CLINICAL STUDY PROTOCOL

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

Study Number: TRCA-301E

NCT Number: NCT03390842

Document Date: 17 October 2018

CLINICAL STUDY PROTOCOL

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Study Number:	TRCA-301E
Investigational Drug:	TRC101
IND Number:	125,832
Indication:	Treatment of metabolic acidosis associated with chronic kidney disease
Investigators:	Multicenter
EudraCT Number:	2017-002562-42
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:	September 05, 2017
Amendment 1:	December 11, 2017
Amendment 2:	May 31, 2018
Amendment 3:	October 17, 2018

Sponsor Clinical Study Protocol Approval

Study Title:	A Blinded, Placebo-Controlled Extension to Study TRCA-301 to Evaluate the Long-term Safety and Durability of Effect of TRC101 in Subjects with Chronic Kidney Disease and Metabolic Acidosis
Study Number:	TRCA-301E
Final Date:	October 17, 2018

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

Signed: _____ Date: _____

[redacted] PhD
[redacted] Clinical Operations
Tricida, Inc.

Principal Investigator's Signature

Study Title:	A Blinded, Placebo-Controlled Extension to Study TRCA-301 to Evaluate the Long-term Safety and Durability of Effect of TRC101 in Subjects with Chronic Kidney Disease and Metabolic Acidosis
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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 European Union Clinical Trials Directive and all other applicable local and/or national laws, regulations and requirements.

Signed:_____ Date:_____

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

TRCA-301E 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.	Synopsis, Section 8.6.3	Added clarification regarding statistical methodology to be used for mixed-effect model repeated measures (MMRM) and analysis of covariance (ANCOVA) analyses.	In the event that the residuals from the MMRM or ANCOVA models are not normally distributed, alternative statistical analyses will be used instead; these will be specified in the Statistical Analysis Plan.

SYNOPSIS

TITLE:

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

PROTOCOL NUMBER:

TRCA-301E

INVESTIGATIONAL PRODUCT:

TRC101

INDICATION:

TRC101 is an oral, non-absorbed hydrochloric acid binder for the treatment of metabolic acidosis associated with chronic kidney disease (CKD).

OBJECTIVES:

To evaluate the long-term safety and durability of effect of TRC101 in CKD patients with metabolic acidosis.

POPULATION:

Subjects with non-dialysis dependent CKD and blood bicarbonate value of ≥ 12 mEq/L who completed the 12-week Treatment Period in Study TRCA-301.

STUDY DESIGN AND DURATION:

This study is a 40-week, blinded, placebo-controlled extension of Study TRCA-301 (a Phase 3, multicenter, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of TRC101 in subjects with CKD and metabolic acidosis). Study sites, other than a designated unblinded staff member, as well as study subjects will be blinded. Tricida will be unblinded when the database for the parent study, TRCA-301, is locked. Eligible subjects who complete the 12-week Treatment Period in Study TRCA-301 may have the option to participate in this extension study. Subjects who discontinue prematurely from Study TRCA-301 will not be eligible for entry in the extension study.

Study periods are as follows:

- Week 12 Visit (1-day screening visit).
- Treatment Period (starting with the Week 12 Visit and continuing for 40 weeks until the Week 52 Visit).
- Follow-up Period (2 weeks after discontinuation of treatment).

After the subject provides informed consent, the subject's eligibility will be evaluated on the basis of laboratory values, vital signs, renal status and pregnancy test (if applicable). Eligible subjects will be treated with TRC101 or placebo once daily (QD) on an out-patient basis for the subsequent 40 weeks (Treatment Period); subjects will continue to receive the same blinded treatment (TRC101 or placebo) that they received in Study TRCA-301. Dosing of oral concomitant medications and study drug will be separated by at least 4 hours.

Study drug dose adjustment and use of oral alkali supplements (for those subjects who were taking them at the Week 12 Visit) is described in the titration algorithm (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. Subjects with a blood bicarbonate level below the normal range (< 22 mEq/L) may have a blinded adjustment of the study drug dose in accordance with the titration algorithm. At any time during the study, the Investigator will evaluate subjects with a confirmed blood bicarbonate level < 12 mEq/L for new acute acidotic processes and discuss them with the Medical Monitor. The Medical Monitor will determine whether the subject may continue in the study.

No addition or dose changes of any other concomitant therapy to raise blood bicarbonate will be allowed. Subjects who enter the study at the Week 12 Visit on an oral alkali supplement will be taken off the supplement if their blood bicarbonate is within the normal range (22 to 29 mEq/L) or above it (> 29 mEq/L),

as described in Appendix 2. If, after removal of alkali supplementation, blood bicarbonate falls below the normal range, the study drug dose will be increased in a step-wise fashion to the maximum daily dose (3 packets). If blood bicarbonate is still below the normal range, the oral alkali therapy the subject was taking at the Week 12 Visit will be re-instated at the same dose the subject was taking at the Week 12 Visit. If the Investigator judges that re-starting alkali treatment poses a safety risk, the risk should be documented. In this situation, alkali will not be re-started.

Subjects will return to the study center for study visits at Weeks 14, 16, 20, 24, 28, 34, 40, 46, and 52 for assessments of safety and durability of effect. Additional unscheduled study visits may be necessary following study drug dose adjustments. Subjects who complete the Treatment Period will enter the 2-week Follow-up Period and return to the study site for two visits: Follow-up 1 (Week 53) and Follow-up 2 (Week 54), for adverse event (AE) 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 52 Visit) will undergo an Early Termination (ET) Visit, during which all Week 52 Visit assessments will be performed, and will be asked to attend Follow-up 1 and 2 Visits in 1 and 2 weeks, respectively. All subjects who discontinue study drug prior to the Week 52 Visit will be contacted by telephone 40 weeks after their Week 12 Visit to ascertain vital status and renal status (i.e., receiving renal replacement therapy or not).

Blood draws for bicarbonate measurements will be performed 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 for a subject is anticipated to be 42 weeks, including the 40-week Treatment Period, and 2-week Follow-up Period. Including the 12-week exposure to study drug in the parent study (TRCA-301), subjects randomized to TRC101 in Study TRCA-301, who complete the Treatment Period in Study TRCA-301E, will have a total of 1-year of exposure to TRC101.

INCLUSION CRITERIA:

1. Have provided written informed consent prior to participation in the study.
2. Have completed the 12-week treatment period and attended the Week 12 Visit in the parent study TRCA-301.
3. Have a blood bicarbonate value of ≥ 12 mEq/L at the Week 12 Visit in Study TRCA-301, based on onsite measurement using the i-STAT point-of-care device.
4. Have adequate peripheral venous access for blood draws.
5. Women who are of childbearing potential must have negative pregnancy test at the Week 12 Visit and be willing to use an acceptable method of birth control 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 the Week 12 Visit that, in the opinion of the Investigator, requires emergency intervention or evaluation for an acute acidotic process.
2. Required dialysis for acute kidney injury or worsening CKD during the parent study TRCA-301.
3. Planned initiation of renal replacement therapy (dialysis or transplantation) within 6 months following study entry.
4. Have a history or current diagnosis of clinically significant diabetic gastroparesis (based on Investigator's judgment) or a history of bariatric surgery.
5. Have a history or current diagnosis of bowel obstruction, swallowing disorders, severe gastrointestinal (GI) disorders, inflammatory bowel disease, major GI surgery, or active gastric/duodenal ulcers.

6. Have a serum calcium ≤ 8.0 mg/dL at the Week 10 Visit in the parent study, TRCA-301.
7. Have active cancer during the 1 year prior to the Week 12 Visit, 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.
8. Inability to consume the study drug, known allergy to the study drug or otherwise comply with the protocol.
9. 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.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Investigational product: TRC101.

Placebo: [redacted] NF Grade.

TRC101 or placebo (up to 3 packets per day) will be self-administered orally as an aqueous suspension, QD, with food, at approximately the same time each day. Concomitant oral medications must be taken at least 4 hours before or after study drug administration. The last dose of study drug will be taken the day before the Week 52 Visit.

SAFETY ASSESSMENTS:

Safety assessments will include AEs, vital signs, physical examination (including body weight), safety laboratory measurements (blood and urine), coagulation (for subjects on vitamin K antagonists or factor Xa inhibitors only), pregnancy test (for woment of childbearing potential only), and electrocardiograms (ECGs).

MAIN ASSESSMENT OF DURABILITY OF EFFECT:

The durability of the effect observed at the end of treatment in the parent study, TRCA-301, will be assessed by blood bicarbonate values.

ENDPOINTS:

Primary Endpoint: Incidence of AEs, SAEs, and AEs leading to withdrawal.

