and be willing to use an acceptable method of birth control from the Screening 1 Visit until 1 month after study 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.

4.3 Exclusion Criteria

Subjects who meet ANY of the following criteria will be excluded from participation in the study.

1. Have any level of low blood 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, acute kidney injury, history of acute renal insufficiency or known ≥ 30% increase in serum creatinine or known ≥ 30% acute or chronic decrease in eGFR 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, or that required hospitalization with a primary cause of heart failure, during the preceding 6 months (see Appendix 3).
5. Have had a heart or kidney transplant.

   Note: Patients on the cadaveric transplant list or being evaluated for a future living donor transplant may be enrolled.

6. Planned initiation of renal replacement therapy (dialysis or transplantation) within 12 weeks following randomization.
7. Have had a stroke or transient ischemic attack (TIA) within the 6 months prior to randomization.
8. Have had a cardiac event within 12 weeks prior to randomization, 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. Note: Subjects who had major CV procedures or percutaneous cardiac procedures during this time frame are excluded, even if the procedures were pre-planned.
10. Have a history or current diagnosis of clinically significant diabetic gastroparesis (based on Investigator's judgment) or a history of bariatric surgery.
11. Have a history or current diagnosis of bowel obstruction, swallowing disorders, severe GI disorders, inflammatory bowel disease, major GI surgery, frequent diarrhea or active gastric/duodenal ulcers.
12. Have liver enzyme (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) or total bilirubin values > 3 × the upper limit of normal (ULN) at Screening based on central laboratory measurements.
13. Have a serum calcium ≤ 8.0 mg/dL at the Screening 1 Visit based on central laboratory measurement.
14. Have a serum potassium value < 3.8 mEq/L or > 5.9 mEq/L at the Screening 1 or Screening 2 Visit.
15. Have active cancer during the 1 year prior to Screening, other than non-melanoma skin cancer, or cancer that is currently being treated or will be treated during the study. Subjects with cancers that are being treated with hormonal therapy only may be permitted with approval of the Medical Monitor.
16. Have received any investigational medication during the last month (28 days or ≥ 5 half-lives [if known], whichever is longer) preceding the Screening 1 Visit.
17. Have used any of the following in the 14 days prior to the Screening 1 Visit: lanthanum carbonate, colesevelam, cholestyramine or sodium or calcium polystyrene sulfonate, calcium acetate, sevelamer, bixalomer, patiromer, and other polymeric binder drugs.
18. Have had a change in doses (including starting or stopping treatment) in the 2 weeks prior to the Screening 1 Visit or during Screening Period to the following: calcium-containing supplements, such as calcium carbonate and calcium citrate; antacids; H2-blockers; proton pump inhibitors. See Section 5.9 for examples of specific drugs.
19. Have had a change in doses (including starting or stopping treatment) in the 4 weeks prior to the Screening 1 Visit or during Screening Period to the following:

sodium bicarbonate, potassium citrate, sodium citrate or other alkali therapy; diuretics; renin-angiotensin-aldosterone system [RAAS] inhibitors, such as angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], aldosterone antagonists [AAs], mineralocorticoid receptor antagonists [MRAs]; non-ophthalmic carbonic anhydrase inhibitors. See Section 5.9 for examples of specific drugs.

Note: For diuretics, dose changes of up to ± 50% relative to the average dose during the Screening Period are considered "stable", and a dose change up to ± 50% between the Screening 1 Visit and the Baseline Visit is considered "stable".

20. Have a known allergy to placebo ([redacted]).

21. Inability to consume the study drug or otherwise comply with the protocol.

22. 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 validity of the study results.

23. Have participated in a previous clinical study of TRC101.

24. Currently breastfeeding.

4.4 Subject Withdrawal

Within the provisions of informed consent and good clinical judgment with respect to the subject's safety, every attempt should be made to have subjects complete both the Treatment Period and Follow-up Period. All subjects will be informed that they have the right to withdraw from the study at any time. If a subject discontinues from the study prematurely the reason given must be fully evaluated and recorded appropriately in source documents and the electronic case report form (eCRF). Subjects withdrawn from the study prematurely will be followed for safety for 2 weeks after receiving the last dose of study drug. If the subject is being withdrawn because of an AE, that AE should be indicated as the reason for withdrawal. The Investigator and the Medical Monitor may exercise his or her medical judgment to discontinue a subject's participation in the study at any time if medically necessary.

Subjects who meet any of the following criteria at any time during the study must be withdrawn from the study and should be medically managed as per standard of care by the Investigator:

- Occurrence of any AE, intercurrent illness or abnormality in laboratory assessment results which, in the opinion of the Investigator or Medical Monitor, warrants the subject's permanent discontinuation of the study drug treatment.
- Treatment with a prohibited concomitant medication. Subjects who require a prohibited concomitant medication for the treatment of an AE or for a short duration may continue on study drug treatment if approved by the Medical Monitor (see Section 5.9 for details).

- Subject's noncompliance, defined as refusal or inability to adhere to the study schedule, study drug self-administration or procedures, that cannot be rectified through additional training or other means.
- At the request of Tricida, IRB/IEC or regulatory authority.
- Withdrawal of consent by subject to participate in the study. Subjects should be encouraged to complete an Early Termination Visit, even if they are withdrawing consent, to ensure adequate safety follow-up.
- Subject is lost to follow-up (the subject did not return for visits and study personnel were unable to contact the subject after at least three documented attempts).
- Received dialysis or underwent renal transplantation.
- Pregnancy. These subjects will be followed until the outcome of pregnancy is known and if subject agrees (see Section 6.12).

Subjects with confirmed bicarbonate < 12 mEq/L should be evaluated by the Investigator for new acute acidotic processes and discussed with the Medical Monitor. The Medical Monitor will determine whether the subject may continue in the study. The subject should be maintained on their study drug dose pending discussion with Medical Monitor.

Subjects who withdraw from the study treatment prematurely prior to the Week 12 visit will undergo an ET Visit and will be asked to attend two follow-up visits.

It is important to collect information explaining why subjects withdrew from the study. This information, together with AEs occurring at those times, may be very informative of the cause-specific reasons for why some subjects remain in the study or on the assigned treatment while others do not. Therefore, although subjects are not obliged to give their reason for withdrawing consent, the Investigator will make a reasonable effort to obtain the reason while fully respecting the subjects' rights. Reasons for withdrawal of consent, when provided by the subject, will be recorded in the eCRF. The procedures described for ET from the study (Section 7.8) will be performed if possible. Every effort will be made to contact a subject who fails to attend a Study Visit, or does not respond by telephone, in order to ensure that the subject is in satisfactory health. The Investigator will immediately inform the Medical Monitor of removal or early withdrawal of a subject from the study.

Subjects withdrawn from the study for any reason will not be replaced.

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Investigational Drug

TRC101 is packaged in labeled packets and dispensed in cartons containing eight (8) packets each. Refer to the current version of the TRC101 Investigator's Brochure for a more detailed description of the investigational drug.

5.1.2 Placebo

Placebo consists of [redacted], National Formulary (NF) Grade, and is packaged in labeled packets and dispensed in cartons containing eight (8) packets each.

5.1.3 Study Drug Dispensing, Packing and Labeling

Labelled cartons of TRC101 and placebo will be shipped to the study site where they will be stored at room temperature (15 to 25 °C) in a secure location.

Study drug will be dispensed by the unblinded Pharmacist or study staff member designated for this role by the Investigator (hereafter referred to as "the Pharmacist") according to the subject's treatment assignment. The exact dispensing instructions will be provided to the Pharmacist by the interactive response technology (IRT) system.

The Pharmacist will be responsible for maintaining complete study drug dispensing, returning, and dosing records for each study subject enrolled at the site.

5.2 Treatment(s) Administered

Randomization will be performed using the IRT system. Approximately 210 subjects will be randomized in a 4:3 ratio to one of the following treatments:

- 6 g TRC101 QD (n~120)
- Placebo QD (n~90)

Subjects with blood bicarbonate values of 12 to 18 mEq/L will be randomized without restriction. Once 105 subjects with blood bicarbonate values of > 18 to 20 mEq/L at baseline (i.e., average of Screening Visit 1, Screening Visit 2, and pre-dose Day 1 values) have been enrolled, randomization may be closed to additional subjects with baseline blood bicarbonate in this range.

TRC101 or placebo will be administered orally as an aqueous suspension, QD with lunch, for 12 weeks.

The Investigator will designate an unblinded Pharmacist to dispense and account for study drug and to train subjects on study drug preparation and administration. The first dose of TRC101 or placebo will be administered at the study site in the morning with food (light meal or snack) and under the supervision of the Pharmacist after the baseline blood samples have been drawn. The Pharmacist will train the subject on how to administer the study drug in accordance with the subject dosing instructions.

Subjects will record the timing of study drug dosing in a dosing diary. Subjects will be instructed to take any oral concomitant treatment at least 4 hours before or after study drug administration. Subjects will be instructed to bring the completed dosing diary with them to each visit to the study site.

The last dose of study drug will be taken the day before the Week 12 Visit (subjects who continue into the extension Study TRCA-301E will continue study drug dosing per the extension study protocol).

5.3 Dosing Regimen

The study drug dose titration algorithm is described in Appendix 2. Dose titrations can only be performed during a clinic visit. If the dose of study drug is changed, the subject will start the new dose at lunch time on the titration day. Dose titrations should be performed on the basis of onsite i-STAT blood bicarbonate measurements only.

The study drug dose will be fixed for the first 4 weeks of the Treatment Period (during this time each subject will receive the study drug dose assigned at randomization [Baseline Visit]); no study drug dose adjustments will be permitted before the Week 4 Visit, except for subjects with elevation of blood bicarbonate ≥ 27 mEq/L. If the blood bicarbonate level is 27 to 30 mEq/L at any time during the Treatment Period through Week 11, the study drug dose will be decreased by 1 packet/day (minimum dose is 0 packets/day). Beginning at the Week 4 Visit, subjects with a blood bicarbonate level below the normal range (< 22 mEq/L) will have a blinded adjustment of the study drug dose in accordance with the titration algorithm (see Appendix 2). The study drug dose will only be titrated if NO dose changes have been made during the previous 14 days. If blood bicarbonate is confirmed to be > 30 mEq/L at any time during the study, the study drug treatment will be interrupted, no study drug will be dispensed to the subject, and the subject will be invited for a visit in approximately 1 week to retest blood bicarbonate. If blood bicarbonate decreases to < 27 mEq/L and the subject is still within the Treatment Period, study drug should be re-started at a lower dose in accordance with the titration algorithm (see Appendix 2). If blood bicarbonate is ≥ 27 mEq/L, the study drug dosing should be withheld until blood bicarbonate is < 27 mEq/L.

