STATISTICAL ANALYSIS PLAN

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

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Study Number:	TRCA-301E
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Plan Prepared by:	[redacted], MS Statistical Consultant [redacted]

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STATISTICAL ANALYSIS PLAN

Study TRCA-301E

Version 1.0

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

Approval:

[redacted] 12Feb 2019

[redacted], PhD Date

[redacted] Clinical Development

Tricida, Inc.

[redacted] 12Feb2019

Date

Project Statistician

[redacted]

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1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
AA	aldosterone antagonist
ACEi	angiotensin-converting enzyme inhibitor
ACR	albumin to creatinine ratio
ADaM	analysis data model
AE	adverse event
ANCOVA	analysis of covariance
AR (1)	first-order autoregressive structure
ARB	angiotensin II receptor blocker
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BSAP	bone-specific alkaline phosphatase
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CFB	change from baseline
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CM	concomitant medication
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CRO	clinical research organization
CSR	clinical study report

Abbreviation	Description
CTX	C-terminal telopeptide
DDD	death, renal replacement therapy, or doubling of serum creatinine
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
eGFR(Cys)	estimated glomerular filtration rate derived from serum cystatin C
ET	early termination
FDA	The Food and Drug Administration
HR	heart rate
ICH	International Council on Harmonisation
IRT	interactive response technology
KDQOL	kidney disease quality of life questionnaire
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent-to-treat
MMRM	mixed-effect model repeated measures
MRA	mineralocorticoid receptor antagonist
n	number of subjects
NTX	N-terminal telopeptide
PP	per-protocol
PT	preferred term
P1NP	procollagen 1 N-terminal propeptide
QTcF	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing, corrected using Fridericia's formula

Abbreviation	Description
RAAS	renin-angiotensin-aldosterone system
REML	restricted maximum likelihood
RRT	renal replacement therapy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SE	standard error
SF-36	36-item Short Form Health Survey
SMQ	Standardised MedDRA Queries
SOC	system organ class
TEAE	treatment-emergent adverse event
TLFs	tables, listings, and figures
TRAP 5b	tartrate-resistant acid phosphatase 5b
USA	United States (of America)
WHO DD	World Health Organization drug dictionary

2 REVISION HISTORY

Version	Date	Document Owner	Revision Summary
1.0	12Feb2019	[redacted]	Original

3 RELEVANT DOCUMENTS: PROTOCOL, AMENDMENTS AND CASE REPORT FORMS

Original Protocol (September 5, 2017)
Protocol Amendment 1 (December 11, 2017)
Protocol Amendment 2 (May 31, 2018)
Protocol Amendment 3 (October 17, 2018)
Case Report Form (CRF) Version 1.0 (December 14, 2017)
CRF Version 2.0 (January 29, 2018)
CRF Version 3.0 (June 29, 2018)

4 COMMITMENT TO GOOD STATISTICAL PRACTICE

4.1 Definition of Good Statistical Practice

Guidance on Statistical Principles for Clinical Trials from International Council 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.

Tricida and [redacted] 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) datasets and Analysis Data Model (ADaM) statistical analysis files for producing analysis results. Other applicable standards include regulatory guidance from the Food and Drug Administration (FDA) and ICH:

- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3)
- ICH Guidance for Good Clinical Practice (ICH E6 [R2])
- ICH Guidance for Statistical Principles for Clinical Trials (ICH E9)

5 PURPOSE OF THE ANALYSIS PLAN

The purpose of this statistical analysis plan (SAP) is to pre-specify the statistical analysis methods for supporting the completion of the clinical study report (CSR) for Study TRCA-301E for investigational product TRC101. This SAP will be used for data analysis and evaluation of the long-term safety and durability of TRC101 effect in chronic kidney disease (CKD) patients with metabolic acidosis. The planned analyses identified in this SAP may be included in regulatory submissions, and/or future manuscripts. The analysis methods described in this plan are considered *a priori*, in that they have been prospectively defined prior to clinical database lock. Exploratory analyses, which are not defined in this SAP, may be performed to support the clinical development program. Any changes from the planned analyses as stated in the study protocol will be documented in the CSR.

6 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.

The durability of effect of TRC101 will primarily be evaluated through the following analyses:

- Responder at the end of treatment (Week 52 Visit) (see definition in Section 10.2.3 and analysis in Section 14.2)
- Change from baseline in serum bicarbonate at the end of treatment (Week 52 Visit) (see definition in Section 10.2.2 and analysis in Sections 14.3)
- Change from baseline in total score of kidney disease quality of life questionnaire (KDQOL) Physical Functioning Survey (Week 52 Visit) (see definition in Section 10.2.16 and analysis in Sections 14.4)
- Change from baseline in the duration of repeated chair stand test (Week 52 Visit) (see definition in Section 10.2.17 and analysis in Sections 14.4)

7 STUDY DESIGN

7.1 Overall Study Design

This study is a 40-week, blinded (Investigators and subjects), 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 completed the 12-week Treatment Period in Study TRCA-301 (the parent study) had the option to participate in this extension study. 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 or early termination [ET]).
- Follow-up Period (2 weeks after discontinuation of treatment).