Secondary Endpoints:

1. 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 52 Visit).
2. CFB in blood bicarbonate at the end of treatment (Week 52 Visit).
3. 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 52 Visit).
4. CFB in repeated chair stand test duration at the end of treatment (Week 52 Visit).

STATISTICAL ANALYSES:

This blinded, placebo-controlled extension to Study TRCA-301 will evaluate the long-term safety and durability of effect of TRC101 in subjects with CKD and metabolic acidosis. This study will enroll eligible subjects who completed the 12-week Treatment Period in Study TRCA-301.

The Safety Analysis Set is defined as all subjects who received any amount of TRC101 or placebo in this extension study. A Modified-Intent-to-Treat analysis set is defined as subjects who rolled over to this extension study and had at least one blood bicarbonate assessment after the Week 12 Visit. Time points will be derived based on the date of first dose of study drug in the parent study, TRCA-301. Baseline values are defined as the Baseline values in the parent study, TRCA-301, unless stated otherwise in the Statistical Analysis Plan (SAP).

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

Safety will be summarized as follows: Treatment-emergent AEs (TEAEs) are defined as those occurring with onset at the Week 12 visit + 1 day. Number and percentage of subjects with 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 12-week intervals and during the entire treatment period (Weeks 12 to 52) with the denominator as the number of subjects at risk at the beginning of each interval. Number (%) of subjects with TEAEs leading to discontinuation of study treatment will be summarized similarly by 12-week interval and during the entire treatment period (Weeks 12 to 52). Clinical laboratory test results, vital signs and ECG findings will be summarized using descriptive statistics by time point. Categorical displays (e.g., frequencies, shift tables) and plots of laboratory values over time may also be used, as appropriate. Study drug dosing and dose titration will be summarized by time point. The incidence and frequency of subjects who meet the dose interruption criterion (confirmed blood bicarbonate value > 30 mEq/L) at any time during the Treatment Period will be summarized by 12-week interval with the denominator as the number of subjects at risk at the beginning of each interval.

Durability of effect will be evaluated as follows: The proportions of subjects who meet the responder definition at each protocol-specified time point will be summarized. 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). The difference in proportion (between TRC101 and placebo subjects) and its exact (Clopper-Pearson) 95% confidence interval (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 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. A comparison between the TRC101 group and placebo group with respect to the proportion of responders at Week 52 will be perfomed using Fisher's exact test. A longitudinal mixed-effect model for repeated measures (MMRM) will be used to assess the CFB in bicarbonate level between the TRC101 group and placebo group at each protocol specified time point. A test comparing the least squares (LS) means of CFB in bicarbonate between the TRC101 group and placebo group at Week 52 will be conducted. An analysis of covariance (ANCOVA) model will be used to assess the CFB in total score of KDQOL Question 3 items and in the repeated chair stand test. Additional analyses for durability of effect will be specified in the SAP. If the residuals from the above mentioned models (i.e., MMRM, ANCOVA) are not normally distributed, alternative analyses to deal with non-normality will be used instead. The SAP will specify these analyses.

Analyses will summarize demographic and baseline characteristics, exposure to study drug, dosing compliance, and concomitant medications. The number and percentage of subjects who used prior and/or concomitant medications will be summarized by Anatomic Therapeutic Chemical (ATC) classification levels. Alkali use will be summarized by visit.

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LIST OF ABBREVIATIONS AND ACRONYMS

ADME	absorption, distribution, metabolism, excretion
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
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
CI	confidence interval
CK	creatine kinase
CKD	chronic kidney disease
CNS	central nervous system
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
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GI	gastrointestinal
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
LDL	low density lipoprotein
LS	least squares
MCH	mean corpuscular hemoglobin
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent-to-treat
MMRM	mixed-effect model repeated measures
NOAEL	no observed adverse effect level
pCO_2	partial pressure of carbon dioxide
pO_2	partial pressure of oxygen
PT	preferred term
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
SE	standard error
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)
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 to 39% of CKD Stage 3 – 5 patients (Eustace 2004; Raphael 2014; Moranne 2009). Left untreated, chronic metabolic acidosis can lead to 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 to 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). Hazards 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 in the United States 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 have limited doses of oral sodium bicarbonate to < 2 g per day resulting in modest increases in blood bicarbonate of 2 to 3 mEq/L. The daily doses of sodium bicarbonate required to increase blood bicarbonate levels by 3 to 4 mEq/L in patients with metabolic acidosis are prohibitively high (6 to 8 g per day introducing 1.6 to 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 (HCl) binder for the treatment of metabolic acidosis in patients with CKD. TRC101 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 proton (H^+) and chloride (Cl^-) binding capacity and Cl^- binding selectivity. The high amine content of the polymer is responsible for its high H^+ and Cl^- binding capacity, and the polymer's extensive crosslinking provides size exclusion properties and selectivity for binding Cl^- over other larger competing anions. The TRC101 mechanism of action involves binding of H^+ and Cl^-, resulting in a net reduction and removal of HCl from the GI tract, which results in an increase in serum bicarbonate levels.

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

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

Lack of TRC101 absorption from the GI tract was demonstrated in both rats and dogs administered a single oral dose of [^{14}C]-TRC101. The results of the radiolabeled TRC101 absorption, distribution, metabolism, and excretion (ADME) studies demonstrating a lack of oral bioavailability are consistent with the physicochemical properties of TRC101 (insolubility in aqueous and organic solvents, particle size averaging 100 micrometers in diameter, and particle stability). The studies demonstrated no radioactivity in tissues or organs other than within the GI tract lumen, no radiolabel detectable in the plasma and blood samples indicating absorption, and ≤ 0.02% of radiolabel appearing in the urine or expired air of rats or in the urine of dogs. The level of radioactivity excreted in the urine and/or expired air was consistent with the level of unincorporated radiolabel measured in a water extraction of the radiolabeled polymer. Given the variability of the retrieval method, nearly complete recovery of the radioactive dose from the feces was observed within the first 48 hours after dosing. It can be concluded that TRC101 is not systemically absorbed following oral administration to rats and dogs.

1.3.4 Nonclinical Toxicology

Nonclinical toxicology studies of TRC101 to date include non-GLP 7-day repeat dose oral toxicology studies in rats and dogs, a GLP 33-day and 28-day repeat dose oral toxicology study with a 2-week recovery in rats and dogs, respectively, and a GLP 26-week and 39-week chronic repeat dose oral toxicology interim analysis in the rat and dog, respectively (4-week recovery analysis pending); 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 and GLP definitive embryofetal development (EFD) studies in the rat and the rabbit. No single dose studies were conducted.

In the 26-week GLP study in male and female Wistar Han rats, the animals received oral doses (via dietary admixture) of TRC101 at total daily doses of 0, 0.5, 1 and 2 g/kg/day. The 26-week dosing period was followed by a 4-week post-dose observation period. Assessments were conducted in a cohort of the animals from each dose group after 13 weeks (interim) and 26 weeks (complete dosing period) of test article administration, as well as following the 4-week recovery period. The assessments included all in-life data collected through Week 13 or 26 and postmortem evaluations associated with the necropsies.

No definitive TRC101-related changes were observed in mortality, clinical observations, body weight, or food consumption measurements; ophthalmologic evaluations; clinical pathology parameters (including serum chemistry, hematology, and blood gas); or organ weights, gross necropsy or histopathology at the end of the treatment. TRC101-related findings were limited to minimal, reversible increases in urine pH at all collection intervals in both sexes at 2 g/kg/day in the 33-day study, with a similar but less pronounced trend in males at 0.5 and 1.0 mg/kg/day. The urine pH observation lacked microscopic correlates, was not considered adverse, but was considered a normal homeostatic process to maintain acid base status in the normal rats. The study results indicate that the rats were capable of compensating for the effects of TRC101 on Cl^- excretion and increased bicarbonate levels through increased excretion of excess bicarbonate in the urine.

Since no adverse TRC101-related effects occurred in rats following doses up to 2 g/kg administered for 26 weeks, this dose was identified as the no observed adverse effect level (NOAEL) in male and female rats. This dose level provides a 13-fold safety margin for the highest proposed clinical dose (9 g/day TRC101), based on a 60-kg subject. In the 39-week oral toxicology study in dogs with a 4-week recovery period the animals were administered oral doses (via capsule) of TRC101 at total daily doses of 0, 0.5, 1, and 2 g/kg/day, divided BID. An interim assessment, including all in-life data and postmortem evaluations collected through the 39-week dosing period, was conducted in a cohort of the animals from each dose group. No TRC101-related changes were observed in mortality, clinical observations, body weight, or food consumption measurements; ECG and ophthalmologic evaluations; clinical pathology parameters (including serum chemistry, hematology, and blood gas); or organ weights, gross necropsy, or histopathology. TRC101-related findings were limited to a mild non-adverse increase in urine pH in both males and females at 2 g/kg. An increase in urine pH is consistent with the pharmacology of TRC101 when animals with normal acid-base balance are administered high doses of TRC101. The high dose of 2 g/kg/day (13-fold safety margin for a 9 g/day human dose) was identified as the NOAEL in male and female dogs in the 13-week interim evaluation.