No dose titration will be allowed after Week 11 (i.e., 77 days after the day of the first dose). Dose titrations are blinded.

The Medical Monitor must be notified within 24 hours of confirmation of a bicarbonate value > 30 mEq/L or < 12 mEq/L. Dose interruptions due to blood bicarbonate elevations should be performed on the basis of i-STAT measurements, except in unusual situations when they may be based on confirmed non-i-STAT blood bicarbonate values > 30 mEq/L, e.g., if i-STAT values cannot be obtained because the subject is hospitalized.

5.4 Missed Doses

Contact the Medical Monitor if a subject has missed more than three consecutive doses of study drug for any reason.

5.5 Selection and Timing of Dose for Each Subject

Subjects will be randomly assigned by the IRT system to one of the available treatment regimens at the Baseline Visit. The dose of study drug may be uptitrated at or after the Week 4 Visit and throughout the Treatment Period until Week 11 (77 days after the first dose of study drug) for blood bicarbonate levels (refer to Appendix 2). Study drug will be administered as an oral suspension in water with lunch, QD from the Baseline Visit through 1 day prior to the Week 12 Visit. If a dose of study drug is adjusted, the subject will start the new dose at lunch time on the titration day.

Dosing times for study drug will be collected by the subject on the dosing diary and recorded on the eCRF.

5.6 Method of Assigning Subjects to Treatment Groups

When a subject who has met all eligibility criteria for the study is identified, the subject will be randomized using the IRT system at the Baseline Visit (Day 1). The IRT system will randomly assign the subject to one of the two treatment groups (placebo or 6 g TRC101) with stratification by baseline blood bicarbonate (≤ 18 mEq/L vs. > 18 mEq/L) and screening eGFR (< 30 mL/min/1.73m^2 vs. ≥ 30 mL/min/1.73m^2), which represents an average of two eGFR values obtained at Screening 1 and Screening 2 Visit.

The randomization treatment assignment will be performed by the IRT system in a blinded manner and the treatment randomization codes for the study will be maintained by the IRT system.

5.7 Blinding

In this study, [redacted] an unblinded Pharmacist or designated unblinded study staff member (the "Pharmacist") for handling (dispensation and collection) of the study drug. These individuals will be responsible for dispensing study drug (including supervision of administration of the first dose of study drug) and collecting used and unused study drug containers and dosing diaries. If study drug dose needs to be adjusted or interrupted per the titration algorithm (see Appendix 2), such adjustments will be performed in a blinded manner in both active and placebo treatment groups. The Pharmacist must not have any other responsibilities for the study except for performing study drug dispensation and collection, assessing dosing compliance and performing drug accountability and entering related data in eCRF. The subjects, Investigators, Medical Monitors, Tricida, site personnel (including all those involved in collection of safety and efficacy information) and CRO staff (except for those responsible for monitoring of unblinded data) will remain blinded to the subject's treatment assignment. The DMC members and the statisticians responsible for reporting to the DMC will be unblinded during the study.

The Pharmacist must not inform the subjects, Investigators, Medical Monitors, Tricida, or other site or CRO personnel about the subjects' treatment assignment. In case of a medical emergency, the Investigator may obtain the treatment assignment for the subject from the IRT system if it is considered important to the management of a medical emergency. In such cases, the Investigator must submit a written report, including all pertinent details, to a Medical Monitor within 24 hours of the unblinding. The Investigator should make every reasonable attempt to contact a Medical Monitor before unblinding the subject.

5.8 Concomitant Therapy

Information on prior and concomitant medications (including prescription, over-the-counter, herbal and naturopathic remedies, etc.) will be collected beginning at the Screening 1 Visit and continuing for the duration of the study (including ET) until the last study visit. A therapy will be considered a concomitant medication if it is administered at any time after randomization (Day 1) and before the completion of the final study visit. A therapy will be considered a prior medication if it is administered at any time during the 28 days prior to the Screening 1 Visit and during the Screening Period (until randomization).

Subjects will be instructed to take any oral concomitant treatment at least 4 hours before or after study drug administration.

If a subject requires a medication, or a change in the dose of a current medication, for treatment of any condition or AE that occurs during the study (including the Screening, Treatment and Follow-up Periods), such medication(s), or the new doses, and the adverse event(s) [AE(s)] will be recorded on the eCRF.

5.9 Restricted Medications

In general, subjects should continue on regular doses of their usual medications. Subjects who are receiving or who have recently received restricted drugs or drug classes prior to the Screening 1 Visit should adhere to restrictions as described in Table 1. The rationale for the restrictions on concomitant medications is provided in Section 1.6.

Changes to alkali treatment are not allowed.

Investigators will be advised to avoid changing doses of RAAS inhibitors or diuretics when possible. However, RAAS inhibitor dose decreases or discontinuation necessary for the management of comorbidities or acute events (e.g., hyperkalemia/worsening hyperkalemia) and diuretic dose increases necessary for the management of comorbidities or acute events (e.g., heart failure, acute kidney injury) are not prohibited.

The use of polymer binder drugs is not allowed during the study; however, use of a potassium binder (e.g., Veltassa or Kayexalate) for a short duration (e.g., up to 4 days on up to two separate occasions) for the management of hyperkalemia is permitted without

interruption of study drug treatment with a dose separation from study drug of at least 4 hours.

Table 1 Restricted Prior and Concomitant Medications

Drug or Drug Class	28 Days or 5 Drug Half-lives (Whichever is Longer) through 15 Days Prior to the Screening 1 Visit	14 Days Prior to the Screening 1 Visit and during the Screening Period	During the Study
Investigational medications	Not allowed	Not allowed	Not allowed
Potassium binders (e.g., Veltassa, Kayexalate)	Allowed	Not allowed	Not allowed [a]
Other polymer binder drugs [b]	Allowed	Not allowed	Not allowed
Sodium bicarbonate potassium citrate, sodium citrate or other alkali therapy	Stable dose	Stable dose	Keep dose stable
Non-ophthalmic carbonic anhydrase inhibitors [c]	Stable dose	Stable dose	Keep dose stable, if possible
Antacids, H2-blockers, proton pump inhibitors, calcium supplements [d]	Allowed	Stable dose	Keep dose stable, if possible
RAAS inhibitors [e]	Stable dose	Stable dose	Keep dose stable, if possible
Diuretics [f]	Stable dose	Stable dose	Keep dose stable, if possible

Note: If a dose change or addition or discontinuation of prohibited or restricted drug(s) is unavoidable for clinical management of the subject, contact a Medical Monitor for approval unless medical urgency precludes this. In all cases, notify a Medical Monitor within 24 hours of the change. "Stable dose" is defined as no starting or stopping of these medications and no change in dose. For diuretics, dose changes of up to ± 50% relative to the average dose during the Screening Period are considered "stable". A dose change up to ± 50% between the Screening 1 Visit and the Baseline Visit is considered "stable".

[a] Short-term treatment (up to 4 days on up to 2 separate occasions) is allowed during the study for treatment of hyperkalemia in consultation with the Medical Monitor. Dose separation window of at least 4 hours from study drug required in these instances.

[b] Lanthanum carbonate, colesevelam, cholestyramine or sodium or calcium polystyrene sulfonate, calcium acetate, sevelamer, bixalomer, and other polymeric drugs.

[c] Examples of carbonic anhydrase inhibitors include acetazolamide, methazolamide, dorzolamide, brinzolamide, zonisamide, topiramate, dichlorphenamide.

[d] Antacid medications include milk of magnesia, proton pump inhibitors (e.g., omeprazole, pantoprazole, esomeprazole, lansoprazole), and H2 receptor antagonists (e.g., cimetidine, ranitidine, famotidine). Calcium supplements (e.g., calcium carbonate, calcium citrate, calcium chloride).

[e] Examples of RAAS inhibitors: lisinopril, enalapril, perindopril, losartan, valsartan, candesartan, spironolactone, eplerenone.

[f] Examples of diuretic drugs: furosemide, torsemide, hydrochlorthiazide, metolazone.

5.10 Restrictions

5.10.1 Prior Therapy

Restrictions regarding prior therapy are as described under Exclusion Criteria (Section 4.3) and in Table 1.

5.10.2 Fluid and Food Intake

For laboratory measurements requiring fasting (including all measurements of blood bicarbonate), a minimum period of fasting (water allowed) should be at least 4 hours. Subjects should be questioned about their most recent food intake at each visit and the information documented in the source documents.

5.10.3 Management of Acidemia (Use of Alkali Therapy)

Subjects may be on a stable dose of oral alkali therapy at Baseline; however, this dose must be kept constant and new oral alkali therapies may not be initiated during the study. If the Investigator judges that a subject requires treatment for sustained, clinically-significant worsening of metabolic acidosis during the study, diet counseling (i.e., reduced protein intake, vegetarian/vegan protein sources) may be implemented as clinically appropriate and in agreement with the Medical Monitor. Subjects with confirmed blood bicarbonate decrease < 12 mEq/L should be investigated for possible causes of acute-on-chronic acidosis and the Investigator should discuss these cases with the Medical Monitor. The subject's study drug dose should be maintained pending discussion with the Medical Monitor.

5.11 Treatment Compliance

The Pharmacist will assess subjects' treatment compliance at every study visit during the 12-week Treatment Period to confirm that the subject is taking study drug according to the protocol instructions and to document compliance in the eCRF as detailed in the eCRF completion guidelines. Compliance will be assessed on the basis of the assigned study drug dose, the duration of treatment, and the quantity of dispensed and returned containers (used and unused). The dosing diary data collected from the study subjects will be used as a secondary means for assessing compliance. Supervised study drug dosing on Day 1 at the study site will occur to ensure subject compliance with dosing instructions. Subjects will be provided with a dosing diary and will be requested to record the time when study drug was taken and the number of packets taken. Subjects will be instructed to save their opened/empty (used) study drug containers and bring them to the next study visit for compliance assessment along with any unopened containers. The Pharmacist will not share any potentially unblinding information with the subject or any other party as described in Section 5.7.

5.12 Storage and Accountability

All study drug supplies must be stored in a secure location under the proper storage conditions, with access restricted to the Pharmacist only. Study drug must be stored at room temperature (15 to 25 °C).

