Statistical Analysis Plan for Study TRCA-301

Official Study Title:

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

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STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TRC101 in Subjects with Chronic Kidney Disease and Metabolic Acidosis
Study Number:	TRCA-301
Investigational Drug:	TRC101
Indication:	Treatment of metabolic acidosis associated with chronic kidney disease
Investigators:	Multicenter
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Sponsor:	Tricida, Inc. 7000 Shoreline Court, Suite 201 South San Francisco, CA 94080, U.S.A.
Plan Version:	23 May 2018 (Final Version 2.0)
Plan Prepared by:	[redacted] MS Statistical Consultant [redacted]

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STATISTICAL ANALYSIS PLAN

Study TRCA-301

Final Version 2.0

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

Approval:

[redacted] 23-MAY-2018

Date

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Table of Contents

List of Tables

1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
ADaM	analysis data model
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BP	blood pressure
CBC	complete blood count
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CFB	change from baseline
CrCL	creatinine clearance
CKD	chronic kidney disease
CM	concomitant medication
CRF	case report form
CRU	clinical research unit
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EU	European Union
FDA	The Food and Drug Administration
K^+	potassium
KDQOL	kidney disease quality of life questionnaire
HR	heart rate
LDL	low density lipoprotein
LS	least squares
ICH	International Council for Harmonisation
IRT	interactive response technology
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent-to-treat

Abbreviation	Description
MMRM	mixed-effect model repeated measures
MNAR	missing not at random
PT	preferred term
REML	restricted maximum likelihood
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SDTM	Study Data Tabulation Model
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
TLFs	tables, listings, and figures
UAGT	urine angiotensinogen to creatinine ratio
WHO	World Health Organization

2 REVISION HISTORY

Version	Date	Document Owner	Revision Summary
Draft 1.0	2 March 2017	[redacted]	First version
Draft 2.0	5 June 2017	[redacted]	Incorporated comments from the FDA's responses dated 24 May 2017.
Final 1.0	04 August 2017	[redacted]	Updates to be in sync with Protocol Amendment 2. Editorial changes made for clarification.
Final 2.0	23 May 2018	[redacted]	Added analyses to describe the population baseline renal risk, to further explore threshold bicarbonate responses, to explore effects of the starting dose and dose titration, to further specify handling of protocol deviations, and to update the per-protocol population definition. This revision also includes minor re-wording to enhance clarity and/or internal consistency.

3 RELEVANT DOCUMENTS: PROTOCOL, AMENDMENTS AND CASE REPORT FORMS

Original Protocol (2 March 2017)
Protocol Amendment 1 (05 June 2017)
Protocol Amendment 2 (03 August 2017)
Protocol Amendment 3 (27 November 2017)
Case Report Form (CRF) Final Version 1.0 (August 2017)
Case Report Form (CRF) Version 2.0 (February 2018)

4 COMMITMENT TO GOOD STATISTICAL PRACTICE

4.1 Definition of Good Statistical Practice

Guidance on Statistical Principles for Clinical Trials from International Conference on Harmonisation (ICH E9) implicitly defines good statistical practice. Good statistical practice includes both appropriate statistical designs to minimize bias and maximize precision of analysis plus operational excellence to assure credibility of results. The scientific design associated with

any clinical trial is found in the protocol and a more detailed, pre-specified statistical analysis plan such as this one presents the final statistical methods.

We interpret the operational side of good statistical practice as a transparent, reproducible, and validated approach to acquiring and analyzing clinical trial data. Reproducible research depends upon process transparency and also provides auditability of the statistical analysis. Analysis transparency requires that a navigable electronic process chain exist from defining the objective of the analysis to creating the results.

4.2 Use of Standards

Data standards are foundational for creating an environment where tools can be leveraged at different points in the analysis process. Data standards for clinical development of drugs have been defined and are maturing under various initiatives through the Clinical Data Interchange Standards Consortium (CDISC). Tricida uses Study Data Tabulation Model (SDTM) data sets and Analysis Data Model (ADaM) statistical analysis files for producing analysis results. Other applicable standards include regulatory guidances from FDA and ICH:

- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3)
- ICH Guidance for Good Clinical Practice (ICH E6)

5 PURPOSE OF THE ANALYSIS PLAN

This statistical analysis plan (SAP) pre-specifies the statistical analysis methods for supporting the completion of the clinical study report (CSR) of Study TRCA-301 for investigational product TRC101. This SAP will be used to analyze the efficacy and safety data collected during the study. The planned analyses identified in this SAP may be included in regulatory submissions, and/or future manuscripts. The analyses described in this plan are considered *a priori*, in that they have been defined prior to clinical database lock and authorized unblinding of treatment assignment. Exploratory analyses, which are not defined in this SAP, may be performed to support the clinical development program. Any post-hoc or unplanned analyses that are performed for the CSR but not defined in this SAP, will be documented in the CSR, as will any changes from the planned analyses as stated in the study protocol.

6 STUDY OBJECTIVES

6.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of TRC101 in chronic kidney disease (CKD) patients with metabolic acidosis (blood bicarbonate 12 to 20 mEq/L).

6.2 Secondary Objective

The secondary objective of the study is to assess the safety of administration of TRC101 in CKD patients with metabolic acidosis (blood bicarbonate 12 to 20 mEq/L).

7 STUDY DESIGN

7.1 Overall Study Design

This is a double-blind, placebo-controlled, parallel-design, 2-arm study. Approximately 210 subjects will be randomized in a 4:3 ratio to receive 6 g TRC101 or placebo once daily (QD). Approximately 55 study centers will participate in this study.

Screening Period: Eligible subjects will be enrolled into the study if they: are 18 to 85 years of age; have a blood bicarbonate value of 12 to 20 mEq/L at Screening 1 and Screening 2; have an average value of blood bicarbonate from Screening 1, Screening 2, and Day 1 pre-dose (i.e., baseline blood bicarbonate) within the 12 to 20 mEq/L range; and have an estimated glomerular filtration rate (eGFR) of 20 to 40 mL/min/1.73m^2 at both the Screening 1 and Screening 2 visits. Additional inclusion and exclusion criteria can be found in the TRCA-301 protocol, Section 4. Randomization of eligible subjects will be based on their baseline blood bicarbonate strata (≤18 versus >18 mEq/L) and Screening eGFR strata (<30 versus ≥30 mL/min/1.73m^2, where Screening eGFR is defined as the average of Screening Visit 1 and Screening Visit 2 values).

Treatment Period: Randomized subjects will receive study drug (placebo or TRC101) for 12 weeks (Treatment Period) on an outpatient basis. The dose of the study drug will be fixed for the first 4 weeks of the Treatment Period, except for subjects with a blood bicarbonate level ≥ 27 mEq/L. Subjects with a blood bicarbonate level of 27 to 30 mEq/L will have their dose of study drug decreased per the titration algorithm (see TRCA-301 protocol, Appendix 2). Subjects with a confirmed blood bicarbonate level of > 30 mEq/L will undergo an interruption of the study drug

dose in accordance with the titration algorithm (see TRCA-301 protocol, Appendix 2). Beginning at the Week 4 Visit, subjects with a blood bicarbonate level below the normal range (12 to < 22 mEq/L) will have an adjustment of the study drug dose in accordance with the titration algorithm (see Protocol Appendix 2). At any time during the study, subjects with a confirmed blood bicarbonate level < 12 mEq/L will be evaluated by the Investigator for new acute acidotic processes and discussed with the Medical Monitor. During the 12-week Treatment Period, subjects will attend eight study visits (Day 1, Weeks 1, 2, 4, 6, 8, 10, and 12) for efficacy and safety assessments (See Table 1 for details).

Follow-up Period: Subjects who complete the Treatment Period will be offered participation in a 40-week extension study (Study TRCA-301E). Subjects who are not willing to participate in the extension study or who are not eligible for it will enter the 2-week Follow-up Period of Study TRCA-301, which consists of Follow-up 1 Visit (Week 13) and Follow-up 2 Visit (Week 14), for adverse event (AE) collection, fasting blood draws and safety assessments (See Table 1 for details).