Reproductive toxicology studies demonstrated no effects of TRC101 on embryo-fetal development or maternal reproductive indices; it was also non-teratogenic. The NOAEL for maternal toxicity and embryo-fetal development was the high dose of 2 g/day for both the rat and rabbit. Because TRC101 is not systemically absorbed, 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.

In conclusion, the nonclinical toxicology studies demonstrate that TRC101 has a very low order of toxicity. The repeat dose toxicology studies in the rat and dog assessed local tolerance; histopathological evaluation of the GI tract indicated that TRC101 was generally well tolerated. The genotoxicity studies demonstrate that TRC101 is neither mutagenic nor clastogenic. The embryo-fetal development studies showed no adverse TRC101-related effects on maternal

reproductive function or embryo-fetal parameters, and showed no effects on male or female reproductive organs in the GLP repeat dose toxicology studies in rat and dog.

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.

Study TRCA-101 has been completed, and results are summarized in this section. All subjects enrolled in this long-term safety extension study will have completed the 12-week Treatment Period of the double-blind, placebo-controlled, Phase 3 study TRCA-301.

1.4.1 Study TRCA-101

Study TRCA-101 was conducted 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. It 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 to 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%). As discussed in Section 1.2, since TRC101 does not contain a counterion, TRC101 administration does not result in sodium load and therefore 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) 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 AEs 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.

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; all GI events 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). In addition, there were 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 ($p < 0.0001$).

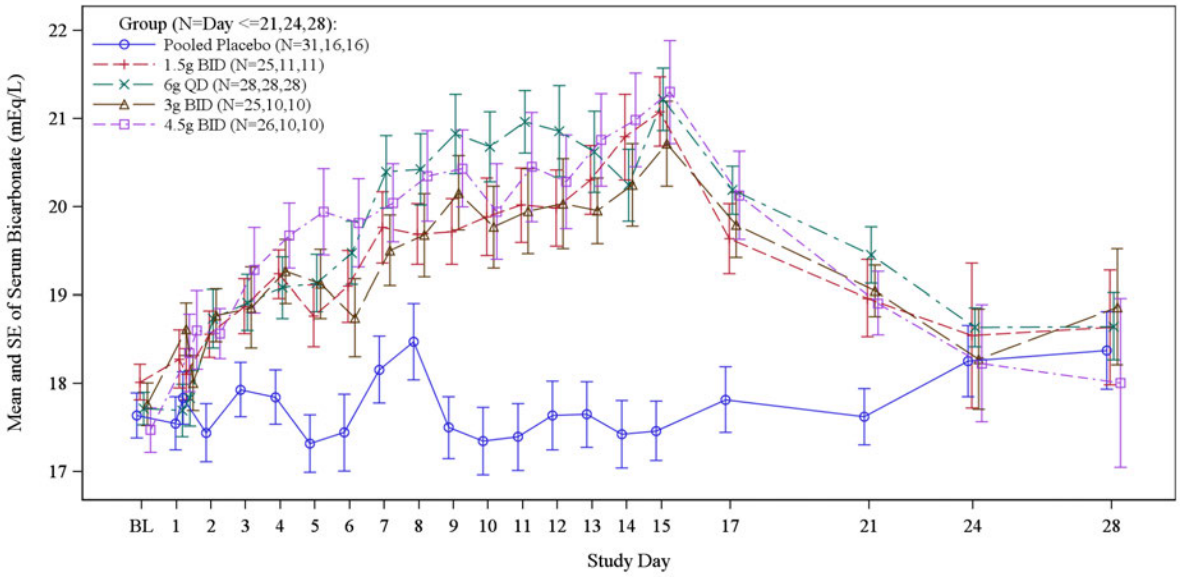
At Day 15, all active doses/dosing regimens evaluated (1.5, 3 and 4.5 g TRC101 BID, and 6 g TRC101 QD) showed statistically significantly ($p < 0.0001$) increased mean serum bicarbonate levels from baseline by approximately 3 – 4 mEq/L and each TRC101 dose increased serum bicarbonate levels to a significantly ($p < 0.0001$) 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, at approximately the same time each day. TRC101 is a high molecular weight, non-absorbed polymer with a site of action in the GI tract; thus, oral administration is the appropriate route. Since doses of 3, 6 and 9 g QD TRC101 will be used in the parent study, TRCA-301, these doses will also be used in this extension study. Placebo QD will be used as a comparator. At each study visit (see Schedule of Events, Appendix 1), blood bicarbonate will be evaluated, and dose(s) of study drug and/or oral alkali supplement (if applicable) will be adjusted as described in Appendix 2 to attempt to maintain bicarbonate in the normal range during the 40-week Treatment Period.

A QD dosing regimen was chosen for this study for consistency with the parent study, TRCA-301. This dosing regimen is more convenient for study subjects than a BID dosing regimen and therefore may result in greater compliance during the 40-week Treatment Period.

The duration of the Treatment Period in this study is 40 weeks so as to provide up to 1 year of continuous exposure data from those subjects who received 12 weeks of treatment with TRC101 in the parent study, TRCA-301.

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

This study is a long-term, blinded, placebo-controlled extension of Study TRCA-301 (the parent study). To have been enrolled in the parent study, subjects must have been non-dialysis dependent CKD patients (eGFR 20 to 40 mL/min/1.73m^2) with chronic metabolic acidosis (blood bicarbonate 12 to 20 mEq/L). At least 50% of subjects must have had a blood bicarbonate level of 12 to 18 mEq/L. Subjects who completed the 12-week Treatment Period in Study TRCA-301 and attended the Week 12 Visit in that study are eligible for enrollment in this extension study if their blood bicarbonate value at the Week 12 Visit is ≥ 12 mEq/L and they meet all other eligbility criteria. Subjects will continue blinded study drug (TRC101 or placebo) treatment in the extension study at a dose based on their blood bicarbonate level as described in Appendix 2.

To make the study generalizable to the intended target population of CKD patients, this study allows the use of common "background" medications taken by patients with CKD and metabolic acidosis (e.g., oral alkali supplements, diuretics, renin angiotensin aldosterone system [RAAS] inhibitors). Restrictions regarding the use of oral alkali therapy are different from those in the parent study, TRCA-301. While both studies allow enrollment of subjects concurrently taking a stable dose of oral alkali, because the primary endpoint measure in Study TRCA-301 is blood bicarbonate level, no changes to concomitant oral alkali are allowed in that study. In contrast, to minimize the long-term sodium load and to allow for management of subjects with eGFR 20 to 40 mL/min/1.73m^2, subjects in this extension study will discontinue background alkali supplementation if their blood bicarbonate is above the lower limit of the normal range (≥ 22 mEq/L; see Appendix 2). Neither Study TRCA-301 nor Study TRCA-301E allows increase in oral alkali supplement dose or initiation of new oral alkali therapy. Investigators will be advised to avoid changing RAAS inhibitor doses during this study, when possible; however, as in the parent study, dose changes necessary for the management of comorbidities or acute events (e.g., hyperkalemia, worsening hyperkalemia) are not prohibited. In addition, Investigators will be advised to avoid changing diuretic doses when possible; however, 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 of TRC101 evaluating the rate of eGFR decline. This study allows the concomitant use of other binder drugs (e.g., lanthanum carbonate, colesevelam, cholestyramine or sodium or calcium polystyrene sulfonate, calcium acetate, sevelamer, patiromer, bixalomer, and other polymeric drugs) with a ≥ 4-hour separation from the study drug dose.

2 STUDY OBJECTIVES

The objectives of this study are to evaluate the long-term safety and durability of effect of TRC101 in CKD patients with metabolic acidosis.