The Pharmacist will verify and acknowledge receipt of study drug by signing and returning all required forms. All study drug dispensed to subjects must be accurately captured in the drug accountability records (forms and/or logs) maintained at the study site. A copy of these records must be returned to Tricida at study completion for drug reconciliation purposes. Study drug designated for this clinical study must not be administered to any subject other than those enrolled in this specific investigation, and may not be utilized for any laboratory or animal research. Subjects should be instructed to return all study drug dispensed to them (including empty containers) at each post-baseline study visit during the Treatment Period. All used, unused, and expired medication and empty study drug containers will be retained until the Study Close-Out Visit unless requested earlier by Tricida. Tricida will provide instructions on where to return all used and unused study drug containers.

6 STUDY PROCEDURES

6.1 Informed Consent

A signed informed consent form (ICF) must be obtained from each subject prior to any study-mandated procedure.

6.2 Demographics and Medical History

The Investigator or qualified designee will collect subject's demographics information and a complete medical and surgical history (including neurologic and psychiatric) at the Screening 1 Visit. Medical history will include information on the subject's prior and concurrent medical conditions and methods of birth control, if applicable. The Investigator or qualified designee will record all findings in source documents, on the medical history eCRF and the concomitant medications eCRF, if applicable.

6.3 Prior and Concomitant Medications

At the Screening 1 Visit the Investigator or qualified designee will collect information regarding the subject's prior prescription and non-prescription medications and nutritional supplements taken within 28 days. The information on concomitant medications will be collected at all subsequent visits during the study. The Investigator or qualified designee will record all findings in source documents and on the concomitant medications eCRF.

6.4 Vital Signs

The Investigator or qualified designee will measure vital signs (systolic/diastolic blood pressure and respiratory rate [in triplicate with measurements recorded approximately

2 minutes apart at the Screening 1, Screening 2, and Week 12 Visits; once for all other time points], heart rate, and temperature) at time points specified in the Schedule of Events (Appendix 1). The same method for measurement of temperature (e.g., oral, tympanic, axillary) should be used throughout the study for an individual subject. Subjects must be in a supine, semi-fowler's (semi-recumbent) or seated position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. The same position must be used for blood pressure measurements for a given subject at each time point. Respiratory rate will be assessed by a full minute count.

All measurements will be recorded on the vital signs eCRF. Abnormal measurements may be repeated at the discretion of the Investigator and must be recorded on the vital signs eCRF. When collection of vital signs, ECG, and/or blood samples is required at the same visit, vital signs should be performed first, followed by ECG and collection of blood samples.

6.5 Complete Physical Examination, Including Body Weight and Height

The Investigator or qualified designee will perform a complete physical examination (including CV, lungs and chest, head and neck, abdomen, musculoskeletal, skin and neurological systems; genitourinary examination not required) and record body weight at the time points indicated in the Schedule of Events (Appendix 1). Height will be measured at the Screening 1 Visit only. Pre-dose abnormal physical examination findings will be reported in the source documents and in the medical history eCRF. Additional examinations should be performed where clinically appropriate. Any new clinically significant physical examination abnormality identified during the study should be reported as an AE and documented on the AE eCRF.

6.6 Repeated Chair Stand Test

The Investigator or qualified designee will administer the repeated chair stand test (Guralnik; 1995) at the time points indicated in the Schedule of Events (Appendix 1). The repeated chair stand test at the Screening 1 Visit will be performed for subject's training purposes only, without collecting the data. The repeated chair stand test in this study will be used as a measure of lower extremity muscle strength. Site staff will be trained to perform the testing in a consistent manner. The procedure details are provided in the Study Reference Manual.

6.7 KDQOL

The Investigator or qualified designee will collect subjects' answers to the Kidney Disease and Quality of Life (KDQOL) Question 3 items (daily activities) at the time points indicated in the Schedule of Events (Appendix 1). The procedure details are provided in the Study Reference Manual.

6.8 12-Lead Electrocardiograms

During the study, 12-lead ECGs will be performed at the time points indicated in the Schedule of Events (Appendix 1). If a subject has serum potassium ≥ 6.0 mEq/L at any time post-Screening, ECGs will be collected more often, as clinically needed, until serum potassium is < 6.0 mEq/L.

The subject must be in a supine position in a rested and calm state for at least 5 minutes before the ECG assessment is conducted. Subjects who are unable to be in the supine position should be in the most recumbent position possible.

All ECGs should be performed with a standardized method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures. Each ECG reading must include the following measurements: heart rate and QRS, QT, RR, and PR intervals. All measurements will be recorded on the ECG electronic case report form (eCRF).

The Investigator or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of Tricida, a copy of the original ECG will be made available. Clinically significant ECG abnormalities/changes meeting a definition of an AE (see Section 6.11.1) should be recorded on the AE eCRF.

6.9 Clinical Laboratory Tests

6.9.1 Laboratory Parameters

The tests listed in Table 2 will be conducted on samples collected and analyzed by standard laboratory procedures at the time points specified in the Schedule of Events (Appendix 1). The bicarbonate test results will be recorded on the eCRF. Missed test(s) that are not done must be reported as such on the eCRFs. Clinically significant laboratory abnormalities will be recorded on the AE eCRF.

All blood draws for bicarbonate measurements must be done with subjects in a fasted state (i.e., no food or drink, other than water, for 4 hours).

Blood bicarbonate assessment using the i-STAT device is mandatory at each study visit. In addition, a secondary measurement of blood bicarbonate using either enzymatic assay or benchtop venous blood gas analysis will be conducted at each study visit at the local laboratory.

Twenty-four-hour urine collections will be done by subjects one day prior to the Baseline Visit and on the day prior to the Week 12 visit. The specimens will be brought to the next clinic visit.

Some of the blood and urine samples taken as shown in the Schedule of Events (Appendix 1) will be stored for evaluation by one or more central laboratories. Instructions for the processing, storage and shipment of the samples to the central laboratories will be provided in a separate laboratory manual.

Table 2 Laboratory Parameters

Test Type	Analytes	Comments
Whole blood bicarbonate (venous)	pH, pCO_2, pO_2 and the calculated values for HCO_3, TCO_2, BE, and O_2 saturation	Conducted with i-STAT point-of-care device with a G3+ cartridge (mandatory)
Venous Blood Gas bicarbonate – benchtop analyzer	pH, pCO_2, pO_2 and the calculated values for HCO_3, TCO_2, BE, and O_2 saturation if reported	Either assay to be conducted at local laboratory or study site but consistent for each subject
Serum Bicarbonate (venous) – enzymatic assay	HCO_3^-	
Serum Chemistry	Albumin, ALT, AST, alkaline phosphatase, bilirubin (total and direct), BUN, calcium, chloride, cholesterol (HDL, LDL, total, and triglycerides), CK, CK-MB (if CK is elevated), creatinine (including eGFR), cystatin C*, glucose, magnesium, phosphate, potassium, sodium	Conducted at central laboratory
Biomarkers	Parathyroid hormone (PTH), serum pre-albumin, 25-hydroxy-vitamin D Urinary biomarkers of bone resorption: N-terminal telopeptide (NTX), C-terminal telopeptide (CTX) Serum biomarkers of bone resorption: tartate-resistant acid phosphatase 5b (TRAP 5b), bone-specific alkaline phosphatase (BSAP), and type 1 procollagen (P1NP) Blood biomarker of bone formation: serum osteocalcin Renal biomarkers: urine angiotensinogen to creatinine ratio (UAGT), urine aldosterone, urine endothelin-1 (ET-1)	Conducted at central laboratory Serum samples and urine samples will be collected and stored in frozen conditions until analyzed
Coagulation	INR	For subjects receiving vitamin K antagonists or factor Xa inhibitors only. Vitamin K antagonists include warfarin and acenocoumaral. Factor Xa inhibitors include apixaban, rivaroxaban, betrixaban, edoxaban and enoxaparin. Conducted at local laboratory

* Cystatin C will be measured at the Baseline and Week 12/ET Visits only.

Table 2 Laboratory Parameters (Cont'd)

Test Type	Analytes	Comments
Hematology	Red blood cell (RBC) count, white blood cell count, white blood cell count differential, hemoglobin, hematocrit and platelet count, RBC indices (e.g., MCV, red cell distribution width [RDW], MCH)	Conducted at central laboratory
Urinalysis	Bilirubin, glucose, ketones, blood, leukocyte esterase, nitrites, pH, protein, urobilinogen, and urine specific gravity	Conducted at central laboratory A reflex microscopic analysis will be performed if the dipstick test is abnormal.
Spot urine tests	Sodium, potassium, chloride, creatinine, albumin	Conducted at central laboratory
24-hour urine collection	Volume Urea nitrogen, sulfate, uric acid, albumin, and creatinine (including albumin to creatinine ratio)	Volume will be measured at study site Assays will be conducted at central laboratory
Hemoglobin A1c	HbA1c	Conducted at central laboratory
Pregnancy test	β-HCG	Conducted at central laboratory (serum pregnancy test) Urine dipstick at study site at the Baseline Visit only

ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-HCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; BE = base excess; CPK = creatine phosphokinase; eGFR = estimated glomerular filtration rate; HCO_3 = bicarbonate, HDL = high-density lipoprotein; HCG = human chorionic gonadotropin; INR = international normalized ratio; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCV = mean cell volume; O_2 = oxygen, RBC = red blood cell; RDW = red cell distribution width; SO_2 = oxygen saturation; TCO_2 = total carbon dioxide

6.10 Dietary Counseling

Dietary counseling will be provided to all study subjects in accordance with dietary recommendations for CKD patients (e.g., KDIGO 2013) at the time points indicated in the Schedule of Events (see Appendix 1). In addition, if a subject requires treatment for sustained, clinically-significant worsening of metabolic acidosis during the study in the judgment of the Investigator, diet counseling (i.e., reduced protein intake, vegetarian/vegan protein sources) may be implemented as clinically appropriate and in agreement with the Medical Monitor.

6.11 Adverse Events

6.11.1 Definition of an Adverse Event

An AE is defined as: "Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment" (*ICH E2A Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, October 1994). An AE can therefore be any unfavorable or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal

(investigational) product, whether or not related to the medicinal (investigational) product. This includes:

- Any new medical condition, sign or symptom or newly diagnosed event that occurs during the AE reporting period, including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period (from the time the subject signs the ICF until the completion of the last study visit assessments);
- A previous condition that has worsened in severity or frequency or changed in character during the AE reporting period;
- Complications that occur as a result of protocol-mandated interventions;
- Signs, symptoms or the clinical sequelae of a suspected drug interaction; and
- Signs, symptoms or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication.