The maximum duration of Study TRCA-301 is anticipated to be 14 weeks per subject for those who continue into the TRCA-301E extension study (i.e., up to 2-week Screening Period and 12-week Treatment Period). For subjects who do not participate in the TRCA-301E extension study, the maximum duration of Study TRCA-301 is anticipated to be 16 weeks (i.e., up to 2-week Screening Period, 12-week Treatment Period and 2-week Follow-up Period). Assessments and procedures for evaluation of efficacy and safety will be conducted per the protocol-specified schedule (see Table 1 for details).

Table 1 Study TRCA-301 Protocol Schedule of Events

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7.2 Randomization and Blinding

Eligible subjects will be randomized in a 4:3 ratio to receive TRC101 or placebo, stratified by their baseline blood bicarbonate value (≤18 versus >18 mEq/L) and screening eGFR value (<30 versus ≥30 mL/min/1.73m^2):

- 6 g TRC101 administered QD for 12 weeks (n≈120)
- placebo administered QD for 12 weeks (n≈90)

At least half of the subjects enrolled in the study will have a baseline blood bicarbonate value of 12 to 18 mEq/L.

In this study, [redacted] each study site must have an unblinded Pharmacist or designated unblinded study staff member (the "Pharmacist") for handling (dispensation and collection) of the study drug. These individuals will be responsible for dispensing study drug (including supervision of administration of the first dose of study drug) and collecting used and unused study drug containers and dosing diaries. If study drug dose needs to be adjusted or interrupted per the titration algorithm (see TRCA-301 protocol, Appendix 2), such adjustments will be performed in a blinded manner in both active and placebo treatment groups. The designated unblinded study staff member(s) 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 the electronic case report forms (eCRFs). The subjects, Investigators, Medical Monitors, Tricida, site personnel (including all those involved in collection of safety information) and CRO staff (except for those responsible for monitoring of unblinded data) will remain blinded to the subject's treatment assignment throughout the study until after the database is locked and access to the randomized treatment codes has been authorized. The DMC members and the statisticians responsible for reporting to the DMC will be unblinded during the study.

The Pharmacist must not inform the subjects, Investigators, Medical Monitors, Tricida, or other site or CRO personnel about the subjects' treatment assignment. In case of a medical emergency,

the Investigator may obtain the treatment assignment for the subject from the interactive response technology (IRT) system if such information is considered important to the management of a medical emergency. In such cases, the Investigator must submit a written report, including all pertinent details, to a Medical Monitor within 24 hours of the unblinding. The Investigator should make every reasonable attempt to contact a Medical Monitor before unblinding the subject. Additional details on study blinding are described in the Blinding Plan.

7.3 Assessments

Table 1 shows the schedule of events of the study.

7.3.1 Efficacy Measurements

Fasting blood bicarbonate levels measured onsite with an i-STAT point-of-care device will be used to determine the primary and secondary efficacy endpoints for this study. Exploratory efficacy measurements include: repeated chair stand test, and kidney disease quality of life questionnaire (KDQOL) Question 3. Other efficacy measurements include blood and urine biomarkers related to bone and kidney health.

7.3.2 Safety Measurements

Safety will be assessed by repeated clinical evaluation, including adverse events, serious adverse events (SAEs), vital signs, physical examination, 12-lead electrocardiograms (ECGs), and clinical laboratory tests (chemistry, hematology, coagulation, and urinalysis) from central laboratories.

7.3.3 Other Measurements

Spot urine will be used to evaluate urine electrolytes. 24-hour urine collections will be used to characterize albumin, sulfate, uric acid and urea nitrogen excretion.

8 SAMPLE SIZE AND POWER

8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is having a change from baseline (CFB) in blood bicarbonate ≥4 mEq/L or having blood bicarbonate in the normal range (22 to 29 mEq/L) at the end of treatment (Week 12 Visit). This outcome is termed a “response”.

The sample size in this study is based on the efficacy results observed in the Phase 1/2 Study TRCA-101. The table below shows 46% of TRC101-treated subjects and 3% of placebo-treated subjects had an increase of ≥4 mEq/L or had blood bicarbonate in the normal range (22 to 29 mEq/L) after 2 weeks of treatment. We assume the full TRC101 treatment effect had not been reached during the short (2-week) treatment period.

Results from Study TRCA-101

Blood Bicarbonate (mEq/L)	Pooled TRC101 (n=104)	Pooled Placebo (n=31)
Number (%) of Subjects at Week 2 (Day 15)		
CFB ≥4	41 (39.4%)	1 (3.2%)
Normal (22 - 29)	37 (35.6%)	0
Composite (CFB ≥4 or Normal)	48 (46.2%)	1 (3.2%)
95% Exact CI of Composite	36.3%, 56.2%	<0.1%, 16.7%

CFB = Change from baseline; CI = confidence interval.

In Study TRCA-301, we expect that 50 to 55% of TRC101-treated and 10% of placebo-treated subjects will have an increase of ≥4 mEq/L or have blood bicarbonate in the normal range at the end of treatment (Week 12 Visit). A Fisher's exact test with a 0.05 two-sided significance level will have over 99% power to detect this difference if the study has 90 placebo and 120 TRC101 subjects. If the true proportion of TRC101 subjects who respond at the Week 12 Visit is indeed between 50% and 55% and if no more than 5% of subjects have missing data at Week 12, the study will have roughly 90% power to result in a 95% confidence limit with a lower bound of at least 35% and 40%, respectively.

8.2 Secondary Efficacy Endpoint

The secondary efficacy endpoint is change from baseline in blood bicarbonate at the end of treatment (Week 12 Visit).

In the Phase 1/2 Study TRCA-101 after 2 weeks of treatment, we observed the following with regard to the change from baseline in blood bicarbonate level:

Results from Study TRCA-101

	TRC101	Placebo
Mean CFB at Week 1 (Day 8)	2.3	0.83
Mean CFB at Week 2 (Day 15)	3.3	-0.18
Common SD	2.5	
Treatment × Time effect	P = 0.2248	
Baseline blood bicarbonate (Covariate)	P <0.0001	
Correlation between Week 1 and Week 2	0.667	0.333

CFB = change from baseline; SD = standard deviation

In Study TRCA-301, we expect to observe the following mean change from baseline in blood bicarbonate over time for each group, with between group variance of 1.871, between time point variance of 0.08, and time point × treatment variance of 0.23.

	Time Point						
Treatment	**Week 1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**
Placebo	0.85	0.75	0.65	0.55	0.45	0.35	0.25
TRC101	2.00	2.50	3.00	3.50	3.75	4.00	4.25

We assume a constant standard deviation to be 3.0 mEq/L and correlation as shown in the table below:

	Week 1	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**
Week 1	1	0.6	0.399	0.265	0.176	0.117	0.078
Week 2	0.6	1	0.6	0.399	0.265	0.176	0.117
Week 4	0.399	0.6	1	0.6	0.399	0.265	0.176
Week 6	0.265	0.399	0.6	1	0.6	0.399	0.265
Week 8	0.176	0.265	0.399	0.6	1	0.6	0.399
Week 10	0.117	0.176	0.265	0.399	0.6	1	0.6
Week 12	0.078	0.117	0.176	0.265	0.399	0.6	1

We calculated power and sample size for the mixed-effect repeated measures (MMRM) model based on (nQuery Advisor software) a univariate two-group repeated measures analysis of variance using the Greenhouse-Geisser correction to nominal degrees of freedom. This study will have 99% power to detect a variance among the group marginal means of 1.871 mEq/L, will have 85% power to detect a variance of 0.08 among the means of the 7 time points (i.e., Weeks 1, 2, 4, 6, 8, 10, and 12), and will have 99% power to detect an interaction between groups and time points with a variance of 0.23, assuming that the between groups error term is 5.32, the within groups

error term is 2.4, the measure of "sphericity" of the covariance matrix, epsilon, is 0.69, (its estimate, the Greenhouse-Geisser correction, has an expected bias of about g1/(2n-2) where g1 is -2.38) when the significance level is 0.05 and the sample size in each of the two groups is 104 subjects (approximation to 90 placebo and 120 TRC101 subjects, respectively).

9 ANALYSIS SETS

9.1 Modified Intent-To-Treat

The modified intent-to-treat (MITT) analysis set is defined as all randomized subjects who had both baseline and at least one post-baseline blood bicarbonate value measured using the i-STAT device. The MITT analysis set will be used for evaluation of efficacy, based on planned treatment assignment.