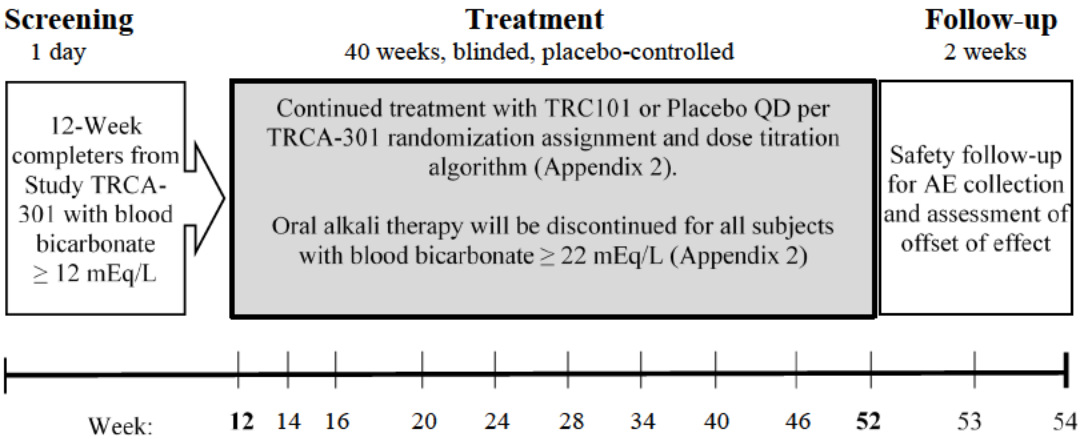
3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This study is a 40-week, blinded, placebo-controlled extension of Study TRCA-301 (a Phase 3, multicenter, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of TRC101 in subjects with CKD and metabolic acidosis). Eligible subjects who complete the 12-week Treatment Period in Study TRCA-301 may have the option to participate in this extension study. Subjects who discontinue prematurely from Study TRCA-301 will not be eligible for entry in this study.

The overall study design is shown in Figure 2.

Figure 2 Study TRCA-301E Study Design Schematic



AE = adverse event; QD = once daily

The study periods are as follows:

- Week 12 Visit (1-day screening visit).
- Treatment Period (starting with Week 12 Visit and continuing for 40 weeks, until Week 52 Visit).
- Follow-up Period (2 weeks after discontinuation of treatment).

After the subject provides informed consent, the subject's eligibility will be evaluated on the basis of laboratory values, vital signs, renal status, and pregnancy test (if applicable). Eligible subjects will continue to be treated with the same study drug they received in the parent study, TRCA-301 (TRC101 or placebo, QD), on an out-patient basis for the subsequent 40 weeks (Treatment Period). The first dose of study drug in this extension study will be taken on the day of the Week 12 Visit, except for those subjects who enter the study

on a dose interruption. Enrollment in Study TRCA-301E is defined by completion of the enrollment procedure in the interactive response technology (IRT) system. The enrollment procedure in the IRT system will be performed once subjects have completed participation in Study TRCA-301, they have provided informed consent for the extension study, and the Investigator (or designee) has determined they have met all TRCA-301E eligibility criteria.

The starting dose of blinded study drug, study drug dose titration, and use of oral alkali supplements (for those subjects who were taking them at the Week 12 Visit), are described in the titration algorithm (Appendix 2). The starting dose of study drug in the 40-week Treatment Period will be the same as the ending dose of study drug in Study TRCA-301, unless the subject meets the criteria for a dose adjustment at the Week 12 visit as described in Appendix 2.

Subjects will return to the study center for study visits at Weeks 14, 16, 20, 24, 28, 34, 40, 46, and 52 for assessments. Additional unscheduled study visits may be necessary following study drug dose adjustments.

Subjects with a confirmed blood bicarbonate level < 12 mEq/L at any time during the study 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.

No addition or up-titration of any other concomitant therapy to raise blood bicarbonate will be allowed. Subjects who enter the study at the Week 12 Visit on an oral alkali supplement will be taken off the supplement if their blood bicarbonate is within or above the normal range as described in Appendix 2. If, after removal of alkali supplementation, blood bicarbonate falls below the normal range, the study drug dose will be increased in a step-wise fashion to the maximum dose of 3 packets QD and, if blood bicarbonate is still below normal, the oral alkali therapy the subject was taking at the Week 12 Visit will be re-instated at the same dose the subject was taking at the Week 12 Visit. If the Investigator judges that re-starting alkali treatment poses a safety risk, the risk should be documented. In this situation, alkali will not be re-started.

Dosing of oral concomitant medications and study drug will be separated by at least 4 hours throughout the Treatment Period in this study.

Subjects who complete the Treatment Period will enter the 2-week Follow-up Period and return to the study site for two visits: Follow-up 1 (Week 53) and Follow-up 2 (Week 54), for adverse event (AE) collection, fasting blood draws and safety assessments as outlined in the Schedule of Events. Subjects who withdraw from the study prematurely (i.e., prior to the Week 52 Visit) will undergo an Early Termination (ET) Visit, during which all Week 52 Visit assessments will be performed, and will attend Follow-up 1 and 2 Visits in 1 and 2 weeks, respectively. Subjects who discontinue study drug prior to the Week 52 Visit will

be contacted by telephone 40 weeks after their Week 12 Visit to ascertain vital status and renal status (i.e., receiving renal replacement therapy or not).

Blood draws for bicarbonate measurements will be performed when subjects are in a fasted state (at least 4 hours) and at approximately the same time of day for each subject.

Assessments will be performed at the time points indicated in the Schedule of Events (Appendix 1). Safety assessments will include: 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. The main assessment to evaluate the durability of effect of TRC101 will be blood bicarbonate level.

3.2 Rationale for Study Design and Control Group

3.2.1 Study Design

The purpose of this study is to define the long-term safety profile of TRC101 and to evaluate the durability of its effect. The study is a 40-week, blinded, placebo-controlled extension that will enroll subjects who complete the randomized, double-blind, placebo-controlled, Phase 3 study, TRCA-301 (the parent study). After the last subject completes the parent study and the TRCA-301 clinical database is locked, Tricida personnel and the blinded statistical group (i.e., not associated with the Data Monitoring Committee [DMC]) will become unblinded to treatment assignment. Importantly, all Investigators, subjects, site personnel and CRO personnel who were blinded in the parent study, TRCA-301, will remain blinded until the clinical database is locked for this extension study.

Please see Section 1.5 for a discussion of the rationale for the starting study drug dose, study drug dose titration regimen and algorithm for discontinuing concomitant oral alkali supplements in subjects who are taking them at the Week 12 Visit. Please see Section 1.6 for a discussion of the rationale for the blood bicarbonate inclusion criteria for this extension study.

3.2.2 Safety Monitoring

The design and conduct of TRCA-301E includes appropriate monitoring for safety and risk mitigation. The Medical Monitor will review 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.

A DMC, established for the parent study, TRCA-301, will continue to review safety during this 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 frequency, format and structure of DMC meetings,

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 preparing the Statistical Analysis Plan (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 (this group will become unblinded when the clinical database for parent study, TRCA-301, is locked).

TRC101, which is a high molecular weight, counterion-free polymer, 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 the study drug dose will be interrupted if blood bicarbonate is confirmed to be > 30 mEq/L. Study TRCA-101 has shown 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, the parent study, TRCA-301, excludes patients with higher risk of inhibition of respiratory response to metabolic acidosis (i.e., chronic obstructive pulmonary disease that is treated with chronic oral steroids, that requires the subject to be on oxygen, or that required hospitalization within the previous 6 months).

Investigators are to 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 42 weeks per subject, including the 40-week Treatment Period and 2-week Follow-up Period. Including the 12-week exposure to study drug in the parent study, TRCA-301, subjects randomized to TRC101 in Study TRCA-

301 who complete the Treatment Period in Study TRCA-301E will have a total of 1-year of exposure to TRC101.

4 STUDY POPULATION SELECTION AND WITHDRAWAL

4.1 Study Population

This study will enroll subjects with non-dialysis dependent CKD and a blood bicarbonate value of ≥ 12 mEq/L who completed the 12-week Treatment Period in Study TRCA-301 (the parent study) and attended the Week 12 Visit. Study TRCA-301 was designed to enroll approximately 210 male and female adult subjects 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 in the parent study were required to 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 safety extension study.

1. Have provided written informed consent prior to participation in the study.
2. Have completed the 12-week treatment period and attended the Week 12 Visit in the parent study TRCA-301.
3. Have a blood bicarbonate value of ≥ 12 mEq/L at the Week 12 Visit in Study TRCA-301, based on onsite measurement using the i-STAT point-of-care device.
4. Have adequate peripheral venous access for blood draws.
5. Women who are of childbearing potential must have negative pregnancy test at the Week 12 Visit and be willing to use an acceptable method of birth control 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 this study.

1. Have any level of low blood bicarbonate at the Week 12 Visit that, in the opinion of the Investigator, requires emergency intervention or evaluation for an acute acidotic process.