For the purposes of this protocol, events that are <u>not</u> considered AEs include:

- Isolated decline in blood bicarbonate or blood pH, even if assessed as clinically significant by the Investigator;
- Anticipated fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study unless judged by the Investigator to be more severe than expected for the subject's underlying condition;
- Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE;
- Placement of a dialysis access
    - If the access placement was prompted by clinically significant renal function decline during the study, then the latter should be reported as an AE and the access placement should be reported as an action taken for the AE.
- Overdose in the absence of other signs/symptoms will not be reported as an AE in its own right; and
- Pregnancy; however, any pregnancy complication should be recorded as an AE.

Out of range laboratory results and abnormal ECGs, vital signs and other safety assessments will be considered AEs if they meet at least one of the following criteria:

- Associated with symptoms or lead to a diagnosis (in such case the symptom or diagnosis should be recorded as an AE);
- Lead to discontinuation of study drug; or

- The abnormality is deemed clinically significant in its own right (i.e., if some action or intervention or alteration of treatment is required or if the Investigator judges the change to be beyond the range of normal physiological fluctuation).

6.11.2 Definition of a Serious Adverse Event

A serious adverse event (SAE) is an untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening. (This refers to a subject who, in the view of the Investigator or Tricida, was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization, with the exception of:
  - Visits to the emergency room or hospital department that do not result in a hospital admission lasting more than 24 hours
  - Elective surgery for a pre-existing condition that has not worsened
  - Routine health assessments requiring admission not associated with any deterioration in condition
  - Social admission (lack of housing, family circumstances, etc.)
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes above (e.g., blood dyscrasias, convulsions).

Either the Investigator or Tricida can determine that an AE meets the definition of serious. If either believes that the event is serious, the event must be considered serious and evaluated by Tricida for expedited reporting.

6.11.3 Definition of a Suspected Adverse Reaction

A suspected adverse reaction is an AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE.

All AEs judged by either the Investigator or Tricida as having a reasonable causal relationship to a study drug will be designated as suspected adverse drug reactions.

6.11.4 Procedures for Eliciting, Recording and Reporting Adverse Events

6.11.4.1 Adverse Event Reporting Period

AEs, including SAEs, will be collected throughout the study period, beginning from the time the subject signs the ICF until the subject's last study visit. Any AE or SAE that is assessed by either the Investigator or Tricida as related to the investigational drug and is ongoing at the last study visit will be followed, whenever possible, until it resolves or becomes stable or the subject is lost to follow-up.

All subjects who have been exposed to investigational product will be evaluated for AEs. Treatment-emergent adverse events (TEAEs) are defined as those that occur on or after the date of the first dose of investigational product. Non-treatment emergent adverse events (e.g., events occurring during Screening) should be recorded as medical history unless related to a study procedure, in which case, they should be recorded as adverse events.

6.11.4.2 Eliciting Adverse Events

Information on AEs and SAEs will be elicited at each AE assessment time point specified in the Schedule of Events (Appendix 1) by asking the subject an open-ended question such as: "Since you were last asked, have you felt unwell or different from usual in any way?" The subject may report AEs spontaneously at any time.

6.11.4.3 Assessing Adverse Events

The Investigator should follow the guidelines for rating severity of adverse events:

Severity	**Definition**
Mild	Awareness of signs or symptoms, but easily tolerated; no disruption of normal activities; symptoms are transient and would not require medication or medical evaluation
Moderate	Discomfort enough to cause interference with usual activities and treatment may be required
Severe	Incapacitating with inability to do work or do usual activities; may require medical evaluation and/or treatment; the investigational product may have been discontinued

It is important to note the distinctions between severe AEs and serious AEs. Severity is a classification of intensity of a specific event, whereas an SAE is an AE that meets any of the regulatory specified criteria required for designation as seriousness described in Section 6.11.2 (e.g., a headache may be severe [interferes significantly with subject's usual function] but would not be classified as serious unless it met one of the criteria for SAEs).

The Investigator will assess relationship of the AE to the investigational drug, TRC101, using the following definitions. A suspected relationship (related, probably, possibly)

between the events and the study drug means, in general, that there are facts (evidence) or arguments to suggest a causal relationship. If the relationship to the study drug is considered to be unlikely or not related, an alternative suspected etiology should be provided if available (e.g., concomitant medications, intercurrent illness/events).

Relationship	**Definition**	**Example**
Related	Causal relationship is certain	The temporal relationship between drug exposure and the AE onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated; the event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
Probable	High degree of certainty for causal relationship	The temporal relationship between drug exposure and AE onset/course is reasonable, there is a clinically compatible response to dechallenge (re-challenge is not required), unlikely to be attributed to disease or other drugs.
Possible	Not reasonably related although a causal relationship cannot be ruled out	The temporal relationship between drug exposure and the AE onset/course is reasonable or unknown, de-challenge information is either unknown or equivocal, could also be explained by disease or other drugs.
Unlikely	Not reasonably related although a causal relationship cannot be ruled out	Disease or other drugs provide plausible explanation.
Unrelated	No possible relationship	The temporal relationship between drug exposure and the AE onset/course is unreasonable or incompatible, or a causal relationship to study drug is impossible.

The Investigator will use the following categories to assess the outcome of each AE:

- Recovered/resolved;
- Not recovered/ not resolved;
- Recovered/resolved with sequelae;
- Fatal; or
- Unknown.

"Fatal" should be recorded as an outcome when the AE results in death. If more than one AE is possibly related to the subject's death, the outcome of death should be indicated for the AE

that, in the opinion of the Investigator, is the most plausible cause of death. All other ongoing AE/SAEs will be recorded as not recovered/not resolved at the time of death.

Although "fatal" is usually an outcome of an event, events such as sudden death or unexplained death should be reported as SAEs.

The action taken with regard to study drug in response to each AE will be assessed by the Investigator using the following categories:

- No action taken;
- Study drug interrupted;
- Study drug discontinued; or
- Not applicable (e.g., subject was not receiving study drug at the time of the AE).

6.11.4.4 Independent Data Monitoring Committee

An independent unblinded DMC will review the safety data during the study conduct. The DMC Charter will describe the data review process and its frequency.

6.11.4.5 Recording Adverse Events

All AEs and SAEs, whether spontaneously reported by the subject or elicited or noted by study staff, will be recorded in the subject's medical record and on the appropriate AE eCRF page. In addition, the SAE Report Form must record each SAE.

All AEs should be recorded using the words of the subject (verbatim term) to describe the AE, with two exceptions: if the verbatim term is vague or ambiguous (e.g., cramps), the study staff should try to obtain clarification by asking a follow-up question (e.g., What kind of cramps?) and record the words the subject used to clarify the event (e.g., menstrual cramps, calf muscle cramps).

If the subject reports a group of symptoms and the Investigator is comfortable with a unifying diagnosis, the diagnosis should be recorded (e.g., rhinopharyngitis instead of runny nose, cough, sore throat and sneezing). If a diagnosis is recorded, signs and symptoms need not be recorded separately. If the Investigator is unable to report a diagnosis, symptoms should be recorded on the AE eCRF.

The following information should be captured for each AE: date of onset and resolution, outcome, severity, seriousness, relationship to the study drug, action taken with the study drug and treatments administered. Any treatment administered as a result of an AE should be recorded on the concomitant medication eCRF.

6.11.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Clinically significant abnormal laboratory tests, vital signs, ECG abnormalities, and physical examination findings before the administration of the first dose of study drug should not be reported as AEs, but rather, as medical history, unless they are expected findings from medical history that has already been reported (e.g., elevated phosphate in a patient with a history of hyperparathyroidism).

Clinically significant new or clinically significantly worsening abnormal laboratory findings (e.g., serum chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., ECGs, vital signs) after the first dose of study drug must be recorded as AEs or SAEs.

Abnormalities resulting in study drug discontinuation, those associated with clinical signs or symptoms, or requiring treatment should be reported as AEs.

6.11.6 Serious Adverse Events Reporting

The Investigator has the obligation to report each SAE to Tricida's designee, [redacted], within **24 hours** of knowledge of the occurrence. This includes events that occur during the Follow-up Period. Additionally, if the Investigator learns of any SAE that occurred after the Follow-up Period for which there is a reasonable possibility of relatedness to the investigational drug, that event must be reported within **24 hours**.

SAEs must be reported by entering the SAE information into the SAE CRF in the electronic data capture (EDC) system. [redacted] Drug Safety will receive notification of the initial SAE via an e-mail alert generated from the EDC system.

If the event meets seriousness criteria and it is not possible to access the EDC, SAE reporting via a paper form will be required. Submit SAE information via paper form as described in Figure 3. The SAE information must be entered onto the SAE eCRF as soon as the EDC system becomes accessible. All SAEs should be followed until they are resolved or stabilized and all relevant information is compiled. Follow-up information must be handled in the same way and reported within the same time frame as the initial report.

Figure 3 **Serious Adverse Event Reporting Instructions if EDC System is Not Available**

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

Drug Safety
[redacted]
E-mail: [redacted]
Fax number: [redacted] (for sites in Europe)
Fax number: [redacted] (for sites in the US)

Scan and e-mail the SAE form and any supporting documentation to [redacted] within 24 hours of becoming aware of the event. Fax number should be used if e-mail service is not available.

Cause of death is required whenever known. If an autopsy was performed, an autopsy report should be provided.

The electronic SAE Form will be completed with the following information at a minimum:

- SAE term
- Date of onset
- Date of resolution (when medically applicable)
- Outcome
- Action taken for the SAE
- Concomitant medications
- Relevant medical history
- Criteria of seriousness (see Section 6.11.2)
- Study drug name, or code if unblinded, and treatment start date
- Severity of the event
- Causality assessment

Additional information must be provided when available including any relevant records (e.g., Hospital Discharge Summary, Autopsy Report/Death Certificate, diagnostic study reports, etc.). Any supporting information provided should not reveal a subject's identity beyond the agreed study identifier. The Investigator should ensure that information reported is accurate and consistent.

Isolated decline in blood bicarbonate or blood pH, even if assessed as clinically significant by the Investigator, will not be captured as an AE for the purpose of this protocol.

All AEs will be evaluated on a regular basis by the Medical Monitor to monitor safety in the study population.