After the subject provided informed consent, the subject's eligibility was to be evaluated based on laboratory values, vital signs, renal status, and pregnancy test (if applicable). Eligible subjects continued to be treated with the same study drug they received in the parent study (TRC101 or placebo, once daily [QD]), on an out-patient basis for the subsequent 40 weeks (Treatment Period). The first dose of study drug in this extension study was taken on the day of the Week 12 Visit.

The maximum duration of Study TRCA-301E was anticipated to be 42 weeks per subject (i.e., 40-week Treatment Period and 2-week Follow-up Period). Assessments and procedures for evaluation of safety were conducted per the protocol-specified schedule (see Table 1 for details).

Enrollment in Study TRCA-301E was defined by completion of the enrollment procedure in the interactive response technology (IRT) system. The enrollment procedure in the IRT system was

performed once subjects had completed participation in Study TRCA-301, they had provided informed consent for the extension study, and the Investigator (or designee) had determined they met all TRCA-301E eligibility criteria.

Table 1 Study TRCA-301E Schedule of Events (Protocol Amendment 3)

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 Physical Functioning Survey		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; ET = early termination; F = follow-up; IRT = interactive response technology; KDQOL = kidney disease quality of life; L = local laboratory assessment; UNS = unscheduled; W = week.

[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 Protocol 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.

7.2 Randomization and Blinding

There is not a separate randomization for this extension study; subjects remained in the same treatment group (TRC101 or placebo) to which they were assigned in the parent study, Study TRCA-301.

The subjects, Investigators, site personnel (including all those involved in collection of safety and efficacy information) and clinical research organization (CRO) staff (except for those responsible for monitoring of potentially unblinding data [i.e., drug accountability]) are blinded to the subject's treatment assignment. To avoid unblinding of blinded site personnel to treatment assignment, strict blinding procedures related to drug accountability are to be adhered to at the site level for this study, similar to those utilized for the parent study. Specifically, designated site staff, with no other responsibilities for the study, are 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.

7.3 Assessments in Study TRCA-301E

Table 1 shows the schedule of events of this study.

7.3.1 Safety Measurements

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

7.3.2 Efficacy Measurements

Efficacy is assessed by

- i-STAT bicarbonate measurements at Weeks 14, 16, 20, 24, 28, 34, 40, 46, 52/ET, 53, and 54.
- KDQOL Physical Functioning Survey and repeated chair stand test results at Weeks 40 and 52/ET.

7.3.3 Other Measurements

Blood and 24-hour urine samples for assessment of biomarkers are scheduled to be collected at Week 52/ET. The 24-hour urine collections at Week 52/ET will also be used to characterize albumin, sulfate, uric acid and urea nitrogen excretion.

8 SAMPLE SIZE AND POWER

No sample size and power calculation were performed since this is an extension to the parent study, TRCA-301.

9 ANALYSIS SETS

TRCA-301E is an extension study in which all subjects continued on their original treatment assignment from the parent study, TRCA-301. To facilitate review of the TRCA-301E data analysis results, some of the tables, listings and figures (TLFs) will include data from all visits since the start of the TRCA-301 study.

9.1 TRCA-301E Safety Analysis Set

The TRCA-301E Safety Analysis Set is defined as all subjects who received any amount of study drug (TRC101 or placebo) in Study TRCA-301E.

9.2 TRCA-301E Modified Intent-To-Treat Analysis Set

The TRCA-301E Modified Intent-To-Treat (MITT) Analysis Set is defined as all randomized subjects who had both baseline and at least one post-baseline serum bicarbonate value measured using the i-STAT device in the parent Study TRCA-301 and at least one serum bicarbonate value after the Week 12 Visit in Study TRCA-301E. The TRCA-301E MITT Analysis Set will be the main evaluation for the durability of TRC101 efficacy, based on the randomized treatment assignment in Study TRCA-301.

9.3 TRCA-301E Per Protocol Analysis Set

The TRCA-301E Per-Protocol (PP) Analysis Set is defined as all subjects in the TRCA-301E MITT Analysis Set who completed both the 12-week Treatment Period of the parent Study TRCA-301 and the 40-week Treatment Period of Study TRCA-301E without important protocol

deviations, and who were treated with study drug and had ≥ 80% study drug dosing compliance in Study TRCA-301E. The TRCA-301E PP Analysis Set will be supportive for evaluation of the primary durability of efficacy endpoints, based on the randomized treatment assignment in Study TRCA-301.