2. Required dialysis for acute kidney injury or worsening CKD during the parent study TRCA-301.
3. Planned initiation of renal replacement therapy (dialysis or transplantation) within 6 months following study entry.
4. Have a history or current diagnosis of clinically significant diabetic gastroparesis (based on Investigator's judgment) or a history of bariatric surgery.
5. Have a history or current diagnosis of bowel obstruction, swallowing disorders, severe gastrointestinal (GI) disorders, inflammatory bowel disease, major GI surgery, or active gastric/duodenal ulcers.
6. Have a serum calcium ≤ 8.0 mg/dL at the Week 10 Visit in the parent study, TRCA-301.
7. Have active cancer during the 1 year prior to the Week 12 Visit, 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.
8. Inability to consume the study drug, known allergy to the study drug or otherwise comply with the protocol.
9. 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.

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, if possible, and recorded appropriately in source documents and the electronic case report form (eCRF). Subjects withdrawn from the study prematurely, for reasons other than withdrawn consent, will be followed for safety for 2 weeks after receiving the last dose of study drug. All subjects who discontinue study drug dosing prior to the Week 52 Visit will be contacted by telephone 40 weeks after their Week 12 Visit to ascertain vital status and renal status (receiving renal replacement therapy or not). 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 their 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 that, 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 for more than 1 week or underwent renal transplantation.
- Pregnancy. These subjects will be followed until the outcome of pregnancy is known and if subject agrees (see Section 6.11).

Subjects with a confirmed blood bicarbonate level < 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. Subjects should be maintained on their study drug dose pending discussion with Medical Monitor.

Subjects who withdraw from the study prematurely prior to the Week 52 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 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 will be performed (Section 7.7) if possible. Every reasonable effort will be made to contact a subject who fails to attend a Study Visit, or does not respond by telephone, 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. 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, which consists of [redacted], National Formulary (NF) Grade, is packaged in labeled packets.

5.1.3 Study Drug Dispensing, Packing and Labeling

Study drug is shipped and dispensed in cartons (kits). Each invidual kit of study drug has a unique number and contains either 8 labelled packets of TRC101 or placebo. Each study drug kit is labeled and secured with a tamper evident seal. TRC101 and placebo kits 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 designated study staff member") according to the subject's treatment assignment in the parent study, TRCA-301. The exact dispensing instructions will be provided to the designated study staff member by the interactive response technology (IRT) system.

The designated study staff member 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

All subjects will initially receive TRC101 or placebo at a dose determined by their ending dose in the parent study, TRCA-301, and the subject's blood bicarbonate level at the Week 12 Visit (see Appendix 2). The doses of TRC101 to be administered in this study are: 0, 3, 6 and 9 g QD, corresponding to 0, 1, 2 and 3 packets of blinded study drug. Placebo will also be administered in doses of 0, 1, 2 and 3 packets. Either upon enrollent into the study or during the study, the blinded study drug may be interrupted per the titration algorithm.

TRC101 or placebo will be self-administered orally as an aqueous suspension, QD, with food, at approximately the same time each day for 40 weeks.

The Investigator will designate a study staff member to dispense and account for study drug. The first dose of study drug will be self-administered on the day of the Week 12 Visit.

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

The last dose of study drug will be taken the day before the Week 52 Visit.

5.3 Dosing Regimen

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

Subjects who completed the 12-week Treatment Period in Study TRCA-301 and attended the Week 12 Visit may enroll in this extension study if their blood bicarbonate value at the Week 12 Visit is ≥ 12 mEq/L and they meet the other entry criteria for this study (see Sections 4.2 and 4.3). Eligible subjects will start the extension study on a study drug dose based on their ending dose in the parent study, TRCA-301, and their blood bicarbonate level at the Week 12 Visit (see Appendix 2).

Blood bicarbonate will be evaluated periodically (see Schedule of Events, Appendix 1), and dose(s) of study drug and/or oral alkali supplement (if applicable) adjusted as described in Appendix 2 to maintain blood bicarbonate in the normal range. In general, the study drug dose will not be titrated if blood bicarbonate is in the normal range. 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 and the subject is still within the Treatment Period, study drug will be re-started at a lower dose in accordance with the titration algorithm (see Appendix 2).

The Medical Monitor must be notified within 24 hours of confirmation of a bicarbonate value > 30 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.

No addition or up-titration of any concomitant therapy to raise blood bicarbonate will be allowed. Subjects who enter the study on an oral alkali supplement will be taken off the supplement if their blood bicarbonate is ≥ 22 mEq/L as described in Appendix 2. If, after removal of alkali supplementation, blood bicarbonate falls below the normal range, the study drug dose will be increased in a step-wise fashion to the maximum dose of 3 packets QD and, if blood bicarbonate is still below normal, the same oral alkali therapy the subject was taking at the Week 12 Visit will be re-instated at the same dose the subject was taking at the Week 12 Visit. If the Investigator judges that re-starting alkali treatment poses a safety risk, the risk should be documented. In this situation, alkali will not be re-started.

5.4 Missed Doses

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

5.5 Selection and Timing of Dose for Each Subject

Subjects will continue to receive the study drug (TRC101 or placebo) to which they were randomized in the parent study, TRCA-301. The dose of study drug will be adjusted in a blinded fashion based on blood bicarbonate level as described in Appendix 2. Study drug will be administered as an oral suspension in water with food, QD, at approximately the same time each day, from the Week 12 Visit through 1 day prior to the Week 52 Visit. If a dose of study drug is adjusted, the subject will start the new dose at the time of the next dose.

5.6 Method of Assigning Subjects to Treatment Groups

Subjects will remain in the same treatment group (TRC101 or placebo) to which they were assigned in Study TRCA-301.

5.7 Blinding

As in Study TRCA-301, in this study [redacted] an unblinded study staff member for handling (dispensation and collection) of the study drug. These individuals will be responsible for dispensing study drug and collecting used and unused study drug containers. If the 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 TRC101 and placebo treatment groups. The unblinded study staff member will 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 electronic case report forms (eCRFs). The subjects, Investigators, 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 be blinded to the subject's treatment assignment. To avoid unblinding of blinded site personnel to treatment assignment, strict blinding procedures related to drug accountability will be adhered to at the site level for this study, similar to those utilized for the parent study. Specifically, designated site staff, who have no other responsibilities for the study, will be responsible for study drug accountability and collection of used and unused study drug. The division of responsibilities between the unblinded staff and other study staff (who are blinded to treatment assignment in the parent study, TRCA-301) are detailed in the study Blinding Plan.

After the last subject completes the parent study and the TRCA-301 clinical database is locked, Tricida personnel and the blinded statistical group (i.e., not associated with the Data Monitoring Committee) will become unblinded to treatment assignments. Importantly, all

Investigators, subjects, site personnel and CRO personnel who were blinded in the parent study, TRCA-301, will remain blinded until the clinical database is locked for this extension study.

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 the 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 concomitant medications (including prescription, over-the-counter, herbal and naturopathic remedies, etc.) will be collected for this extension study beginning at the Week 12 Visit and continuing for the duration of the study (including ET) through 2 weeks following Week 52 for subjects completing the study and through 2 weeks following the ET visit for subjects discontinuing study drug treatment prior to Week 52. A therapy will be considered a concomitant medication if it is administered at any time after the Week 12 Visit and before the completion of the final study visit.

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 Treatment and Follow-up Periods), such medication(s), or the new doses, and the 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 Week 12 Visit should adhere to restrictions as described in Table 1. The rationale for the restrictions on concomitant medications is provided in Section 1.6.

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.

If a change in antihypertensive drug is required, the Investigator should, if possible, avoid adding or changing the doses of medications that cause changes in serum electrolytes (e.g., diuretics and RAAS inhibitors); however, dose changes of these types of medications necessary for the management of comorbidities or acute events (e.g., hyperkalemia or worsening hyperkalemia, heart failure, acute kidney injury) are not prohibited.

Table 1 Restricted Prior and Concomitant Medications

Drug or Drug Class	Week 12 Visit	During the Study
Investigational medications	Not allowed	Not allowed
Potassium binders (Veltassa [patiromer], Kaexalate (sodium polystyrene sulfonate])	Not allowed	Use is allowed with dose separation window of ≥ 4 h from the study drug dose
Other polymeric binder drugs [a]	Not allowed	Use is allowed with dose separation window of ≥ 4 h from the study drug dose
Sodium bicarbonate, potassium citrate, sodium citrate or other alkali therapy	Stable dose	No initiation of new alkali therapy or alkali dose increases beyond the Week 12 Visit dose. Instructions for discontinuation and re-starting the original dose is provided in Appendix 2
Non-ophthalmic carbonic anhydrase inhibitors [b]	Stable dose	Keep dose stable, if possible
Antacids, H2-blockers, proton pump inhibitors, calcium supplements [c]	Stable dose	Keep dose stable, if possible
RAAS inhibitors [d]	Stable dose	Keep dose stable, if possible, but dose changes necessary for the management of comorbidities or acute events (e.g., hyperkalemia/worsening hyperkalemia) are not prohibited
Diuretics [e]	Stable dose	Keep dose stable, if possible, but dose changes necessary for the management of comorbidities or acute events (e.g., heart failure, acute kidney injury) are not prohibited

"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 Week 12 dose is considered "stable".