6.11.6.1 SAE Expedited Reporting

For each AE assessed by either the Investigator or Tricida to be serious, Tricida will determine (1) if the event was unexpected (i.e., the nature or severity is not expected from the information provided in the Investigator's Brochure) and (2) if the event was a suspected adverse reaction. If the event is determined to be a serious, unexpected suspected adverse reaction (SUSAR), Tricida will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority and Investigators. The Investigator is responsible for notifying his/her respective IRB/IEC.

6.11.6.2 Unblinding Treatment Allocation

Generally, Tricida should only report SUSARs for which the treatment allocation of the subject is unblinded to the pertinent regulatory authorities. Investigators should only receive blinded information unless unblinded information is judged necessary for safety reasons.

When an event may be a SUSAR, the blind should be broken only for that specific subject. The blind should be maintained for individuals responsible for the ongoing conduct of the study (e.g., management, monitors and investigators) and those responsible for data analysis and interpretation of results at the conclusion of the study (e.g., biometrics personnel).

Unblinded information should only be accessible to those who need to be involved in the safety reporting to pertinent regulatory authorities, IECs/IRBs, and the Medical Monitor (i.e., the individual performing ongoing safety evaluations during the study).

6.12 Procedures for Reporting Pregnancy Exposure and Birth Events

Should a female subject become pregnant or be suspected of being pregnant while participating in this study, the study drug will be permanently discontinued, and the event must be reported to Tricida's designee, [redacted] on the Pregnancy Notification Form within **24 hours** of receipt of information by the study staff.

The Investigator is also responsible for following up the pregnancy at 3 monthly intervals until delivery or termination. Pregnancies should initially be reported in the Pregnancy Notification Form and sent by e-mail to the following address: [redacted]

When the outcome of the pregnancy is known, study staff will complete the Pregnancy Outcome Form and e-mail it to the following address: [redacted].

While pregnancy is not considered an AE or SAE, any pregnancy complication should be recorded as AEs or SAEs (if applicable). Fatalities, elective or spontaneous abortions, and congenital abnormalities/birth defects must be reported as SAEs.

7 STUDY ACTIVITIES

A complete schedule of study events is presented in Appendix 1. See Table 2 for a description of the analytes measured in each laboratory panel.

7.1 Screening 1 Visit (Week -2)

The Screening 1 Visit will occur within 2 weeks of the Baseline Visit. Subjects should present to the clinic in a fasted state (except water) to ensure that they will be fasted for at least 4 hours prior to blood draws during the visit. The following procedures will be performed:

- Obtain informed consent (must be done prior to any of the following procedures including asking subjects to discontinue any prohibited medications)
- Assign a unique subject identification number using the IRT system
- Evaluate eligibility (inclusion/exclusion criteria)
- Record demographic data (including sex, age, race, and ethnicity) and medical history
- Record all prescription and non-prescription medications taken within 28 days
- Collect vital signs (blood pressure [in triplicate], heart rate, temperature, and respiratory rate [in triplicate])
- Record body weight and height
- Draw fasting blood for the following assessments at local laboratory: i-STAT bicarbonate, enzymatic serum bicarbonate assay or venous blood gas bicarbonate assay, coagulation (for subjects receiving vitamin K antagonists or factor Xa inhibitors only)
- Draw fasting blood for the following assessments at central laboratory: serum chemistry panel, hematology panel, hemoglobin A1c, serum pregnancy test (for women of childbearing potential only)
- Obtain urine for spot urine and urinalysis assessments at central laboratory
- Record AEs

7.2 Screening 2 Visit (Week -1)

Subjects who meet eligibility criteria based on the results of the Screening 1 Visit will return for confirmatory bicarbonate and eGFR measurements at the Screening 2 Visit. Screening 1 and Screening 2 Visits must be at least 5 days apart.

- Evaluate eligibility (blood bicarbonate, eGFR, systolic blood pressure)
- Record prior medications
- Collect vital signs (blood pressure [in triplicate], heart rate, temperature, and respiratory rate [in triplicate])

- Perform a complete physical examination
- Train subject on the repeated chair stand test without collecting the data
- Draw fasting blood for the following assessments at local laboratory: i-STAT bicarbonate, enzymatic assay serum bicarbonate or venous blood gas bicarbonate assay
- Draw fasting blood for assessment of serum chemistry panel at central laboratory
- Provide instructions on collecting 24-hour urine sample starting one day prior to the Baseline Visit and dispense necessary supplies
- Record AEs

7.3 Laboratory Re-Testing and Subject Re-Screening

The Investigator may repeat a failed Screening blood or urine laboratory assessment once per analyte during the Screening Period (including Screening 2 and Baseline Visits) if he/she feels the original result was unexpected (e.g., due to a lab error, etc.). When Screening laboratory values required for study eligibility are repeated, eligibility should be determined based on the most recent value.

If a central laboratory eGFR value from Screening 2 Visit is not available, eGFR can be calculated using CKD-EPI equation based on onsite serum creatinine measurement at the Baseline Visit to establish subject's eligibility. For eGFR, the most recent creatinine at the Screening 1 Visit and the most recent creatinine from Screening 2 Visit should be used. If a central laboratory eGFR value and a local eGFR value are both available at the time of randomization, the central laboratory value should be used for eligibility determination.

For blood bicarbonate, the most recent value available from each of the three visits (Screening 1, Screening 2, Day 1) should be used for eligibility determination.

Re-screening of subjects who fail to meet eligibility criteria will be allowed provided the Medical Monitor approves, the subject repeats the Informed Consent process and all Screening evaluations are repeated; a new subject identification number will be assigned each time a subject is re-screened.

7.4 Baseline Visit (Day 1)

Following completion of the Screening Period, subjects who meet eligibility criteria based on the results of the Screening 1 and 2 Visits will return to the study site for the Baseline Visit on Day 1 (within 2 weeks of Screening 1 Visit) for confirmatory blood bicarbonate measurement. Subjects must present to the site in a fasted state.

The following procedures will be performed:

- Evaluate eligibility (blood bicarbonate and eGFR)

- Record prior/concomitant medications
- Collect vital signs (blood pressure, heart rate, temperature, and respiratory rate) up to 1 hour prior to administration of the first dose of study drug
- Collect body weight any time prior to administration of the first dose of study drug
- Perform repeated chair stand test
- Collect answers to KDQOL questions
- Record ECG (triplicate) any time prior to administration of study drug
- Draw fasting blood for the following assessments at local laboratory: i-STAT bicarbonate, enzymatic assay serum bicarbonate or venous blood gas bicarbonate assay, coagulation (for subjects receiving vitamin K antagonists or factor Xa inhibitors only)
- Draw fasting blood for the following assessments at central laboratory: serum chemistry panel, hematology panel, and biomarker panel
- Obtain urine sample for urine dipstick pregnancy test (women of childbearing potential only)
- Obtain urine for the following assessments at central laboratory any time prior to administration of first dose of study drug: spot urine, urinalysis, and urine biomarker panel
- Obtain 24-hour urine sample for assessment at central laboratory
- Randomize subject using the IRT system
- Dispense study drug per IRT assignment and drug dosing diary [to be done by the Pharmacist only]
- Instruct subject on study drug dosing and diary completion procedures and supervise administration of the first dose [to be done by the Pharmacist only]
- Record AEs
- Dietary counseling
- Schedule next study visit

7.5 Week 1, Week 2, and Week 10 Visits

The allowed visit window is ± 1 day for all visits during the Treatment Period. The following procedures and assessments will be performed at the Week 1, Week 2, and Week 10 Visits. Subjects must present to these visits in a fasted state.

- Record concomitant medications
- Collect vital signs (blood pressure, heart rate, temperature, and respiratory rate)

- Draw fasting blood for the following assessments at local laboratory: i-STAT bicarbonate, enzymatic assay serum bicarbonate or venous blood gas bicarbonate assay, coagulation (for subjects receiving vitamin K antagonists or factor Xa inhibitors only)
- Draw fasting blood for assessment of serum chemistry panel at central laboratory
- **At Week 2 Visit only:** record 12-lead ECG
- **At Week 10 Visit only:** provide instructions on collecting 24-hour urine sample starting one day prior to the Week 12 Visit and dispense necessary supplies
- Dispense the study drug per IRT assignment and dosing diary [to be done by the Pharmacist only]
- Collect used and unused study drug containers since the previous visit and corresponding dosing diary, assess dosing compliance and perform drug accountability [to be done by the Pharmacist only]
- Record AEs
- Schedule the next study visit

7.6 Week 4 and Week 8 Visits

The allowed visit window is ± 1 day for all visits during the Treatment Period. The following procedures and assessments will be performed at the Week 4 and Week 10 Visits. Subjects must present to these visits in a fasted state.

- Record concomitant medications
- Collect vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Collect body weight
- Perform a complete physical examination
- Draw fasting blood for the following assessments at local laboratory: i-STAT bicarbonate, enzymatic assay serum bicarbonate or venous blood gas bicarbonate assay, coagulation (for subjects receiving vitamin K antagonists or factor Xa inhibitors only)
- Draw fasting blood for assessment of serum chemistry panel at central laboratory
- Dispense the study drug per IRT assignment and dosing diary [to be done by the Pharmacist only]
- Collect used and unused study drug containers since the previous visit and corresponding dosing diary, assess dosing compliance and perform drug accountability [to be done by the Pharmacist only]
- Record AEs
- Schedule the next study visit

7.7 Week 6 Visit

The allowed visit window is ± 1 day for all visits during the Treatment Period. The following procedures and assessments will be performed at the Week 6 Visit. Subjects must present to this visit in a fasted state.

- Record concomitant medications
- Collect vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Record 12-lead ECG
- Draw fasting blood for the following assessments at local laboratory: i-STAT bicarbonate, enzymatic assay serum bicarbonate or venous blood gas bicarbonate assay, coagulation (for subjects receiving vitamin K antagonists or factor Xa inhibitors only)
- Draw fasting blood for the following assessments at central laboratory: serum chemistry panel, hematology panel, hemoglobin A1c, and serum pregnancy test (for women of childbearing potential only)
- Obtain urine for the following assessments at central laboratory: spot urine, urinalysis, and urine biomarker panel
- Dispense the study drug per IRT assignment and dosing diary [to be done by the Pharmacist only]
- Collect used and unused study drug containers since the previous visit and corresponding dosing diary, assess dosing compliance and perform drug accountability [to be done by the Pharmacist only]
- Record AEs
- Dietary counseling
- Schedule the next study visit

7.8 Week 12 or Early Termination Visit (ET)

The following assessments will be performed at the Week 12 Visit for subjects who completed the entire Treatment Period or ET Visit for subjects who withdrew from the study early. Subjects must present to this visit in a fasted state. The last dose of study drug should be taken on Day 84 of the study, regardless of the date of the Week 12 visit; however, every effort should be made to conduct the Week 12 visit on Day 85, which is in exactly 12 weeks from Day 1 (Baseline Visit).