9.2 Per-Protocol

The per-protocol (PP) analysis set is defined as MITT subjects, who completed the 12-week treatment period without important protocol deviations (See Section 12.2) and with ≥80% study drug dosing compliance. The PP analysis set, which will be based on the planned treatment assignment, will be used for evaluation of efficacy.

9.3 Safety Analysis Set

The safety analysis set is defined as all subjects who received any amount of study drug (TRC101 or placebo). The safety analysis set, which will be based on the actual treatment received, will be used for evaluation of safety. Placebo-treated subjects who received any amount of TRC101 during the treatment period will be assigned to the TRC101 treatment group from the time when TRC101 was received.

10 GENERAL CONSIDERATIONS

The analysis sets as defined in Section 9 will be used for efficacy and safety analyses. Subject listings of all analysis data that support summary tables and/or figures will be provided along with their source data from the eCRFs. Measurements from subjects excluded from the pre-defined analysis sets or extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables unless specified otherwise but will be included in the subject listings.

In general, subject listings will be sorted by treatment group, subject number, assessment date (time, and parameter, as applicable).

For most summary statistics, data will be analyzed and displayed by treatment group. Unless otherwise specified, descriptive statistics for continuous variables will include the number of subjects with data to be summarized (n), mean, standard deviation (SD), median, minimum and maximum. The same number of decimal places as in the observed value will be presented when reporting minimum and maximum; 1 more decimal place than in the observed value will be presented when reporting mean and median; and 2 more decimal places than in the observed value will be presented when reporting SD.

All categorical/qualitative data will be presented using frequency counts and percentages. All percentages will be presented to 1 decimal place, unless otherwise specified. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies. Where individual variable values are missing, categorical data will be summarized based on reduced denominators (i.e., only subjects with available data will be included in the denominators). For summaries of AEs and concomitant medications (CMs), the percentages will be based on the number of subjects who received study drug.

Results of statistical analyses will be reported using summary tables, listings, and figures (TLFs). The ICH numbering convention will be used for all TLFs. The following conventions will be followed:

- Unless otherwise noted, all statistical testing will be two-sided and will be performed at the 0.05 significance level.
- Tests will be declared statistically significant if the calculated p-value is <0.05, unless otherwise specified.

All analyses and summaries will be produced using SAS® version 9.4 or higher.

Note that while the SAP predominantly uses the term ‘blood bicarbonate’ the TLFs will use ‘serum bicarbonate’.

10.1 Definitions and Derived Variables

10.1.1 Age

Age (years) will be calculated as the number of years between date of birth and date of informed consent, expressed as an integer.

10.1.2 Study Day

Study Day, which follows the CDISC SDTM standard, is defined as (Assessment date – date of first study drug dosing) + 1, where the assessment date is on or after the date of first study drug dosing; (Assessment date – date of first study drug dosing), where the assessment date is before the date of first study drug dosing.

10.1.3 Estimated Glomerular Filtration Rate

eGFR data will be used in data analysis. The eGFR value will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula from both serum creatinine and serum cystatin C that will be reported from the central laboratory. The primary analysis for change in eGFR will be based on serum creatinine. Because of the potential for changes in muscle mass related to bicarbonate correction, eGFR calculated from serum cystatin C levels will be evaluated at baseline and Week 12.

The CKD-EPI formula can be expressed as a single formula using serum creatinine (mg/dL):

$$eGFR = 141 \times \text{minimum}(\text{Serum Creatinine}/\kappa, 1)^{\alpha} \times \text{maximum}(\text{Serum Creatinine}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

Where κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of S_{Cr}/κ or 1 and max indicates the maximum of S_{Cr}/κ or 1

The CKD-EPI formula can be expressed as a single formula using serum cystatin C (mg/L):

$$eGFR = 133 \times \text{minimum}(\text{Serum cystatin C}/0.8, 1)^{-0.499} \times \text{maximum}(\text{Serum cystatin C}/0.8, 1)^{-1.328} \times 0.996^{Age} \times 0.932\ [\text{if female}]$$

10.1.4 Anion Gap

Serum anion gap will be derived as [serum sodium (mEq/L) + serum potassium (mEq/L)] – [serum chloride (mEq/L) + serum bicarbonate (mEq/L)]. Urine anion gap will be derived as urine sodium (mEq/L) + urine potassium (mEq/L) – urine chloride (mEq/L).

10.1.5 Multiple Records at a Time Point

For analysis purposes, the mean value of multiple measurements collected at the same position (i.e., supine, standing, etc.) on the same visit day will be summarized for the corresponding protocol defined time point. All collected measurements and the mean values will be listed.

10.1.6 Baseline Values

Baseline values for all efficacy and safety variables are defined as the last non-missing assessment prior to the first dose of study drug, unless otherwise specified.

10.1.7 Baseline Blood Bicarbonate Value Using i-STAT

Blood bicarbonate values are measured onsite using an i-STAT point-of-care device. Baseline blood bicarbonate is defined as the average of the values of blood bicarbonate collected at the Screening 1 Visit, Screening 2 Visit, and Baseline Visit (i.e., Day 1 pre-dose).

10.1.8 Baseline Blood Bicarbonate Subgroups

For exploratory efficacy analysis, subjects will be classified according to their baseline blood bicarbonate stratum (≤ 18 mEq/L or >18 mEq/L).

10.1.9 Screening and Baseline eGFR Value

The Screening eGFR value is defined as the average of the values of eGFR used to determine eligibility and calculated from the serum creatinine at the Screening 1 and Screening 2 Visits using the CKD-EPI formula. The creatinine measurements used for determining eligibility may have been analyzed at the central or local laboratory. This Screening eGFR value will be used for the randomization strata.

The Baseline eGFR value is defined as the average of values of eGFR collected at the Screening 1 Visit, Screening 2 Visit, and Baseline Visit (i.e., Day 1 pre-dose), based on serum creatinine measured by the central laboratory. This value will be used for derivation of change from baseline and will serve as a covariate in statistical models.

10.1.10 Screening eGFR Subgroups

For exploratory efficacy analysis and/or safety analysis, subjects will be classified according to their Screening eGFR stratum. The Screening eGFR subgroups are:

- <30 mL/min/1.73m^2
- ≥30 mL/min/1.73m^2

10.1.11 Baseline Blood pH and Base Excess Values Using i-STAT

Blood pH and base excess are measured onsite using an i-STAT point-of-care device. The baseline value of each of these two parameters is defined as the average of the measurements collected at the Screening 1 Visit, Screening 2 Visit, and Baseline Visit (i.e., Day 1 pre-dose).

10.1.12 24-hour Urine Excretion of Uric Acid, Sulfate, Creatinine, Albumin, and Urea Nitrogen

If timed urine was collected for more or less than 24 hours, the daily excretion will be normalized and reported as weight unit of the analyte during a 24-hour period.

10.1.13 24-hour Creatinine Clearance

The 24-hour creatinine clearance (mL/min) will be calculated as (urine concentration of creatinine in mg/dL × urine volume over 24 hours in mL)/(serum creatinine in mg/dL × 1440).

10.1.14 Baseline Electrocardiogram Parameters

12-lead ECG parameters will be collected in triplicate on Day 1 pre-dose. The average of the ECG intervals and heart rate measurements will be used as baseline. Screening values will be used as baseline for subjects who did not have any ECG measurements on Day 1 pre-dose.

10.1.15 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as all AEs that begin on or after the time of the first dose of study drug (also see Section 11.4.1). Related AEs are those reported by investigators as possibly related, probably related, or related to study drug.

10.1.16 Concomitant Medications and Concurrent Procedures

Prior medications are defined as all prescription and over-the-counter medications that were taken within 28 days (whether continuing or not) prior to the study drug administration. Concomitant medications are defined as all prescription and over-the-counter medications that are used concurrently (from Day 1 to Week 14). A prior medication can also be a concomitant medication if it continued after the first dose of study drug.

10.1.17 Alkali Therapy

Oral alkali therapies are medications containing active ingredients of sodium bicarbonate, potassium bicarbonate, potassium citrate, or sodium citrate. Baseline alkali therapies are those medications that were used at the start of study treatment.

10.2 Analysis Windows

Clinical visits may occur outside protocol-specified windows. Therefore, instead of relying solely on visit labels in the clinical database, analysis visits and their windows are defined using Study Day (See Section 10.1.2). For the purposes of data analysis and summary, assessments and/or measurements will be flagged based on the collection date/time that is closest to the protocol-scheduled time point (or target Study Day). Analysis visit windows are presented in Table 2 by type of assessments and/or measurements.