[a] Lanthanum carbonate, colesevelam, cholestyramine, sevelamer, bixalomer, and other polymeric drugs.

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

[c] 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).

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

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

5.10 Restrictions

5.10.1 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.

5.10.2 Management of Acidemia (Use of Alkali Therapy)

Subjects may be on a stable dose of oral alkali therapy in this study; however, this dose must be kept the same as at the Week 12 Visit 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 unblinded study staff member will assess subjects' treatment compliance at every study visit during the 40-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). 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 unblinded study staff member 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 designated study staff only. Study drug must be stored at room temperature (15 to 25 °C).

Site personnel 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 study visit during the Treatment Period. All study drug containers (including used, empty, unused, and expired) 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. Week 12 study procedures that are outlined in the parent study protocol, TRCA-301, will be performed under the parent study ICF.

6.2 Concomitant Medications

Information on concomitant medications (including prescription, over-the-counter, herbal and naturopathic remedies, etc.) will be collected at the Week 12 Visit (as part of the parent study, TRCA-301) and will continue to be collected for the duration of this study. The Investigator or qualified designee will record all findings in source documents and on the concomitant medications eCRF.

6.3 Vital Signs

The Investigator or qualified designee will measure vital signs (systolic/diastolic blood pressure, respiratory rate, heart rate and temperature) at time points specified in the Schedule of Events (Appendix 1). The vital sign measurements performed at the Week 12 Visit will be conducted as part of the parent study, TRCA-301. 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.

6.4 Complete Physical Examination, Including Body Weight

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). The physical examination performed at the Week 12 Visit will be conducted as part of the parent study, TRCA-301. 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.

6.5 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 Week 12 Visit will be conducted as part of the parent study, TRCA-301. 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.

6.6 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 KDQOL assessment at the Week 12 Visit will be conducted as part of the parent study, TRCA-301. The procedure details are provided in the Study Reference Manual.

6.7 12-Lead Electrocardiograms

During the study, 12-lead ECGs will be performed at the time points indicated in the Schedule of Events (Appendix 1). The ECG performed at the Week 12 Visit will be conducted as part of the parent study, TRCA-301. If a subject has serum potassium $\geq$ 6.0 mEq/L at any time, ECGs will be collected more often, as clinically needed, until serum potassium is < 6.0 mEq/L.

The subject must be in 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 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 6.10.1) should be recorded on the AE eCRF.

6.8 Clinical Laboratory Tests

6.8.1 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). Laboratory assessments performed at the Week 12 Visit will be conducted as part of the parent study, TRCA-301. The blood 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 specimens will be brought to the clinic at the visits specified in the Schedule of Events (Appendix 1). Twenty-four hour urine collections will be done by subjects one day prior to the specified visits. The 24-hour urine test at the Week 12 Visit will be conducted as part of the parent study, TRCA-301.

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
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, 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
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
Hemoglobin A1c	Glycated hemoglobin	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.

Table 2 Laboratory Parameters (cont'd)

Test Type	Analytes	Comments
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.
Pregnancy test	β-HCG	Conducted at central laboratory (serum pregnancy test) Urine dipstick at study site at the Week 12 Visit only

* Cystatin C will be measured at the Week 12 and Week 52/ET Visits only

ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-HCG = beta human chorionic gonadotropin; BSAP = bone-specific alkaline phosphatase; BUN = blood urea nitrogen; BE = base excess; CK = creatine kinase; CTX = C-terminal telopeptide; eGFR = estimated glomerular filtration rate; ET-1 = urine endothelin-1; 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; NTX = N-terminal telopeptide; O_2 = oxygen, P1NP = type 1 procollagen; RBC = red blood cell; RDW = red cell distribution width; SO_2 = oxygen saturation; TCO_2 = total carbon dioxide; TRAP-5b = tartate-resistant acid phosphatase 5b; UAGT = urine angiotensinogen to creatinine ratio

6.9 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.

6.10 Adverse Events

6.10.1 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 for Study TRCA-301 (see Section 6.10.4.1).

- 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 not 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).

6.10.2 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.

6.10.3 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.

6.10.4 Procedures for Eliciting, Recording and Reporting Adverse Events

6.10.4.1 Adverse Event Reporting Period

AEs, including SAEs, will be collected throughout the study period, beginning from the time of enrollment until the completion of the last study visit assessments (2 weeks after the Week

52 visit for subjects who complete the study and until 2 weeks after the ET visit for subjects who discontinue study drug prematurely). For subjects who do not undergo an ET visit following early discontinuation of study drug, the AE reporting period will end 2 weeks after the last dose of study drug. 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 day after the Week 12 Visit .

6.10.4.2 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.

6.10.4.3 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 6.10.2 (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).

6.10.4.4 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.

6.10.4.5 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.

6.10.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments

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 enrollment into this study 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.

6.10.6 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 eCRF 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 6.10.2)
- 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.

6.10.6.1 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.

6.10.6.2 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. 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).

6.11 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. Since Week 12 Visit values will be used to determine eligibility in this study, no re-screening is allowed.

7.1 Week 12 Visit

Following completion of the assessments required at the Week 12 Visit in the parent study, TRCA-301, subjects who meet eligibility criteria may be enrolled in this extension study. 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 if this has not already been done prior to this visit (must be done prior to any procedures required only for this extension study)
- Evaluate eligibility (inclusion and exclusion) criteria
- Obtain urine sample for urine dipstick pregnancy test (for women of childbearing potential only)
- Determine whether any changes to oral alkali supplementation are required for subjects taking them using titration algorithm in Appendix 2
- Dispense study drug per IRT assignment [to be done by the designated study staff only]
- Schedule next study visit

The following Week 12 Visit assessments, procedures and laboratory tests will be performed for the parent study, TRCA-301:

- Record concomitant medications
- Collect vital signs (blood pressure [in triplicate], heart rate, temperature, and respiratory rate [in triplicate]).
- Perform complete physical examination, including body weight
- Perform repeated chair stand test
- Collect answers to KDQOL questions
- Record ECG (triplicate)
- 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 the central laboratory: serum chemistry panel, hematology panel, blood biomarker panel, hemoglobin A1c, and serum pregnancy test (for women of childbearing potential only)
- Obtain urine for the following assessments at the 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, assess dosing compliance and perform drug accountability [to be done by the Pharmacist only]
- Record AEs
- Dietary counseling

7.2 Week 14 Visit

The allowed visit window is ± 4 days. The following procedures and assessments will be performed. 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 the following assessments at the central laboratory: serum chemistry panel

- Determine whether any changes to oral alkali supplementation are required for subjects who were taking them at the Week 12 Visit using titration algorithm in Appendix 2
- Dispense study drug per IRT assignment [to be done by the designated study staff only]
- Collect used and unused study drug containers since the previous visit, assess dosing compliance and perform drug accountability [to be done by the designated study staff only]
- Record AEs
- Schedule the next study visit

7.3 Week 16 and Week 46 Visits

The allowed visit windows are: ± 4 days for Week 16 and ± 7 days for Week 46. The following procedures and assessments will be performed. 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 the following assessments at the central laboratory: serum chemistry panel and serum pregnancy test (for women of childbearing potential only).
- **At Week 46 Visit only:** provide instruction on collecting 24-hour urine sample starting one day prior to the Week 52 Visit and dispense necessary supplies
- Determine whether any changes to oral alkali supplementation are required for subjects who were taking them at the Week 12 Visit using titration algorithm in Appendix 2
- Dispense study drug per IRT assignment [to be done by the designated study staff only]
- Collect used and unused study drug containers since the previous visit, assess dosing compliance and perform drug accountability [to be done by the designated study staff only]
- Record AEs
- Schedule the next study visit

7.4 Week 20 and Week 40 Visits

The allowed visit windows are: ± 4 days for Week 20 and ± 7 days for Week 40. The following procedures and assessments will be performed. Subjects must present to these visits in a fasted state.

- Record concomitant medications
- Collect vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- **At Week 40 Visit only:** perform repeated chair stand test
- **At Week 40 Visit only:** collect answers to KDQOL questions
- 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 the central laboratory: serum chemistry panel, hematology panel, and serum pregnancy test (for women of childbearing potential only)
- Obtain urine for the following assessments at the central laboratory: spot urine and urinalysis
- Determine whether any changes to oral alkali supplementation are required for subjects who were taking them at the Week 12 Visit using titration algorithm in Appendix 2
- Dispense study drug per IRT assignment [to be done by the designated study staff only]
- Collect used and unused study drug containers since the previous visit, assess dosing compliance and perform drug accountability [to be done by the designated study staff only]
- Record AEs
- Dietary counseling
- Schedule the next study visit

7.5 Week 24 and Week 34 Visits

The allowed visit windows are: ± 4 days for Week 24 and ± 7 days for Week 34. The following procedures and assessments will be performed. Subjects must present to these visits in a fasted state.