- Record concomitant medications
- Collect vital signs (blood pressure [in triplicate], heart rate, temperature, and respiratory rate [in triplicate])
- Collect body weight

- Perform a complete physical examination
- Perform repeated chair stand test
- Collect answers to KDQOL questions
- Record 12-lead ECG (triplicate)
- Draw fasting blood for the following assessments at local laboratory: i-STAT bicarbonate, enzymatic assay serum bicarbonate or venous blood gas bicarbonate assay, coagulation (for subjects receiving vitamin K antagonists or factor Xa inhibitors only)
- Draw fasting blood for the following assessments at central laboratory: serum chemistry panel, hematology panel, hemoglobin A1c, biomarker panel and serum pregnancy test (for women of childbearing potential only)
- Obtain urine for the following assessments at central laboratory: spot urine, urinalysis, and urine biomarker panel
- Obtain 24-hour urine sample for assessment at central laboratory
- Collect used and unused study drug containers since the previous visit and corresponding dosing diary, assess dosing compliance and perform drug accountability [to be done by the Pharmacist only]
- Record AEs
- Dietary counseling
- Schedule the next study visit

7.9 Follow-up 1 Visit (Week 13)

The allowed visit window is ± 1 day for all visits during the Follow-up Period. The following assessments will be performed at the Week 13 Visit. Subjects must present to this visit in a fasted state.

- Record concomitant medications
- Collect vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Draw fasting blood for the following assessments at local laboratory: i-STAT bicarbonate, enzymatic assay serum bicarbonate or venous blood gas bicarbonate assay, coagulation (for subjects receiving vitamin K antagonists or factor Xa inhibitors only)
- Draw fasting blood for assessment of serum chemistry panel at central laboratory
- Record AEs
- Schedule the next study visit

7.10 Follow-up 2 Visit (Week 14)

The allowed visit window is ± 1 day for all visits during the Follow-up Period. The following assessments will be performed at the Week 14 Visit. Subjects must present to this visit in a fasted state.

- Record concomitant medications
- Collect vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Collect body weight
- Record 12-lead ECG (triplicate)
- Draw fasting blood for the following assessments at local laboratory: i-STAT bicarbonate, enzymatic assay serum bicarbonate or venous blood gas bicarbonate assay, coagulation (for subjects receiving vitamin K antagonists or factor Xa inhibitors only)
- Draw fasting blood for the following assessments at central laboratory: serum chemistry panel and hematology panel
- Obtain urine sample for central laboratory assessment of spot urine and urinalysis
- Record AEs

7.11 Unscheduled Visit

An unscheduled visit may be performed at any point during the study if an adjustment of study drug dose is required or at the discretion of the Investigator to follow-up on an abnormal finding or adverse event, or for another reason. The allowed visit window for a 1-week visit required per the titration algorithm is ± 1 day. In all cases, the reason for the unscheduled visit should be documented. Procedures during the unscheduled visit should be determined by the reason for the visit but could include:

- Record concomitant medications
- Collect vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Perform a complete physical examination
- Record 12-lead ECG
- Central or local laboratory testing: In general, for laboratory tests that are being analyzed at the central laboratory, the unscheduled testing should be done through the central laboratory, however, if rapid results are needed, local laboratory testing may also be performed.
- Perform study drug accountability and dispensation per IRT assignment (if applicable) [to be done by the Pharmacist only]
- Record AEs

7.12 End-of-Study

Subjects who complete the 12-week Treatment Period will be offered participation in a 40-week extension study (TRCA-301E). For subjects who are enrolled in the extension study, end-of-study in Study TRCA-301 is defined as completion of the Week 12 Visit.

For subjects who are not willing to participate in, or who are not eligible for, the extension study, end-of-study in Study TRCA-301 is defined as completion of the Follow-up 2 (Week 14) Visit.

For those subjects who withdrew from Study TRCA-301 prematurely, end-of-study is defined as the time of the subject's last data collection.

8 PLANNED STATISTICAL METHODS

8.1 General Considerations

A statistical analysis plan (SAP) will provide details of planned analyses and summary documents, such as tables, listings, and figures. This section presents an overview of the planned analyses. Final analyses are not limited to the summaries described herein. If circumstances arise during the study that make these analyses inappropriate or if improved methods become available, the SAP may be revised. The SAP will describe in detail the plans for dealing with subjects who drop out of the study.

Any revisions (both alternative and additional methods) to the SAP, and reasons for such revisions, will be described in the final study report.

All continuous study assessments will be summarized by treatment group (6 g TRC101 or placebo) and time point, as applicable, using descriptive statistics (n, mean, median and appropriate percentiles, standard deviation, minimum, and maximum). All categorical study assessments will be summarized by treatment group and time point, as applicable, using frequency counts and percentages. Two-sided 95% confidence intervals will be reported for the efficacy estimates.

8.2 Determination of Sample Size

Primary efficacy endpoint: A sample size of 120 subjects in the TRC101 group and 90 subjects in the placebo group will have high power to detect differences between the TRC101- and placebo-treated groups. The sample size calculation is based on the data from the Phase 1/2 Study TRCA-101, where 3% of placebo and 46% of TRC101 treated subjects had an increase in blood bicarbonate of ≥ 4 mEq/L or had blood bicarbonate in the normal range at Week 2. We assume the full TRC101 treatment effect had not been reached during this short treatment period. In Study TRCA-301, we expect that 50 to 55% of TRC101-treated and 10% of placebo-treated subjects will have an increase of ≥ 4 mEq/L or have

blood bicarbonate in the normal range at the end of treatment (Week 12 Visit). A Fisher's exact test with a 0.05 two-sided significance level will have over 99% power to detect this difference when 90 placebo subjects and 120 TRC101 subjects are enrolled. If the true proportion of TRC101 subjects who respond at the Week 12 Visit is indeed between 50% and 55% and if no more than 5% of subjects have missing data at Week 12, the study will have roughly 90% power to result in a 95% confidence limit with a lower bound of at least 35% and 40%, respectively.

Sample size calculation for the secondary efficacy endpoint will be documented in the SAP.

8.3 Analysis Populations

Two populations will be analyzed in this study. The SAP may define additional analysis set(s).

Modified intent-to-treat (MITT) analysis set:	All randomized subjects who had both baseline and at least one post-baseline blood bicarbonate value. Post-baseline is defined as a blood bicarbonate value obtained after the first dose of study drug.
Safety analysis set:	All subjects who received any amount of study drug (TRC101 or placebo)

8.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be listed by treatment group, study site and subject, and will be summarized by treatment group. Frequencies and percentages will be presented for the categorical variables and descriptive statistics will be presented for continuous variables.

8.5 Statistical Analysis of Efficacy

Efficacy data will be summarized by treatment group for subjects in the MITT analysis set based on the randomized treatment group assignment. Number and percentage of subjects, along with exact (Clopper-Pearson) 95% confidence intervals (CI) of the percentage, will be provided for all scheduled time points when summarizing categorical efficacy variables. Descriptive statistics will be provided for all scheduled time points when summarizing continuous efficacy variables.

Statistical significance will be declared at the 0.05 level with a two-sided test. In order to control family-wise error rate, formal statistical testing for the primary and secondary endpoints will be performed sequentially. At Week 12, Fisher’s exact test will be used to compare the group proportions for the primary efficacy endpoint. Only when the primary efficacy result is statistically significant will the formal test be performed using an MMRM model to compare the group means at Week 12 for the secondary efficacy endpoint.

8.5.1 Efficacy Variable

The efficacy analysis will include bicarbonate results that will be collected at baseline through the end of the 12-week treatment from the i-STAT device. The i-STAT bicarbonate data will be used to determine the CFB in bicarbonate over time. Baseline bicarbonate is defined as the mean of the bicarbonate values collected at Screening visits and on Day 1 pre-dose. CFB in bicarbonate will be calculated for each time point subsequent to the first dose of study drug. Descriptive statistics of efficacy data will be provided for all scheduled time points.

8.5.2 Efficacy Endpoints

Primary Efficacy:

Having a CFB in blood bicarbonate ≥ 4 mEq/L or having a blood bicarbonate in the normal range (22 to 29 mEq/L) at the end of treatment (Week 12 Visit).

Secondary Efficacy:

CFB in blood bicarbonate at the end of treatment (Week 12 Visit).

Exploratory Efficacy:

1. CFB in the total score of the KDQOL Question 3 items (daily activities) at the end of treatment (Week 12 Visit).
2. CFB in repeated chair stand test duration at the end of treatment (Week 12 Visit).

8.5.3 Efficacy Analysis

Efficacy data will be summarized by treatment group for subjects in the MITT analysis set based on the randomized treatment group assignment.

8.5.3.1 Primary Efficacy Analysis

The number and proportions (expressed as percentages) of subjects who are responders at each time point and at the end of treatment will be calculated. Responders are defined as having a CFB in blood bicarbonate ≥ 4 mEq/L or having a blood bicarbonate in the normal range (22 to 29 mEq/L). The difference in proportion of responders between TRC101 and placebo subjects and its exact (Clopper-Pearson) 95% CI, as well as the p-value from Fisher's exact test comparing the TRC101 group and the placebo group will be reported by time point. The exact 95% CIs of the proportions will also be summarized by treatment group and time point. A formal test for the difference (TRC101 – placebo) in proportion (= 0) will be conducted at Week 12 using the Fisher's exact test. If this formal test is statistically significant, a second formal test for the proportion of TRC101 responders at Week 12 will be conducted.