Table 2 Analysis Visit Windows

Protocol Scheduled Time Point	Target Study Day	Analysis Visit Windows (Study Day)				
		All Other Assessments	Hematology Urinalysis Spot Urine Pregnancy Tests	Repeated Chair Stand KDQOL Biomarkers 24-Hour Urine Collection	ECG	Body Weight
Screening 1	-14	≤ -8*	≤ -8*	-	-	-
Screening 2	-1	-7 to -1*	-	-	-	-
Day 1	1	1*	-7 to 1*	-14 to 1*	-14 to 1*	≤ 1*
Week 1	8	2 to 11	-	-	-	-
Week 2	15	12 to 22	-	-	2 to 28	-
Week 4	29	23 to 36	-	-	-	2 to 42
Week 6	43	37 to 50	2 to 63	-	29 to 63	-
Week 8	57	51 to 64	-	-	-	43 to 70
Week 10	71	65 to 78	-	-	-	-
Week 12	85	79 to 90	64 to 91	≥2	64 to 91	71 to 91
Week 13	92	91 to 97	-	-	-	-
Week 14	99	≥98	≥92	-	≥92	≥92

* Use visit designation for scheduled visits; otherwise use the visit window.

11 STATISTICAL AND ANALYSIS ISSUES

11.1 Adjustments for Covariates

The baseline blood bicarbonate and baseline eGFR, as continuous covariates, will be included in an MMRM model for analysis of change from baseline in blood bicarbonate. Other baseline values of continuous efficacy variables will be included in MMRM models (see Section 14.4.2) or analysis of covariance (ANCOVA) models (see Section 14.7) as covariates.

Two stratification variables, Baseline blood bicarbonate (≤18 versus >18 mEq/L) and Screening eGFR (<30 versus ≥30 mL/min/1.73m^2), are utilized in the randomization. They will be used as subgroups (see Section 11.10) to evaluate primary and secondary efficacy variables. Other baseline characteristics, such as age, sex, race, baseline alkali therapy, and geographic region, may also be used as subgroups (see Section 11.10).

11.2 Handling Dropouts or Missing Data

Missing data will not be imputed, unless otherwise specified. Early termination visits will be mapped to the next scheduled visit for inclusion in summary tables, where appropriate. For example, subjects who terminate after Week 11 (e.g., have assessments through Week 11) would have their early termination assessments mapped to the next scheduled visit (i.e. Week 12) based on the analysis window (See Section 10.2).

Every effort will be made to ensure completeness of data collection. If severity or relationship of an AE to study drug is not recorded, the severity or relationship will be imputed as "severe" or relationship as "possibly related", for analysis purposes. In the subject listing, both collected and imputed values will be presented.

11.3 Handling of Efficacy Data

The primary analysis will not impute missing (blood bicarbonate) data. For the primary analysis, missing data in both placebo and TRC101 will be assumed to be missing at random (MAR). Subject withdrawal patterns in the placebo and TRC101 groups will be assessed. Sensitivity analyses for the primary and secondary efficacy endpoints (Section 14.5) will use multiple imputation models assuming the data are missing not at random (MNAR).

11.4 Handling of Safety Data

11.4.1 Adverse Events

All AE verbatim terms reported on the eCRFs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA® version 20.0). TEAEs are defined as any AEs, regardless of relationship to study drug, that have an onset or worsening in severity on or after the first dose of study drug. If it cannot be determined whether the AE is treatment-emergent because of a partial onset date, the event will be counted as a TEAE. Adverse events with incomplete start dates will be considered TEAEs, if:

- Onset time is missing but the onset date is on Day 0 or Study Day 1.
- Day and month are missing and the year is equal to or after the year of the first date of study drug dosing;
- Day is missing and the year is after the year of the first date of study drug dosing;
- Day is missing and the year is equal to the year of the first date of study drug dosing and the month is equal to or after the month of the first date of study drug dosing; or
- Year is missing.

Related AEs are those with relationship to study drug reported as "possible", "probable" or "related".

11.4.2 Concomitant Medications

All medication verbatim terms reported on the eCRFs will be mapped according to the World Health Organization (WHO) Drug Dictionary (WHO DD Enhanced version, March 1st, 2017, B2 format). The medications will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and preferred names. A prior medication is considered to be any medication that is taken prior to the first study drug dosing. A concomitant medication is considered to be any medication taken after the start of study drug dosing. Specifically, concomitant medications are medications:

- that are continued from Screening and continued after the first study drug dosing,
- with start dates or stop dates within the Treatment Period

If start date is missing, the medication will be considered to have started prior to the study. Such a medication may also be considered concomitant, depending on the stop date or lack thereof. If the stop date of a concomitant medication is missing, then the medication will be treated as ongoing. If the start date of a medication is missing, the stop date will be used to determine whether

or not it is concomitant. Medications with other incomplete start dates will be identified as concomitant using the same algorithm as above for TEAEs, if the stop date information is insufficient for the determination.

During the study, alkali dose will be monitored; the protocol specifies that the dose of oral alkali, if any, should not change during the study. Any change in equivalent dose during the study when the type of alkali has changed (e.g. sodium citrate to sodium bicarbonate) will be identified.

11.5 Interim Analyses and Data Monitoring

There will be no interim analyses of efficacy. Safety data monitoring is described in Section 15.9.

11.6 Multicenter Considerations

Thirty-seven (37) study centers in Europe and the United States randomized at least 1 subject in the study as follows: European Union (EU) countries (8 sites with 82 subjects); Non-EU countries (17 sites with 108 subjects); and the United States (12 sites with 27 subjects). Data from all study centers will be pooled for efficacy and safety analyses as well as for summaries. Because the number of subjects at each center is likely to be small, no analyses will be performed by center. Geographic region (i.e., EU, Non-EU, and US), in which study sites in certain geographic locations will be pooled together, will be used for subgroup analyses. The table below lists these study centers with their site identification number, country and geographic region category.

Table 3 Country Code and Geographic Region Category

Site Identification Number	Country Code	Country Name	Geographic Region
11	BGR	Bulgaria	EU
21	HRV	Croatia	EU
41	HUN	Hungary	EU
44	HUN	Hungary	EU
46	HUN	Hungary	EU
49	HUN	Hungary	EU
71	SVN	Slovenia	EU
72	SVN	Slovenia	EU
31	GEO	Georgia	Non-EU
32	GEO	Georgia	Non-EU
33	GEO	Georgia	Non-EU

Table 3 Country Code and Geographic Region Category

Site Identification Number	Country Code	Country Name	Geographic Region
34	GEO	Georgia	Non-EU
35	GEO	Georgia	Non-EU
36	GEO	Georgia	Non-EU
37	GEO	Georgia	Non-EU
61	SRB	Serbia	Non-EU
64	SRB	Serbia	Non-EU
65	SRB	Serbia	Non-EU
81	UKR	Ukraine	Non-EU
83	UKR	Ukraine	Non-EU
84	UKR	Ukraine	Non-EU
85	UKR	Ukraine	Non-EU
86	UKR	Ukraine	Non-EU
87	UKR	Ukraine	Non-EU
88	UKR	Ukraine	Non-EU
52	USA	United States	USA
53	USA	United States	USA
54	USA	United States	USA
55	USA	United States	USA
56	USA	United States	USA
57	USA	United States	USA
58	USA	United States	USA
59	USA	United States	USA
91	USA	United States	USA
92	USA	United States	USA
93	USA	United States	USA
95	USA	United States	USA

11.7 Multiple Comparisons, Multiplicity

In order to control family-wise error rate, formal statistical testing for the primary and secondary endpoints will be performed sequentially. At the Week 12 Visit, a formal comparison between the TRC101 and the placebo groups will be performed using Fisher's exact test for the proportion of subjects having a CFB in blood bicarbonate ≥4 mEq/L or having blood bicarbonate in the normal range. Only when this comparison is statistically significant at the two-sided 0.05 level, will a

formal test for the secondary efficacy endpoint (CFB in blood bicarbonate at the Week 12 Visit) be performed. A MMRM model will be used to compare the group least squares (LS) means of change in blood bicarbonate at Week 12.

11.8 Use of an "Efficacy Subset" of Subjects

All efficacy analyses will be performed using the MITT analysis set, based on the assigned treatment group. In addition, the primary and secondary efficacy analyses will use the PP analysis set as a supportive evaluation of efficacy of TRC101.