- Record concomitant medications
- Collect vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Record 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 the central laboratory: serum chemistry panel and serum pregnancy test (for women of childbearing potential only)
- Determine whether any changes to oral alkali supplementation are required for subjects who were taking them at the Week 12 Visit using titration algorithm in Appendix 2
- Dispense study drug per IRT assignment [to be done by the designated study staff only]
- Collect used and unused study drug containers since the previous visit, assess dosing compliance and perform drug accountability [to be done by the designated study staff only]
- Record AEs
- Schedule the next study visit

7.6 Week 28 Visit

The allowed visit window is ± 7 days. The following procedures and assessments will be performed. Subjects must present to these visits in a fasted state.

- Record concomitant medications
- Collect vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Perform complete physical examination, including body weight
- 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 the central laboratory: serum chemistry panel, hematology panel, and serum pregnancy test (for women of childbearing potential only)
- Obtain urine for the following assessments at the central laboratory: spot urine and urinalysis
- Determine whether any changes to oral alkali supplementation are required for subjects who were taking them at the Week 12 Visit using titration algorithm in Appendix 2
- Dispense study drug per IRT assignment [to be done by the designated study staff only]

- Collect used and unused study drug containers since the previous visit, assess dosing compliance and perform drug accountability [to be done by the designated study staff only]
- Record AEs
- Schedule the next study visit

7.7 Week 52 or Early Termination (ET) Visit

The Week 52 visit will occur no earlier than the 1-year anniversary of the Day 1 Visit in the parent study TRCA-301. The following assessments will be performed at the Week 52 Visit for subjects who completed the entire Treatment Period (allowed visit window is + 7 days) or the 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 the day before the Week 52 Visit.

- Record concomitant medications
- Collect vital signs (blood pressure [in triplicate], heart rate, temperature, and respiratory rate [in triplicate])
- Perform complete physical examination, including body weight
- Record ECG (triplicate)
- Perform repeated chair stand test
- Collect answers to KDQOL questions
- 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 the central laboratory: serum chemistry panel, hematology panel, blood biomarker panel, hemoglobin A1c, and serum pregnancy test (for women of childbearing potential only)
- Obtain urine for the following assessments at the 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, assess dosing compliance and perform drug accountability [to be done by the designated study staff only]
- Record AEs
- Dietary counseling
- Schedule the next study visit

- All subjects who discontinue study drug prior to Week 52 will be contacted by telephone 40 weeks after their Week 12 Visit to ascertain vital status and renal status (i.e., receiving renal replacement therapy or not).

7.8 Follow-up 1 Visit (Week 53)

The allowed visit window is ± 2 days for all visits during the Follow-up Period. The following assessments will be performed. 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 the following assessments at the central laboratory: serum chemistry panel
- Record AEs
- Schedule the next study visit

7.9 Follow-up 2 Visit (Week 54)

The allowed visit window is ± 2 days for all visits during the Follow-up Period. The following assessments will be performed. 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 the central laboratory: serum chemistry panel, hematology panel, and serum pregnancy test (for women of childbearing potential only)
- Obtain urine for the following assessments at the central laboratory: spot urine and urinalysis
- Record AEs

7.10 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 to +3 days. 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, including body weight
- Record 12-lead ECG (triplicate)
- 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. Blood bicarbonate testing should be performed using the i-STAT device.
- Determine whether any changes to oral alkali supplementation are required for subjects who were taking them at the Week 12 Visit using titration algorithm in Appendix 2
- Perform study drug accountability and dispensation per IRT assignment (if applicable) [to be done by the designated study staff only]
- Record AEs
- Dietary counseling

7.11 End-of-Study

End-of-Study is defined as completion of the Follow-up 2 (Week 54) Visit. For those subjects who withdrew prematurely from the study, end-of-study and the premature termination date are defined as the date of the subject's last data collection.

Subjects who complete the 40-week Treatment Period (Week 52 Visit) are considered to have completed the study even if they did not return for the follow-up visits.

Subjects who discontinue study drug treatment prior to Week 52 will be contacted by telephone to determine vital status and renal status (i.e., receiving renal replacement therapy or not). AE, SAE and concomitant medication data collection will stop after the Follow-up 2 Visit.

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 statistical 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. If the methods of the SAP and those in this section do not agree, the SAP prevails.

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 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 time point, as applicable, using frequency counts and percentages.

8.2 Determination of Sample Size

No sample size calculation was performed, since this is an extension to Study TRCA-301 into which eligible patients who choose to participate will be enrolled.

8.3 Analysis Populations

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

Safety analysis set:	All subjects who received any amount of study drug in this extension Study TRCA-301E.
Modified intent-to-treat (MITT) analysis set	Subjects who rolled over to this extension Study TRCA-301E and had at least one blood bicarbonate assessment after the Week 12 Visit.

8.4 Reference Date and Baseline

Time points will be based on the date of first dose of study drug in Study TRCA-301 (the parent study). Baseline values are defined as the Baseline value in Study TRCA-301, unless stated otherwise in the SAP.

8.5 Demographics and Baseline Characteristics

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

8.6 Statistical Analysis of Durability of Effect

Primary durability of effect will be evaluated using the MITT analysis set based on the randomized treatment group assignment. Number and proportion (expressed in 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 two-sided significance level of 0.05.

8.6.1 Durability of Effect Variable

The analysis for durability of effect will include blood bicarbonate results that will be collected at Week 12 Visit through the end of the 40-week treatment from the i-STAT device. The i-STAT blood bicarbonate data will be used to determine the CFB in bicarbonate over time. Baseline blood bicarbonate is defined as the mean of the bicarbonate values collected at Screening visits and on Day 1 pre-dose in Study TRCA-301 (the parent study). CFB in blood bicarbonate will be calculated for each time point subsequent to the Week 12 Visit. Descriptive statistics will be provided for all scheduled time points.

8.6.2 Durability of Effect Endpoints

Durability of Effect Endpoints are:

1. 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 52 Visit).
2. CFB in blood bicarbonate at the end of treatment (Week 52 Visit).
3. CFB in the total score of the KDQOL Question 3 items (daily activities) at the end of treatment (Week 52 Visit).
4. CFB in repeated chair stand test duration at the end of treatment (Week 52 Visit).

8.6.3 Analysis of Durability of Effect

The number and proportions (expressed as percentages) of subjects who are responders at each time point and at the end of treatment (Week 52) 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 proportion of subjects who are responders and the exact 95% CIs of the proportion will also be presented by treatment group and time point. A comparison between the the TRC101 group and the placebo group with respect of the proportion of responders at Week 52 will be perfomed using Fisher's exact test.

A longitudinal mixed-effect model for repeated measures (MMRM) will be used to analyze the CFB in bicarbonate. The model will include the CFB in bicarbonate as the dependent variable, treatment, time point (Weeks 12, 14,…, 52), and treatment by time point interaction as fixed effects, subject as a random effect, and the baseline bicarbonate and baseline eGFR as continuous covariates. An unstructured covariance structure will be used. The least squares (LS) mean of CFB in bicarbonate, standard error of the 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), standard error (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. A test comparing the LS means of CFB in blood bicarbonate between treatment groups will be conducted at the end of treatment (Week 52 Visit).

An analysis of covariance (ANCOVA) model will be used to assess the CFB in total score of KDQOL and in the repeated chair stand test. The model will include the CFB value as the dependent variable, treatment as a fixed effect, and the baseline value as a covariate. The least squares (LS) mean of CFB value, standard error of LS mean, and two-sided 95% CIs of the LS mean from the ANCOVA model will be reported by 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 ANCOVA model will be reported.

In order to evaluate the potential effect of missing data on the durability of effect, sensitivity analyses for responders will be performed using multiple imputation models under a MNAR assumption for the MITT analysis set. The SAP will describe these additional analyses.

If the residuals from the above mentioned models (i.e., MMRM, ANCOVA) are not normally distributed, alternative analyses to deal with non-normality will be used instead. The SAP will specify these analyses.