8.5.3.2 Secondary Efficacy Analyses

The secondary efficacy analysis will compare the TRC101 group with the placebo group in LS mean CFB in blood bicarbonate at the end of treatment (Week 12 Visit). The null hypothesis is that there is no mean difference between the TRC101 group and the placebo group. The alternative hypothesis is that the means differ. The secondary efficacy endpoint will be assessed using a longitudinal mixed-effect model for repeated measures (MMRM). The model will include the CFB in bicarbonate as the dependent variable, treatment, time point (Weeks 1, 2, …, 12), and treatment by time point interaction as fixed effects, subject as a random effect, the baseline bicarbonate and baseline eGFR as continuous covariates. An unstructured covariance structure will be assumed. The least squares (LS) mean of CFB in bicarbonate, standard error of LS mean, and two-sided 95% CIs of the LS mean from the mixed model will be reported by time point and treatment group. The LS mean difference from placebo (i.e., TRC101 – placebo), SE of the LS mean difference, 95% CIs of the LS mean difference, and p-values of the LS mean difference from the mixed model will be reported by time point. Only when the primary efficacy endpoint is statistically significant will formal testing be performed for the secondary efficacy endpoint. Meeting the secondary endpoint will be declared if the two-sided p-value at Week 12 is <0.05 and the primary efficacy endpoint is statistically significant.

8.5.3.3 Sensitivity Analyses and Exploratory Efficacy Endpoint Analyses

In order to evaluate the potential effect of missing data on the primary and secondary efficacy results, sensitivity analyses will be performed using multiple imputation models under a MNAR assumption for the MITT analysis set. These analyses will be described in the SAP.

The SAP will also describe the analysis methods for the exploratory efficacy endpoints.

8.6 Safety Analysis

Safety will be summarized by treatment group for subjects in the safety analysis set. The number and percentage of subjects with treatment-emergent AEs (TEAEs) classified by system organ class (SOC) and preferred term (PT); number (%) of subjects experiencing TEAEs by severity, causality, seriousness and action taken with regard to study drug will be summarized by treatment group. The number (%) of subjects with TEAEs leading to discontinuation of study treatment will also be summarized by treatment group. Subjects will be counted only once at each SOC and PT level of summary. Clinical laboratory test results, vital signs and ECG findings will be summarized using descriptive statistics by treatment group and time point. Categorical display methods (e.g., frequencies, shift tables) and plots of laboratory values over time may also be used, as appropriate. Worsening or newly observed, clinically significant physical examination findings will be reported as adverse events.

8.7 Other Assessments or Analyses

Exposure to study drug, dosing compliance, and concomitant medications will be summarized by treatment group. The number and percentage of subjects who used prior and/or concomitant medications will be summarized by Anatomic Therapeutic Chemical (ATC) classification levels and treatment group. At each level of ATC classification, subjects will be counted once.

9 DATA HANDLING AND RECORD KEEPING

9.1 Source Data

Source documents are original documents, data, and records (e.g., case histories, progress notes of the physician, nurses' notes, medical records, hospital records, clinical and office charts, laboratory notes, memoranda, or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, and records kept at the pharmacy or laboratories). Source data are contained in source documents and must be adequate to reconstruct all data transcribed onto the eCRFs and to evaluate the study. Examples of source data include clinical findings, observations, enrollment summary information and ICF procedures, assessment of clinical significance for laboratory results, AE severity and seriousness, and Investigator's opinion of AE relatedness to TRC101.

The Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation for all subjects.

Source documentation should be available at monitoring visits to verify entries made on eCRFs, as needed. Source documentation should also be available for verification by auditors and/or inspectors, as needed.

9.2 Case Report Forms / Electronic Data Record

An eCRF is designed to record all of the protocol-required information to be reported to Tricida on each study subject. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported on subjects' eCRFs. Data reported on the eCRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. An explanation should be given for all missing data.

All eCRF data and query resolutions must be completed only by the clinical study personnel designated by the Investigator. All site staff will have proper training prior to accessing the EDC system.

Any change or correction to an eCRF will be tracked via an audit trail within the EDC system. The audit trail will contain the original data value, new data value, date changed, the user who made the change, and the reason(s) for the change.

CRFs should be completed in a timely manner to support the study timeline (i.e., the site should not wait for a monitoring visit before entering data into the eCRF).

Data from the eCRFs and queries will be tracked and entered into a 21 CFR Part 11 compliant clinical database. The database system will be a secured, password-protected system with full audit trail utility.

Subject data will be reviewed via programmed quality checks and manually via data listings review by Tricida and its designee. Data that appear inconsistent, incomplete, or inaccurate will be queried for site clarification. Data corrections will be updated to the database and tracked in the audit trail. AEs and concomitant medications will be coded using industry standard dictionaries (e.g., Medical Dictionary for Regulatory Activities [MedDRA] and World Health Organization [WHO] Drug dictionary).

The Investigator is responsible for reviewing, verifying, and approving all subject data (i.e., eCRFs and resolved queries).

9.3 Data Handling

The final data will be transferred to the SAS-system for data analyses in accordance with the SAP. The MedDRA dictionary will be used for coding of AEs and concomitant diseases. Concomitant medication will be coded using the WHO Drug Dictionary ATC code.

9.4 Deviations from the Protocol

Deviations from the protocol will be judged during the study and/or when an individual subject's eCRF is completed (monitored).

The SAP will define major and minor protocol deviations for use in the statistical analysis, if applicable.

9.5 Record Retention and Archiving

The Investigator must maintain adequate records for the study including completed CRFs, medical records, laboratory reports, signed ICFs, drug disposition records, adverse experience reports, information regarding subjects who discontinued, all correspondence with the IRB/IEC and Tricida, and other pertinent data.
Before site initiation Tricida will provide an Investigative Site File (ISF)/Regulatory Binder to each site. The ISF will include essential documents as defined by the ICH Good Clinical Practice (GCP) guideline and applicable local requirements.

The Investigator will be responsible for the update and maintenance of the ISF, which will be reviewed periodically by Tricida or its designee. If an audit occurs, these documents will be reviewed during an audit by Tricida or an inspection by the Regulatory Authorities.

All study-related documents and records should be archived according to ICH guidelines for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product or such longer period as may otherwise be instructed by Tricida in writing or as otherwise required by applicable regulatory requirements.

The Investigator is to retain all records until notified by Tricida. The Investigator will notify Tricida in writing of the relocation of any study records away from the research facility after study closure. The Investigator must receive Tricida's consent in writing prior to the destruction of any study records, or in the event of loss of any study records.

10 QUALITY CONTROL AND QUALITY ASSURANCE

The integrity and quality of subject data will be ensured by providing training and process instructions for the completion of the eCRFs, performing quality control checks, conducting ongoing clinical data review (including medical and safety reviews), and performing source data verification and data reconciliation.

Tricida employees or designees will conduct site monitoring visits at regular intervals in accordance with FDA and International Conference on Harmonization (ICH) guidelines. The Investigator will permit Tricida or designee monitors to review and inspect facilities, and all records relevant to this study.

The Investigator will also permit Tricida or designee auditors, the IRB/IEC, FDA or other Regulatory Authority inspectors to review and inspect facilities, procedures, and all records relevant to this study. These records include, but are not limited to: subject signed ICFs, source documentation, regulatory and essential documents, CRFs, and drug accountability records. The Investigator should notify the Medical Monitor immediately of any regulatory inquiries, investigations, site visits (whether announced or unannounced), correspondence or communication that relates to the study, and shall consult and cooperate with Tricida in responding to any such event, including providing documents, information and access as requested by Tricida.

The following steps will be taken to ensure that the study is conducted by the investigational site in compliance with the study protocol, GCP and other applicable regulatory requirements:

- Investigator meeting and/or Investigator site initiation.
- Routine site monitoring.

- Documented protocol and GCP training.
- eCRF and query review against source documents.
- Collection of local laboratory normal ranges and laboratory documentation.

11 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

11.1 Good Clinical Practice

The study will be conducted in accordance with US FDA regulations, the ICH E6 guidelines for GCP, the Declaration of Helsinki, and IRB or IEC requirements. The study will also be conducted in accordance with the European Union Clinical Trials Directive 2001/20/EC (EUCTD) for sites in the European Union (EU) and all other applicable local and national laws and regulations governing the conduct of human clinical studies.

11.2 Institutional Review Board / Ethics Committee

All Investigators participating in this study must be governed under an appropriate Institutional Review Board (IRB) or IEC. The applicable IRB or IEC should review and approve this protocol, the ICF, the Investigator's Brochure and any information to be given to the subject before a site can begin conducting any study-related activities. A copy of the IRB/IEC approval letter for the protocol and the ICF must be provided to Tricida prior to investigational product shipment. The IRB/IEC must approve any subject recruitment materials before the material is used for subject recruitment.

Subsequently, the Investigator is responsible for obtaining re-approval by the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Copies of the Investigator's annual report and other required reports to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to Tricida. The Investigator must also inform the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, expedited reports of SAEs submitted to regulatory authorities, and other significant safety concerns according to the IRB/IEC policy. Written documentation of IRB/IEC approval of protocol amendments must be received before the amendment is implemented. After completion or termination of the study, Investigators will notify their IRB/IECs. The Investigator will comply with all IRB/IEC policies throughout the duration of the study.

11.3 Ethical Conduct of the Trial

The Investigator is responsible for assuring that the study is conducted in accordance with current local and national regulations, ICH GCP guidelines, and other applicable laws, regulations and requirements governing the conduct of human clinical trials.

The Investigator will not deviate from the protocol without prior written approval from Tricida, except in medical emergencies. In the event of a medical emergency, the Investigator must notify the Medical Monitor immediately. Any other change to the protocol must be implemented by Tricida as an amendment to the protocol and must be approved by the IRB/IEC prior to implementation.

The Investigator must inform the governing IRB/IEC of all protocol changes in accordance with the IRB/IEC's established procedure. No deviation from the protocol of any type will be permitted without complying with the established IRB/IEC procedures.

If an Investigator chooses to advertise for subjects, whether in professional or consumer publications, radio, or television, all advertising must be approved by Tricida and the IRB/IEC prior to initiation.

Financial details and insurance are covered in the Clinical Trial Agreement and Clinical Trial Insurance Policy.

11.4 Subject's Information and Informed Consent

Individual subject's medical information obtained as a result of this study is considered confidential and disclosure to unauthorized parties is prohibited. Subject's confidentiality will be assured by utilizing subject identification code numbers and/or initials, instead of names. If results of this study are reported in medical journals or at meetings, the subject's identity will not be disclosed.

With the subject's authorization, medical information may be provided to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare.