11.9 Active-Control Studies

The placebo group will serve as a comparator in this study.

11.10 Examination of Subgroups

Subjects will be categorized into the following subgroups for the purposes of exploring primary and secondary efficacy endpoints. These subgroups may also be used for safety evaluations. Forest plots will be generated to display the primary and secondary results from the above subgroups, along with the overall results.

- Baseline blood bicarbonate (≤18 versus >18 mEq/L)
- Screening eGFR (<30 versus ≥30 mL/min/1.73m^2)
- Age (<65 versus ≥65 years)
- Sex (Male versus Female)
- Race (White versus Non-White)
- Baseline alkali use (Yes versus No)
- Geographic region (EU, Non-EU, US)
- Dose titration status during the study (no titration, any up-titration, any down-titration)

12 STUDY PATIENTS

12.1 Subject Disposition

Enrollment and disposition will be summarized by treatment group and overall for all randomized subjects. All enrolled subjects are defined as those who signed the informed consent form. The subject disposition summary will include:

- Number of randomized subjects
- Number of subjects randomized but not dosed
- Number of subjects in the MITT analysis set
- Number of subjects in the safety analysis set
- Number of subjects in the PP analysis set
- Number of subjects who completed the 12-week treatment period
- Number of subjects who completed the study (i.e., completed the Week 14 visit or rolled over to Study TRCA-301E)
- Number of subjects who prematurely discontinued from the study
    - The primary reason for withdrawal from the study
- Number of subjects who entered in Study TRCA-301E

A listing of disposition will be provided for all enrolled subjects. Subjects who are excluded from MITT or PP analysis sets will be listed, along with reasons for the exclusions.

12.2 Protocol Deviations

Protocol deviations will be classified by deviation type (i.e., important) and category (e.g., eligibility criteria, out of window visit, SAE reporting, missed or out of window procedures, etc.). All deviations will be identified prior to database lock and important deviations will be presented in listing(s). Important protocol deviations (referred to in the protocol as "major protocol deviations") are defined per ICH guidance. Important deviations will be summarized by deviation category and treatment group. Important protocol deviations will be defined for this study prior to database lock and are described in detail in the Protocol Deviation Adjudication Memo. Protocol deviation categories include:

- Investigational product
- Informed consent
- Key eligibility criteria
- Other eligibility criteria
- SAE reporting
- Out of window procedure
- Procedure - missed or not interpretable
- Out of window visit
- Missed visit

- Restricted medications
- Randomization
- Stratification
- Blinding
- Other

12.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all randomized subjects. Demographic characteristics will include age, age group (< 65 or ≥ 65 years), sex, race, and ethnicity. The following baseline characteristics will be summarized: baseline alkali use (Yes or No), geographic region, baseline weight, height, body mass index (BMI), baseline systolic blood pressure (SBP) and baseline SBP group (≤ 135 or > 135 mmHg). In addition, the following selected baseline laboratory test results will be summarized: Screening eGFR, Screening eGFR group (< 30 or ≥ 30 mL/min/1.73m^2), baseline eGFR, baseline blood bicarbonate, baseline blood bicarbonate group (≤ 18 or > 18 mEq/L), baseline serum potassium, baseline urine albumin to creatinine (ACR) ratio, baseline urine ACR group (< 30 mg/g; or ≥ 30 mg/g and ≤ 300 mg/g; or > 300 mg/g), baseline serum albumin, baseline serum phosphate, and baseline serum calcium. Furthermore, baseline 5-year and 2-year kidney failure risk (%) will be calculated using the 8-variable kidney failure risk prediction equation (Tangri, et al. JAMA. 2011;305(15):1553-1559). All of the above information will be listed by subject in the following categories: demographic information, baseline characteristics, and selected baseline laboratory test results. A listing will compare the randomization stratification variables in the IRT system with the Screening eGFR group (< 30 or ≥ 30 mL/min/1.73m^2) and Baseline blood bicarbonate group (≤ 18 or > 18 mEq/L).

12.4 Medical History

Medical history will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA®) Dictionary (version 20.0). Selected medical history items (by preferred term), CKD etiology, and selected recurrent signs and symptoms will be summarized by treatment group. Medical history, selected medical history terms, and kidney

disease history (primary cause and recurring signs and symptoms) will be summarized for all randomized subjects and listed by treatment group and subject identification number.

13 STUDY DRUG AND OTHER MEDICATIONS

13.1 Prior and Concomitant Medications

Prior and concomitant medications (see definition in Section 11.4.2) will be summarized by treatment group using WHO DD ATC class and preferred name. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than one medication within an ATC class and preferred name. At each summary level subjects are counted once if they reported one or more medications at that level. Each summary will be ordered by descending frequency of incidence of ATC class and preferred name within each ATC class.

13.2 Restricted Medications

The concomitant use of restricted medications as defined in the Study TRCA-301 protocol, Section 5.9 Table 1 will be summarized and listed separately, using the same dictionary mapping as described above or based on manual medical review. Number (%) of subjects who used new or changed dose of oral alkali and calcium supplements will be summarized. Summary of certain new/dose changed antihypertensive medications given systemically (i.e., diuretics and renin-angiotensin-aldosterone system [RAAS] inhibitors, such as angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], aldosterone antagonists [AAs], renin inhibitors, mineralocorticoid receptor antagonists [MRAs], β-blockers, calcium channel blockers, alpha-adrenergic antagonists drugs, and direct vasodilators) regardless of stated indication will also be provided. Calcium supplements are defined as orally administered calcium carbonate, calcium acetate, calcium citrate, and other calcium salts taken for any indication.

13.3 Exposure to Study Drug, Study Treatment Compliance, and Dose Titration

Summaries will include the total number of packets dispensed, total number of packets consumed, total dose (g) consumed, study drug compliance, and duration (days) of exposure during the study treatment period.

Total dose (g) consumed is derived as the sum of the assigned dose level (i.e., subjects assigned to the TRC101 treatment group consumed 3 g TRC101 per packet) for all empty packets returned.

Study drug compliance (expressed in percentage) will be derived in the following way:

- Using the drug accountability data, the compliance is defined as 100%×the total number of empty packets returned divided by the total number of packets dispensed.

If a subject terminated from the study early and did not return packets, the packets dispensed at the last visit prior to termination will not be included in the calculations for study drug dosing or compliance.

The duration of study drug exposure is defined as the number of days on treatment from the first dose of study drug until the last dose of study drug. Study drug exposure will be summarized with descriptive statistics by treatment group.

Furthermore, number (%) of subjects with and without dose titration of study drug and those with dose uptitration, dose downtitration, and dose interruption during the treatment period will be summarized by treatment group and overall using subject counts, percentages and the exact 95% CI of the percentages. Number (%) of subjects who were dispensed a minimum and a maximum 0, 1, 2 or 3 study drug packets per day over various time intervals will be summarized by treatment group. Mean daily dose of study drug dispensed will also be summarized by treatment group and time interval. Denominators for percentages will be based on the number of subjects who remained active in the study during each time interval of interest.

The drug accountability information, including reasons or comments for incomplete or missed doses, will be listed in a patient listing. Subject dosing diary information will also be listed.

14 EFFICACY ANALYSES

14.1 Efficacy Endpoints

14.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is having a change from baseline in blood bicarbonate ≥ 4 mEq/L or having a blood bicarbonate level in the normal range (22 to 29 mEq/L) at the end of treatment (Week 12 Visit). This outcome is termed “response”.

14.1.2 Secondary Efficacy Endpoint

The secondary efficacy endpoint is CFB in blood bicarbonate at the end of treatment (Week 12 Visit).

14.1.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints identified in the study protocol are:

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

Additional exploratory efficacy endpoints (not specified in the study protocol) include:

1. CFB in parathyroid hormone (PTH)
2. CFB in serum pre-albumin
3. CFB in 25-hydroxy-vitamin D
4. CFB in urinary biomarkers of bone resorption:
    a. N-terminal telopeptide (NTX)
    b. C-terminal telopeptide (CTX)
5. CFB in serum biomarkers of bone resorption:
    a. Tartrate-resistant acid phosphatase 5b (TRAP 5b)
    b. Bone-specific alkaline phosphatase (BSAP)
    c. Type 1 procollagen (P1NP)
6. CFB in urine renal biomarkers:
    a. Urine angiotensinogen to creatinine ratio (UAGT)
    b. Urine aldosterone
    c. Uric acid
    d. Sulfate
    e. Urine endothelin-1 (ET-1)
7. CFB in serum osteocalcin (biomarker of bone formation)

If any biomarker samples have not been analyzed by the time of database lock, these assessments will be deferred and samples analyzed with those from the TRCA-301E study.