8.7 Safety Analysis

Safety will be summarized for subjects in the safety analysis set. The following will be summarized by 12-week interval with denominator as the number of subjects at risk at the beginning of each interval: 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. The number (%) of subjects with TEAEs leading to discontinuation of study treatment will also be summarized similarly by 12-week interval. Subjects will be counted

only once at each interval, SOC and PT level of summary. Clinical laboratory test results, vital signs and ECG findings will be summarized using descriptive statistics by time point. Categorical display methods (e.g., frequencies, shift tables) and plots of laboratory values over time may also be used, as appropriate. Blood bicarbonate values and their change from Baseline values will be descriptively summarized by time point. The incidence and frequency of subjects who meet the dose interruption criterion (confirmed blood bicarbonate > 30 mEq/L) at any time during the Treatment Period will be summarized by 12-week interval with the denominator as the number of subjects at risk at the beginning of each interval. Worsening or newly observed clinically significant physical examination findings will be reported as adverse events.

8.8 Other Assessments or Analyses

Exposure to study drug, dosing compliance, and concomitant medications will be summarized. Alkali use will be summarized by visit. The number and percentage of subjects who used prior and/or concomitant medications will be summarized by Anatomic Therapeutic Chemical (ATC) classification levels and 12-week interval with denominator as the number of subjects at risk at the beginning of each interval. At each time interval and 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 study drug.

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 electronic case report form (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 electronic data capture (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 through programmed quality checks and manually through review of data listings by Tricida and its designee. Data that appear inconsistent, incomplete, or inaccurate will be queried for clarification be the site. 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 important protocol deviations for use in the statistical analysis.

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 for sites in the European Union and all other applicable local and national laws and regulations governing the conduct of human clinical studies.

11.2 Institutional Review Board / Independent Ethics Committee

All Investigators participating in this study must be governed under an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (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 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	W12	W14	W16	W20	W24	W28	W34	W40	W46	W52/ET [a]	F1	F2	Visit [q]
	Timing	Week 12	Week 14	Week 16	Week 20	Week 24	Week 28	Week 34	Week 40	Week 46	Week 52/ET	Week 53	Week 54	
Informed Consent		X												
Eligibility Criteria		X												
Concomitant Medications		X [b]	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs [c]		X [b]	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight		X [b]					X				X		X	X
Physical Exam [d]		X [b]					X				X			X
Repeated Chair Stand Test		X [b]							X		X			
KDQOL Question 3		X [b]							X		X			
ECG [e]		X [b]				X		X			X		X	X
Fasting i-STAT Bicarbonate [f]		L [b]	L	L	L	L	L	L	L	L	L	L	L	L
Fasting Blood Bicarbonate (Enzymatic Serum or Venous Blood Gas Assay) [g]		L [b]	L	L	L	L	L	L	L	L	L	L	L	L
Fasting Serum Chemistry		C [b]	C	C	C	C	C	C	C	C	C	C	C	C
Coagulation [h]		L [b]	L	L	L	L	L	L	L	L	L	L	L	L
Pregnancy Test [i]		C [b], L		C	C	C	C	C	C	C	C		C	C
Hematology		C [b]			C		C		C		C		C	C
Hemoglobin A1c		C [b]									C			C
Biomarkers (Blood and Urine) [j]		C [b]									C			
Urinalysis and Spot Urine Tests		C [b]			C		C		C		C		C	C
Training on 24-Hour Urine Collection and Dispensing Supplies										X				
24-Hour Urine Collection [k]		C [b]									C			
Dispensation of Study Drug [l]		X	X	X	X	X	X	X	X	X				X
Discontinue/Re-start Oral Alkali Supplement for Subjects Taking it at Week 12 Visit per Appendix 2 [m]		X	X	X	X	X	X	X	X	X				X
Daily Self-Administration of Study Drug		X [n]												
Study Drug Dosing Compliance and Accountability [o]		X [b]	X	X	X	X	X	X	X	X	X			X
Adverse Event Collection		X [b,p]	X	X	X	X	X	X	X	X	X	X	X	X
Dietary Counseling		X [b]			X				X		X			X

Notes: All blood draws for bicarbonate measurements must be done with subjects in a fasted state (at least 4 hours, except water). Allowed visit windows are: ± 4 days for Week 14, 16, 20, 24 Visits; ± 7 days for Week 28, 34, 40, 46 and 52 Visits (Week 52 Visit must not occur earlier than the 1-year anniversary of the Day 1 Visit in the parent study TRCA-301); and ± 2 days for Follow-up 1 and 2 Visits.

Abbreviations: C = central laboratory assessment; ECG = electrocardiogram; L = local laboratory assessment; UNS = unscheduled.

[a] The Week 52 visit will occur no earlier than the 1 year anniversary of the Day 1 visit in study TRCA-301. Subjects who discontinue the study prior to Week 52 are required to undergo an Early Termination Visit with all Week 52 Visit procedures to be performed. All subjects who discontinue study drug prior to Week 52 will be contacted by telephone at the Week 52 Visit timepoint to ascertain vital status and renal status (i.e., receiving renal replacement therapy or not).

[b] Data collected for the Week 12 Visit in Study TRCA-301 will serve as the Week 12 Visit data in this extension study.

[c] Vital signs include: blood pressure and respiratory rate (both in triplicate, measurements taken approximately 2 minutes apart at Week 12 and Week 52 Visits; once at all other time points), heart rate, and temperature.

[d] 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).

[e] 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.

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

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

[h] 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.

[i] For women of childbearing potential, blood samples will be collected for serum pregnancy tests at the visits indicated. At the Week 12 Visit, a urine sample will be collected for a urine dipstick pregnancy test conducted at the study site.

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

[k] Instruct subjects on collecting 24-hour urine samples 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 Week 12 and Week 52 Visits.

[l] Dispense study drug per IRT instructions. Instruct subject to take study drug with food at approximately the same time each day, at least 4 hours apart from all oral concomitant medications.

[m] Oral alkali supplement (for subjects taking one at the Week 12 Visit only), should be discontinued or re-started based on blood bicarbonate level and study drug dose as described in Appendix 2.

[n] The last dose of study drug shall be administered 1 day before the Week 52 Visit.

[o] Instruct subject to bring all used and unused study drug containers to each visit. Collect all study drug containers at the Week 52 Visit or at ET Visit.

[p] Adverse events with a start date during the parent study, TRCA-301, that are ongoing at the time of enrollment in TRCA-301E and adverse events with an onset following enrollment in TRCA-301E will be recorded.

[q] 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 and Oral Alkali Supplement Titration Algorithm

<table>
<tr><th>Blood Bicarbonate (mEq/L)</th><th>Study Drug</th><th>Oral Alkali Supplement[a]</th></tr>
<tr><td>< 12[b]</td><td colspan="2">At Week 12 Visit: Do not enroll subject in Study TRCA-301E
During Treatment Period: Evaluate for new acute acidotic process, contact Medical Monitor. Maintain dose(s) pending discussion with Medical Monitor.</td></tr>
<tr><td>12 to < 22</td><td>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.</td><td>Maintain dose until next scheduled visit.</td></tr>
<tr><td>22 to < 27</td><td>Maintain dose until next scheduled visit.</td><td rowspan="2">Discontinue oral alkali supplement until the next scheduled visit. If bicarbonate remains ≥ 22 mEq/L, do not re-instate oral alkali. If bicarbonate is < 22 mEq/L at the next scheduled visit, increase study drug dose by one packet and retest bicarbonate at the next scheduled visit. If a subject who was taking oral alkali at the Week 12 Visit had their oral alkali discontinued, AND they are receiving the maximum dose of study drug (i.e., 3 packets) AND their blood bicarbonate value is < 22 mEq/L, re-instate the same oral alkali supplement subject was taking at the Week 12 Visit at the same dose taken at the Week 12 Visit[c]. If the Investigator judges that re-starting alkali treatment poses a safety risk, the risk should be documented. In this situation, alkali will not be re-started.</td></tr>
<tr><td>27 to 30</td><td>Maintain dose.
Invite subject for a visit in approximately 1 to 2 weeks to retest blood bicarbonate.</td></tr>
<tr><td>> 30[b]</td><td>Interrupt (hold) study drug.
Invite subject for a visit in approximately 1 week to retest blood bicarbonate.
If blood bicarbonate at that visit is:
≤ 30 mEq/L, restart study drug at a lower dose (1 packet/day less than before dose interruption) except for subjects on 1 packet/day prior to dose interruption, who will restart study drug at 1 packet/day dose.
> 30 mEq/L, continue to hold the dose and retest again in approximately 1 week.</td><td>Discontinue oral alkali supplement.</td></tr>
</table>

[a] For subjects taking an oral alkali supplement at Week 12 only.
[b] Blood bicarbonate values of < 12 mEq/L or > 30 mEq/L must be confirmed by a repeated measurement from a separate blood draw.
[c] The Week 12 dose is defined as the average daily dose prescribed during Week 12.