In compliance with GCP guidelines, all subjects will be informed of the purpose of the research, the possible risks, and their right to withdraw at any time from the study without prejudice and without jeopardy to their future medical care at the center. Each subject must agree to cooperate in all aspects of the study and must give informed written acknowledgment (signed ICF) to the Investigator prior to participation in the study; such ICF shall be in a form that has been prior approved by Tricida and IRB/IEC. If the ICF is revised during the study, active subjects must sign the new version in order to continue participating in the study. For any updated or revised ICF, the subject record should state that written informed consent was obtained for the updated/revised consent form for continued participation in the study. The ICF should be revised whenever there are changes to procedures in the amended protocol associated with procedures in the ICF or when new information becomes available that may affect the willingness of the subject to participate; such revised ICF to be prior approved by Tricida and IRB/IEC. Every subject will be given a copy of each version of the form that he/she signs before and during the study.

No subject is to participate in study activities until informed consent has been obtained. Documentation of the informed consent process and subject information discussion must appear in the subject's medical record, and include a statement that informed consent was obtained prior to participation in the study. Signed acknowledgments (ICFs) must remain in the subjects' files and be available for verification by monitors, auditors, and/or regulatory agency inspectors at any time. The final IRB/IEC-approved ICF must be provided to Tricida for regulatory purposes.

11.5 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB/IEC/Regulatory Authority, in accordance with local legal requirements. Tricida and the Investigator must ensure that all ethical and legal requirements have been met before the first subject is enrolled in the study at the investigational site.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Regulatory Authority approval prior to implementation (if appropriate).

All amendments will be distributed to all protocol recipients, with appropriate instructions.

11.6 Premature Termination of the Study

If Tricida, DMC, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to subjects if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at Tricida's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- Failure to enroll subjects at an acceptable rate

11.7 Confidentiality

All study findings and documents shall be regarded as confidential information of Tricida. The Investigator and members of his/her research team must not disclose such information without prior written approval from Tricida.

The anonymity of participating subjects must be maintained. Subjects will be identified on eCRFs and other documents submitted to Tricida (or designee) by their subject number, not by name. Documents not to be submitted to Tricida (or designee) that identify the subject (e.g., the signed ICF) must be maintained in confidence by the Investigator.

Signed ICFs must be available for verification by monitors, auditors, and/or regulatory agency inspectors at any time.

11.8 Liability and Insurance

Prior to the start of the study, Tricida (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a Clinical Trial Agreement that will be signed by the institution and/or Investigator and Tricida (or its designee).

The institution and Investigator are required to have adequate current insurance to cover any liabilities arising out of its conduct of the study, including insurance to cover claims for negligence and/or malpractice. Tricida will provide insurance coverage for the research study as required by local and/or national regulations.

11.9 Publication Policy

By signing the study protocol, the Investigator agrees with Tricida's use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. In addition, the Investigator agrees that, if necessary, the authorities will be notified of the Investigator's name, address, qualifications and extent of involvement in this study.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with Tricida in advance and receiving Tricida's prior written approval of such publication.

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13 APPENDICES

Appendix 1: Schedule of Events

Study Activity	Period	Screening		Treatment								Follow-up		UNS
	Visit Name	S1	S2	D1	W1	W2	W4	W6	W8	W10	W12 [a]	F1	F2	Visit [v]
	Timing	Week -2 [b]	Week -1 [c]	Day 1	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 13	Week 14	
Informed Consent		X												
Subject ID Number Assignment in IRT		X												
Eligibility Criteria		X	X	X										
Demographics and Medical History		X												
Prior/Concomitant Medications [d]		X	X	X [t]	X	X	X	X	X	X	X	X	X	X
Vital Signs [e]		X	X	X [t]	X	X	X	X	X	X	X	X	X	X
Body Weight and Height [f]		X [f]		X [t]			X		X		X		X	
Physical Exam [g]			X				X		X		X			X
Repeated Chair Stand Test			X [u]	X							X			
KDQOL				X							X			
ECG [h]				X [t]		X		X			X		X	X
Fasting i-STAT Bicarbonate [i]		L	L	L [t]	L	L	L	L	L	L	L	L	L	L
Fasting Blood Bicarbonate (Enzymatic Serum or Venous Blood Gas Assay) [j]		L	L	L [t]	L	L	L	L	L	L	L	L	L	L
Coagulation [k]		L		L [t]	L	L	L	L	L	L	L	L	L	L
Fasting Serum Chemistry		C	C [l]	C [t]	C	C	C	C	C	C	C	C	C	C
Hematology		C		C [t]				C			C		C	
Hemoglobin A1c		C						C			C			
Pregnancy Test [m]		C		L [t]				C			C			
Biomarkers (Blood and Urine) [n]				C [t]							C			
Urinalysis and Spot Urine Tests		C		C [t]				C			C		C	
Training on 24-Hour Urine Collection and Dispensing Supplies			X							X				
24-Hour Urine Collection [o]				C [t]							C			
Randomization in IRT				X [t]										
Dispensation of Study Drug and Dosing Diary [p, q, r, s]				X	X	X	X	X	X	X				X
Onsite Study Drug Dosing [q]				X										
Study Drug Dosing Compliance and Accountability [r, s]					X	X	X	X	X	X	X			X
Adverse Event Collection		X	X	X	X	X	X	X	X	X	X	X	X	X
Dietary Counseling				X				X			X			

Notes: (1) All blood draws for bicarbonate measurements must be done with subjects in a fasted state (at least 4 hours, except water). (2) Weekly visits should be targeted to occur on the same day of the week as Day 1 (e.g., always on Wednesday). Allowed visit windows are ± 1 day for all study visits during the Treatment and Follow-up Periods.

Abbreviations: C = central laboratory assessment; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; ID = identification; KDQOL = kidney disease quality of life; L = local laboratory assessment; UNS = unscheduled.

[a] Subjects who terminate the study early are required to undergo an Early Termination Visit with all Week 12 Visit procedures to be performed.

[b] Screening 1 Visit must occur within 2 weeks of Baseline Visit.

[c] Screening 1 and Screening 2 Visits must occur at least 5 days apart.

[d] At Screening 1 Visit, record all prescription and non-prescription medications and nutritional supplements taken within 28 days.

[e] Vital signs include: blood pressure and respiratory rate (both in triplicate, measurements taken approximately 2 minutes apart at Screening 1, Screening 2, and Week 12 Visits; once at all other time points), heart rate, and temperature.

[f] Height will only be collected at the Screening 1 Visit.

[g] Complete physical examination will include an examination of cardiovascular, lungs and chest, head and neck, abdomen, musculoskeletal, skin and neurological systems (genitourinary examination not required).

[h] ECG will be collected in triplicate, 30 seconds apart. The subject must be in a supine position, or in the most recumbent position possible, in a rested and calm state for at least 5 minutes before the ECG assessment is conducted. All ECGs should be performed prior to blood draws whenever possible.

[i] The i-STAT G3+ cartridge must be used and measurement taken from a whole blood sample within 10 min of the blood draw.

[j] Either enzymatic or venous blood gas assay but consistent for each subject as soon as possible in accordance with local laboratory requirements.

[k] For subjects receiving vitamin K antagonists or factor Xa inhibitors only. Vitamin K antagonists include warfarin and acenocoumaral. Factor Xa inhibitors include apixaban, rivaroxaban, betrixaban, edoxaban and enoxaparin.

[l] If necessary, at the Screening 2 Visit, eGFR may be assessed based on local serum creatinine measurement to confirm eligibility.

[m] For women of childbearing potential, blood samples will be collected for serum pregnancy tests at the Screening 1, Week 6, and Week 12 Visits, and a urine sample will be collected for a urine dipstick pregnancy test at the Baseline Visit.

[n] Blood and urine samples will be collected and stored under frozen conditions as specified in the laboratory manual.

[o] Instruct subjects on collecting 24-hour urine samples prior to Baseline and Week 12 Visits and dispense necessary supplies. Subjects should collect urine samples at home in accordance with the Urine Collection Instructions and return the collected specimens at the Baseline and Week 12 Visits.

[p] Dispense study drug per IRT instructions and provide the dosing diary. Instruct subject to take study drug with lunch, at least 4 hours apart from all oral concomitant medications.

[q] Administer the first dose of study drug on the morning of Day 1, with a snack, while the subject is at the site.

[r] Instruct the subject to bring the dosing diary to each visit. Review dosing diary vs. study drug supplies and assess dosing compliance. Record dosing diary information at each visit in eCRF. Collect the dosing diary at the Week 12 or at the ET Visit.

[s] Instruct subject to bring all used and unused study drug to each visit. Collect all used and unused study drug at the Week 12 Visit or at the ET Visit.

[t] Procedure to be performed prior to administration of the first dose of study drug.

[u] Train the subjects on repeated chair stand test at the Screening 2 Visit. No eCRF data will be collected.

[v] Possible procedures during the unscheduled visit are listed. The actual procedures should be determined by the Investigator based on the reason for the unscheduled visit. In all cases, reason for the visit and recording of adverse events and concomitant medications should be done.

Appendix 2: Study Drug Titration Algorithm

Blood Bicarbonate (mEq/L)	Before Week 4 Visit	Week 4 through Week 11
< 12*	Evaluate for new acute acidotic process, contact Medical Monitor. Maintain dose pending discussion with Medical Monitor	Evaluate for new acute acidotic process, contact Medical Monitor. Maintain dose pending discussion with Medical Monitor.
12 to < 22	Maintain dose until next scheduled visit.	Increase the study drug dose by 1 packet/day (maximum dose is 3 packets/day). Only increase the dose if **NO** dose changes have been made during the previous 14 days. Retest blood bicarbonate at next scheduled visit.
22 to < 27	Maintain dose until next scheduled visit.	
27 to 30	Decrease the study drug dose by 1 packet/day (minimum dose is 0 packets/day). Invite subject for a visit in approximately 1 week to retest blood bicarbonate. Only decrease the dose if **NO** dose changes have been made during the previous 14 days.	
> 30*	Interrupt (hold) study drug. Invite subject for a visit in approximately 1 week to retest blood bicarbonate. If blood bicarbonate at that visit is: • < 27 mEq/L, restart study drug at a lower dose (1 packet/day less than before dose interruption). • ≥ 27 mEq/L, continue to hold the dose and retest again in approximately 1 week.	

* Blood bicarbonate value of < 12 mEq/L or > 30 mEq/L must be confirmed by a repeated measurement from a separate blood draw.

Appendix 3: New York Heart Association (NYHA) Classification of Heart Failure

Class	Patient Symptoms
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
Class II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results fatigue, palpitation, dyspnea (shortness of breath).
Class III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV	Unable to carry out any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Source: www.heart.org, accessed 30September2015