14.2 Efficacy Variables

14.2.1 Change from Baseline in Blood Bicarbonate

Blood bicarbonate values will be measured onsite using an i-STAT point-of-care device. Change from baseline in blood bicarbonate will be calculated as the measured value minus the baseline

value (see definition in Section 10.1.7) subsequent to the first dose of study drug. In other words, a positive change will indicate an increase in blood bicarbonate relative to baseline.

14.2.2 Categorical Change in Blood Bicarbonate

Binary indicator variables will be used to identify the frequencies of increases in post-baseline blood bicarbonate levels at each time point. The categories for the primary efficacy analysis are:

- an increase in blood bicarbonate from baseline ≥ 4 mEq/L
- blood bicarbonate value within 22 to 29 mEq/L

As additional exploratory efficacy analyses, the following categories will be evaluated:

- an increase in blood bicarbonate from baseline ≥2 mEq/L
- an increase in blood bicarbonate from baseline ≥3 mEq/L
- an increase in blood bicarbonate from baseline ≥5 mEq/L
- an increase in blood bicarbonate from baseline ≥6 mEq/L
- an increase in blood bicarbonate from baseline ≥7 mEq/L

14.2.3 Additional Change from Baseline Variables

As exploratory and other efficacy analyses, the following change from baseline variables will be calculated as the measured value minus the baseline value subsequent to the first dose of study drug. They will be measured once at baseline and once post baseline.

- CFB in the total score of the KDQOL Question 3 items (daily activities)
- CFB in repeated chair stand test duration
- CFB in parathyroid hormone
- CFB in serum pre-albumin
- CFB in 25-hydroxy-vitamin D
- CFB in urinary biomarkers of bone resorption (NTX and CTX)
- CFB in serum biomarkers of bone resorption (TRAP 5b, BSAP, and P1NP)
- CFB in urine renal biomarkers (UAGT, aldosterone, and ET-1)
- CFB in serum osteocalcin

14.3 Primary Efficacy Analysis

The primary analysis will be performed on the MITT analysis set, with the PP analysis set as supportive.

14.3.1 Reporting Results

The number and proportions (expressed as percentages) of subjects who are responders at each time point and at the end of treatment will be calculated. A responder is defined as a subject who has a change from baseline in blood bicarbonate ≥ 4 mEq/L or has 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 two-sided exact (Clopper Pearson) 95% CI, as well as the p-value from Fisher's exact test comparing the TRC101 group and the placebo group, will be reported by time point. The exact 95% CIs will also be presented by treatment group and time point.

14.3.2 Statistical Hypotheses

The two hypothesis tests will be used to evaluate the primary efficacy endpoint:

1. The null hypothesis is that there is no difference between treatment groups in proportion of subjects who are responders at Week 12. The alternative hypothesis is that there is a difference between treatment groups in proportion at Week 12

   H_0: $\pi_{TRC101} - \pi_{placebo} = 0$;
   H1: $\pi_{TRC101} - \pi_{placebo} \neq 0$.

2. The null hypothesis is that the proportion of TRC101 treated subjects who are responders at Week 12 is less than or equal to U (0.35 or 35%). The alternative hypothesis is that the TRC101 proportion at Week 12 is greater than U.

   H_0: $\pi_{TRC101} \leq U$;
   H1: $\pi_{TRC101} > U$.

14.3.3 Statistical Testing

Statistical testing for the above hypotheses will be performed in the following sequence. The first formal test for the difference (TRC101 – placebo) in proportion (≠ 0) will be conducted at the Week 12 Visit using the Fisher's exact test. With successful rejection of the null hypothesis #1 (Section 14.3.2), the second formal test for TRC101 proportion ≤ 0.35 will be conducted at the Week 12 visit, using the two-sided 95% confidence lower limit. If the lower limit of the 95% CI for TRC101 treated subjects is above U (0.35 or 35%), the null hypothesis #2 (Section 14.3.2) will be rejected.

14.4 Secondary Efficacy Analysis

The secondary analysis will be performed on the MITT analysis set, with the PP analysis set as supportive. All scheduled blood bicarbonate values collected through the Week 12 visit will contribute to the analysis. The efficacy variable, the change from baseline in blood bicarbonate value, will be calculated for each time point after the first dose through the Week 12 visit (i.e., Weeks 1, 2, … , 12). Missing data will not be imputed for the main analysis but will be imputed for the sensitivity analysis (Section 14.5). The analysis will test the difference in LS means between TRC101 and placebo at Week 12.

14.4.1 Statistical Hypothesis

For the secondary efficacy endpoint (i.e., the CFB in blood bicarbonate at Week 12 comparing TRC101 with placebo), the null hypothesis is the two means of CFB in blood bicarbonate are equal ($\mu_{TRC101} = \mu_{placebo}$). The alternative hypothesis is the two means of CFB in blood bicarbonate are not equal ($\mu_{TRC101} \neq \mu_{placebo}$).

14.4.2 Statistical Model

The MMRM model will define the CFB in blood bicarbonate as the dependent variable, set treatment, time point, and treatment by time point interaction as fixed effects, subject as a random effect, and the baseline eGFR and baseline blood bicarbonate as continuous covariates. Within-subject correlations will be modeled using an unstructured covariance structure. Time ordering is a repeated measure within subjects. Errors for different subjects are assumed independent with an unstructured covariance structure. The estimation method for the model will be restricted maximum likelihood (REML).

In the event the MMRM model with an unstructured covariance structure does not converge, the following covariance structures will be used as substitution in the order below. Each subsequent covariance structure will be used only if each previous covariance structure was used and the model did not converge.

1. Toeplitz covariance structure (assuming measurements from samples taken closer together in time are more highly correlated than those from samples taken farther apart)

2. First order of auto-regressive [AR(1)] covariance structure (assuming measurements from samples taken closer together in time are more highly correlated than those from samples taken farther apart)
3. Compound symmetry covariance structure (assuming equal correlation for measurements from a subject, regardless of how far apart in time when they were taken)

14.4.3 Reporting Results

The least squares (LS) mean of CFB in blood bicarbonate, standard error (SE) of the LS mean, two-sided 95% CI of the LS mean, and p-value from the mixed model will be reported by treatment group and time point. The LS mean difference of the CFB in blood bicarbonate between the TRC101 group and the placebo (i.e., TRC101 – placebo), SE of the LS mean difference, 95% CI of the LS mean difference, and the p-value of the LS mean difference from the mixed model will be provided by time point.

In addition, descriptive statistics for blood bicarbonate at baseline and at each scheduled post-baseline time point, along with CFB in blood bicarbonate, will be summarized by treatment and time point. Graphs will be produced to show:

- LS mean ± 95% CI of change from baseline in blood bicarbonate (from the mixed model) by treatment group over time
- Arithmetic mean ± SE of change from baseline in blood bicarbonate (from descriptive statistics) by treatment group over time
- LS mean ± 95% CI of blood bicarbonate (from the mixed model) by treatment group over time
- Arithmetic mean ± SE of blood bicarbonate (from descriptive statistics) by treatment group over time

14.4.4 Statistical Testing

Using the above described mixed model (Section 14.4.2), LS $\text{mean}_{\text{TRC101}}$ = LS $\text{mean}_{\text{placebo}}$ at the Week 12 Visit will be formally tested for statistical significance, only when the primary efficacy endpoint is statistically significant. In order to maintain the family-wise error rate, a statistically significant TRC101 effect (LS mean difference >0) will be declared if the two-sided p-value at Week 12 is <0.05 and the primary efficacy endpoint is statistically significant.

14.5 Sensitivity Analyses for Primary and Secondary Efficacy Endpoints

In order to evaluate the potential effect of missing data on the primary and secondary efficacy results, sensitivity analyses will be performed using multiple imputation models under a MNAR assumption for the MITT analysis set. We will use a multiple imputation method with Copy Reference (CR) method using estimated means in the placebo group. The method is based on the assumption that subjects who stop taking TRC101 will no longer benefit from it in the future, and thus will tend to have outcomes similar to those in the placebo group. Although the scientific justification of the method seems reasonable, it is important to note that any such sensitivity analysis still relies on untestable assumptions about unobserved data, so does ignoring the missing data as the primary outcome.

Multiple imputation inference involves the following three steps:

1. The missing bicarbonate data are filled in *m* times to generate *m* complete datasets using SAS® PROC MI based on multiple imputation method CR. We will set *m* to be 100.
2. The analysis methods described in Sections 14.3.1 and 14.4.2 will be applied to the *m* completed datasets.
3. The results from the *m* completed datasets are combined using SAS® PROC MIANALYZE for confirmatory of the primary and secondary efficacy analyses.

14.6 Subgroup Analyses of the Primary and Secondary Efficacy Endpoints

Subgroups defined in Section 11.10 will be used to explore the effect of the primary and secondary efficacy endpoints by intrinsic and extrinsic factors. The subgroup analyses for the primary efficacy endpoint will be analyzed as described in Section 14.3.1. The subgroup analyses for the secondary efficacy endpoint will be analyzed as described in Sections 14.4.2 and 14.4.3.

14.7 Exploratory Efficacy Analyses - KDQOL and Repeated Chair Stand Test

The exploratory efficacy variables, the total score of the KDQOL Question 3 items (daily activities) and the repeated chair stand test duration (time, in seconds, to complete five stands), will be collected at baseline and once at the Week 12 Visit or early termination; ANCOVA models will be used for the analyses. The KDQOL Short Form (version 1.3) Question 3 individual item scores (i.e., item a-j) will be transformed as described in the KDQOL Short Form scoring manual

(Hays, 1997). Scores of 1, 2, and 3 will be recoded to 0, 50, and 100, respectively. The total score of the KDQOL Question 3 items is defined as the average of recoded item (i.e., item a-j) scores. The ANCOVA models will comprise the CFB value (i.e., total score of the KDQOL Question 3 items [daily activities] or repeated chair stand test duration, accordingly) as the dependent variable; treatment group as a fixed effect; and the baseline value, the baseline eGFR, and baseline blood bicarbonate as continuous covariates. The LS mean of CFB values, SE of the LS mean, two-sided 95% CI of the LS mean, and p-value from the ANCOVA model will be reported by treatment group. The LS mean difference of the CFB values between the TRC101 group and the placebo (i.e., TRC101 – placebo), SE of the LS mean difference, 95% CI of the LS mean difference, and the p-value of the LS mean difference will also be provided.

Individual items of the KDQOL Question 3, the total score, and change from baseline in total score will be presented in a subject listing. Repeated chair stand time to complete five stands, change from baseline in duration, reason for failed test, single chair stand result (with or without help, without or without using arm to stand) will be provided in subject listing.

14.8 Other Efficacy Analyses

14.8.1 Individual Components of the Primary Endpoint

In addition to assessing the primary efficacy for subjects in MITT and PP analysis sets (Section 14.3.1), we will also assess the components of the primary efficacy endpoint (1) having CFB in blood bicarbonate ≥4 mEq/L and (2) having a blood bicarbonate in the normal range (22 to 29 mEq/L). The proportion (expressed as percentages) of MITT subjects with a component at each time point and at the end of treatment will be reported as described in the previous Section 14.3.1.

14.8.2 Categorical Change in Blood Bicarbonate

The proportions (expressed as percentages) of subjects with increases in their blood bicarbonate by ≥ 2, ≥ 3, ≥ 4, ≥ 5, ≥ 6, and ≥ 7 mEq/L at each time point and at the end of treatment will be reported as described in the Section 14.3.1 for MITT subjects.

14.8.3 Change from Baseline in Biomarkers at Week 12

Efficacy variables, such as parathyroid hormone, serum pre-albumin, 25-hydroxy-vitamin D, urinary biomarkers of bone resorption (NTX and CTX), serum biomarkers of bone resorption (TRAP 5b, BSAP, and P1NP), urine renal biomarkers (aldosterone, uric acid, sulfate, and ET-1), and serum osteocalcin, all collected at baseline and once post baseline (at Week 12 Visit or early termination) will be analyzed using ANCOVA models similar to those described in Section 14.7, except for UAGT. Aldosterone, uric acid, sulfate, CTX, NTX, endothelin-1, and angiotensinogen are measured in the 24-hour urine collection.

For UAGT, geometric mean and 95% CI of the geometric mean, along with n, min and max, will be presented by treatment group and time point. The ANCOVA models will comprise the natural logarithm of the post baseline UAGT value as the dependent variable; treatment group as a fixed effect; and the natural logarithm of baseline value, the baseline eGFR, and baseline blood bicarbonate as continuous covariates. The geometric LS mean and two-sided 95% CI of the geometric LS mean from the ANCOVA model will be reported by treatment group. The geometric LS mean ratio (TRC101/placebo), 95% CI of the geometric LS mean ratio, and the p-value will also be provided. The geometric (LS) mean and its 95% CI will be obtained by exponentiating the (LS) mean and 95% CI on the natural log-scale.

14.8.4 Subgroup Analysis of Change in i-STAT Blood Bicarbonate Over Time

The treatment effect on i-STAT blood bicarbonate in subjects from different randomization strata (i.e., baseline blood bicarbonate ≤18 versus >18 mEq/L and screening eGFR <30 versus ≥30 mL/min/1.73m^2) and dose titration status (i.e., receiving only 2 packets throughout entire study, up-titrated to 3 packets at any time, and down-titrated to 1 or 0 packet at any time) will be evaluated. The blood bicarbonate values, as measured by an i-STAT point-of-care device, along with change from baseline values, will be summarized by treatment and time point for each stratum and each titration status.

15 SAFETY ANALYSES

One of the study objectives is to assess the safety of TRC101. Safety will be evaluated by adverse events, clinical laboratory test results, vital signs, body weight, ECG findings, and physical examination and by the incidence of blood bicarbonate values > 30 mEqL. All analyses of the safety data will be performed using the safety analysis set, based on the actual treatment a subject received. All descriptive statistics (described in Section 10) will be presented by treatment group in the safety analysis set.

15.1 Safety Variables

Safety variables include:

1. AEs, SAEs and withdrawal of study drug due to AE
2. Having met the high bicarbonate dose interruption criterion (confirmed > 30 mEq/L) at any time during the Treatment Period
3. Laboratory test results
4. Vital signs
5. Body weight
6. Findings from 12-lead ECG

15.2 Adverse Events

TEAEs are defined in Section 11.4.1. All reported AEs (including non-TEAEs) will be listed. All TEAE summary tables will present the number and percentages of subjects reporting TEAEs. A summary of TEAEs by severity, seriousness, and relation to study drug will be tabulated. In addition, TEAEs will be summarized by MedDRA system organ class and preferred term. Subjects can have more than one TEAE per system organ class and preferred term. These summaries will include the following:

- All TEAEs
- TEAEs by worst severity
- Study drug related TEAEs
- Serious TEAEs
- TEAEs leading to study drug discontinuation (if any)
- Death (if any)

At each level of subject summarization, subjects are counted once if they reported at least one TEAE at that level. If a subject reported the same TEAE on multiple occasions, the highest severity (severe > moderate > mild) or study drug relationship (related > probable > possible > unlikely > unrelated) recorded for the event will be summarized. Each summary will be ordered by descending incidence of system organ class and preferred term within each system organ class, based on the Total column.

15.3 Incidence of High Bicarbonate

A summary table will be provided with number and percentage of subjects who had a bicarbonate > 30 mEq/L by time interval during the Treatment Period. The table will also include total number of subjects and total number of occurrences during the Treatment Period.

15.4 Clinical Laboratory Evaluation

Clinical laboratory test results from central laboratories (serum chemistry, hematology, coagulation, spot urine, 24-hour urine and urinalysis) will be summarized using descriptive statistics at baseline and at each scheduled post-baseline time point, unless otherwise specified. Changes from baseline will also be summarized by time point. Serum anion gap values from serum chemistry and urine anion gap from spot urine (Section 10.1.4) will be derived and summarized descriptively, in a similar way as collected laboratory results.

For urine albumin to creatinine ratio (from spot urine), the geometric mean and 95% CI of the geometric mean, along with n, min and max, will be presented by treatment group and time point. At post baseline time point, geometric mean fold rise and 95% CI of geometric mean fold rise will also be presented. The geometric mean and its 95% CI will be obtained by exponentiating the mean and 95% CI on the natural logarithm of urine albumin to creatinine ratio. The geometric mean fold rise and its 95% CI will be obtained by exponentiating the mean and 95% CI on the difference in natural logarithm of urine albumin to creatinine ratio from baseline.

Categorical display methods (e.g., frequencies, shift tables) for laboratory values over time may also be used, as appropriate. The number and percentage of subjects with any out of range chemistry and hematology values (i.e., above upper limit of normal, below lower limit of normal,

above a pre-specified level or below a pre-specified level) will be summarized by time point. Tricida chose these pre-specified levels for laboratory tests because they are more appropriate for the study population than normal ranges for healthy subjects (See Table 4 below).

Table 4 Pre-Specified Threshold Levels for Selected Laboratory Tests

Laboratory Category	Test Name	Pre-Specified Level
Chemistry	Sodium	< 132 mEq/L
Chemistry	Potassium	< 3.0, < 3.5, > 5.0, > 6.0 mEq/L
Chemistry	Blood bicarbonate	< 10, < 12, > 30, > 32 mEq/L
Chemistry	Creatinine	> 25% increase from baseline
Chemistry	eGFR (based on creatinine and Cystatin C)	< 10 mL/min/1.73m^2, < 15 mL/min/1.73m^2 (among those with eGFR > 18 mL/min/1.73m^2 at baseline) > 30%, > 40%, and > 50% decrease from baseline
Chemistry	Glucose	> 250 mg/dL
Hematology	Hemoglobin	< 9 g/dL
Hematology	Hematocrit	< 27%

Furthermore, in order to examine possible off-target effects of TRC101, the following descriptive summary statistics will be generated:

- CFB in serum potassium for the subset of subjects whose baseline serum potassium is >5.0 mEq/L, any time during the study treatment,
- CFB in serum phosphate for the subset of subjects whose baseline serum phosphate is >5.5 mg/dL, any time during the study treatment, and
- CFB in low density lipoprotein (LDL) for the subset of subjects whose baseline LDL is > 120 mg/dL, any time during the study treatment

Urinalysis results (other than pH and specific gravity), urine microscopic findings, and pregnancy test results will be listed, but not summarized.

From the 24-hour urine collection, the following data will be summarized and listed:

- Change in creatinine clearance (CrCL in mL/min), defined as [24-hour urine volume (mL) * 24 urine Cr (mg/dL)]/[Serum Cr (mg/dL)*1440]
- Change in 24-hour urea nitrogen excretion
- Change in 24-hour albumin excretion
- Change in 24-hour sulfate excretion
- Change in 24-hour uric acid excretion

All laboratory results will be listed. Laboratory results that are above or below normal limits will be flagged in the listings. In addition, laboratory results that meet or exceed the pre-specified levels (i.e., are above [or below as appropriated] the pre-specified levels as shown in the above table) will be flagged.

15.4.1 Summary of Change from Baseline in eGFR

The eGFR values are derived from the central laboratory serum creatinine using the CKD-EPI formula (Section 10.1.3). The eGFR values, CFB and percent CFB will be summarized descriptively by treatment group and time point. Graphs will be produced to show:

- Arithmetic mean ± SE of CFB in eGFR by treatment group over time
- Arithmetic mean ± SE of eGFR by treatment group over time

Because treatment of acidosis may increase muscle over time, a cystatin based eGFR will be used to evaluate eGFR changes independent of muscle mass changes. The eGFR derived from the central laboratory serum cystatin C values, using the CKD-EPI formula (Section 10.1.3), were measured at baseline and once post baseline. The eGFR values will be summarized at baseline and post baseline along with the CFB and percent CFB in eGFR will be summarized by treatment group.

15.4.2 Summary of Change from Baseline in Blood pH and Base Excess

This analysis will evaluate blood pH and base excess measured by the i-STAT point-of-care device. The blood pH and base excess values and CFB in blood pH and base excess will be summarized by treatment group and time point. All measurements from the i-STAT point-of-care device will be listed.

15.4.3 Bicarbonate Measurements from Local Laboratory

Blood bicarbonate concentrations from the local laboratory, using either the enzymatic assay or a benchtop venous blood gas analyzer, will be listed by subject. Other parameters measured by the benchtop venous blood gas analyzer will also be included in the listing.

15.5 Vital Signs

Descriptive statistics for blood pressure, heart rate, respiratory rate, and temperature, including baseline values and change from baseline values, will be summarized by treatment group and time

point. In addition, number and percentage of subjects with any out of range values (i.e., above a pre-specified level or below a pre-specified level) will be summarized by time point. Tricida chose these pre-specified levels for vital signs because they are more appropriate for the study population than normal ranges for healthy subjects. The pre-specified thresholds levels for vital signs (See Table 5 below).

Table 5 Pre-Specified Threshold Levels for Vital Signs

Vital Sign	Pre-Specified Level
Systolic blood pressure	< 100, > 190 mmHg, > 30% increase or decrease from baseline
Diastolic blood pressure	> 95 mmHg, > 20% increase or decrease from baseline
Heart rate	< 40, > 100 beats/min
Respiratory rate	< 10, > 20 breaths/minute, increase or decrease from baseline by ≥ 6 breaths/minute

All vital signs parameters will be listed. The listing will flag any vital signs that exceed the levels provided in the table above.

15.6 Body Weight

Descriptive statistics for body weight measurements, including baseline values and change from baseline values, will be summarized by treatment group and time point. Body weight measurements will be listed along with vital signs.

15.7 12-lead Electrocardiograms

Listings will present ECG data, such as clinical interpretation of ECGs, ECG rhythm and assessments of heart rate (HR), and intervals of QRS, QT, and PR. The baseline cardiac rhythm will be descriptively summarized. Descriptive statistics for observed values and change from baseline at each time point will be presented for these 12-lead ECG interval and HR assessments. In addition, the number and percentage of subjects with any abnormal values (i.e. outside a pre-specified threshold) will be summarized by treatment and time point. The pre-specified levels of ECG QTc thresholds are consistent with FDA guidance (See Table 6 below).

Table 6 Pre-Specified Threshold Levels for ECG Parameters

ECG Parameter	Pre-Specified Level
PR	> 200 msec
QTcF	> 450, > 480 or > 500 msec, > 30 or > 60 msec increase from baseline
Heart rate	< 40, > 100 beats/minute

All ECG parameters will be listed. The listing will flag any results that outside the above levels provided in the table above.

15.8 Physical Examination

Abnormal clinically significant findings are reported as Medical History or Adverse Events depending on date of onset. Abnormal non-clinically significant findings from physical examinations will be listed.

15.9 Safety Monitoring

The Medical Monitor will review blinded safety data on an ongoing basis to identify potential adverse safety trends. The Medical Monitor will routinely review central laboratory results on an ongoing basis. The Data Monitoring Committee (DMC) will review safety data periodically. Details of the DMC safety data review can be found in the Data Safety Monitoring Committee charter.

16 CHANGES RELATIVE TO THE PROTOCOL-SPECIFIED ANALYSIS

16.1 Other Efficacy Analyses

SAP Section 14.8 contains additional efficacy and dosing analyses that were not described in the protocol as follows:

- Additional categorical thresholds of bicarbonate increase ($\geq$2 mEq/L and $\geq$3 mEq/L) was added to further understand potential treatment effect on bicarbonate increase in lower ranges.
- Baseline descriptor of kidney failure risk at 2 and 5 years (i.e., Kidney Failure Risk Equation score) was added to describe baseline kidney failure risks in the study population.

- Analyses exploring the effects of starting dose and dose titration.

While the protocol specified one of the safety endpoints as "Having met the high bicarbonate dose interruption criterion (confirmed > 30 mEq/L) at any time during the Treatment Period.", SAP Section 15.3 describes summaries of subjects who had a bicarbonate > 30 mEq/L event. Removing the "confirmed" qualifier should capture any subjects potentially meeting the high bicarbonate dose interruption criterion at any time during the Treatment Period.

17 Reference

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3. Hays RD, et al. Kidney Disease Quality of Life Short Form (KDQOL-SF^{tm}), Version 1.3: A Manual for Use and Scoring. Rand, 1997.