9.4 Phase 3 Safety Analysis Set

The Phase 3 Safety Analysis Set is defined as all subjects who received any amount of study drug (TRC101 or placebo) in the parent Study TRCA-301, regardless of subjects' enrollment in the extension Study TRCA-301E. All data collected during both studies (TRCA-301 and TRCA-301E) will be included in the Phase 3 Safety Analysis Set.

9.5 Randomized and Enrolled Subjects

All randomized subjects are those 217 subjects who were randomized in the parent Study TRCA-301. Subjects enrolled in the extension Study TRCA-301E are those 196 subjects who completed Study TRCA-301 and rolled over into the extension study. The disposition summary will include all randomized subjects. Summaries for baseline characteristics and medical histories will consist of the TRCA-301E enrolled subjects.

10 GENERAL CONSIDERATIONS

The analysis sets as defined in Section 9 will be used for analyses of safety and durability of effect. Subject listings of all analysis data that support summary tables and/or figures will be provided. Measurements from subjects excluded from the pre-defined analysis sets or extra measurements (such as unscheduled or repeat assessments) will be included in the subject listings, but not included in summary tables, unless specified otherwise. In general, subject listings will be sorted by treatment group, subject number, study ID, assessment date, and assessment time (as applicable).

10.1 Convention for Data Presentation

For most summary statistics, data will be analyzed and displayed by treatment group, where applicable. 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 n will be presented as an integer; the same level of precision as in the observed/reported value will be presented when reporting minimum and maximum; 1 more level of precision than in the observed/reported value will be presented when reporting mean and median; and 2 more levels of precision than in the observed/reported 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 the nearest tenth, 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 (TRC101 or placebo).

Results of statistical analyses will be reported using 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.

Final analyses and summaries will be produced using SAS® version 9.4. Mock-shells of TLFs for the CSR are presented in Appendix 19.5.

10.2 Definitions and Derived Variables

10.2.1 Baseline Values

Baseline values for all safety and efficacy variables are defined as the last non-missing assessment prior to the first dose of study drug in the parent Study TRCA-301, unless otherwise specified.

10.2.1.1 Baseline Serum Bicarbonate Value Using i-STAT

Serum bicarbonate values are measured onsite using an i-STAT point-of-care device. The Baseline Bicarbonate is defined as the average of the values of serum bicarbonate collected at the Screening 1 Visit, Screening 2 Visit, and Baseline Visit (i.e., Day 1 pre-dose) in the parent Study

TRCA-301. This value will be used for derivation of change from baseline in serum bicarbonate and will serve as a covariate in statistical models, as appropriate.

10.2.1.2 Screening and Baseline Estimated Glomerular Filtration Rate Values

The Screening estimated glomerular filtration rate (eGFR) value is defined as the average of the values of eGFR collected at the Screening 1 and Screening 2 Visits, based on serum creatinine measurements, in the parent study, Study TRCA-301.

The Baseline eGFR value is defined as the average of the eGFR collected at the Screening 1 Visit, Screening 2 Visit, and Day 1 pre-dose, as measured by the central laboratory in the parent Study TRCA-301. All available eGFR measurements from these three protocol-specified visits will be included in the baseline value calculation. This value will be used for derivation of the change from baseline in eGFR and will serve as a covariate in statistical models, as appropriate.

10.2.1.3 Baseline Serum Creatinine

The Baseline Creatinine value is defined as the average of the serum creatinine collected at the Screening 1 Visit, Screening 2 Visit, and Day 1 pre-dose, as measured by the central laboratory in the parent Study TRCA-301. All available serum creatinine measurements from these three protocol-specified visits will be included in the baseline value calculation. This value will be used for derivation of the change from baseline in serum creatinine.

10.2.1.4 Baseline Urine Albumin-to-Creatinine Ratio

The baseline spot urine albumin-to-creatinine ratio (Baseline spot ACR) is defined as the geometric mean of the ACR measurements collected at the Screening 1 Visit and Day 1 Visit, as measured by the central laboratory in the parent Study TRCA-301. All available ACR measurements from these two protocol-specified visits will be included in the baseline value calculation. The baseline ACR from the 24-hour urine sample (Baseline 24-hour ACR) will be derived by the ratio of albumin and creatinine from a sample of that urine on or prior to the Day 1 Visit.

10.2.1.5 Baseline Electrocardiogram Parameters

12-lead ECG parameters were collected in triplicate on Day 1 pre-dose in the parent Study TRCA-301. The mean of the ECG intervals and heart rate measurements will be used as baseline and for derivation of the change from baseline values.

10.2.2 Change from Baseline Value

The change from baseline value will be calculated as the measured value subsequent to the first dose of study drug in the parent Study TRCA-301 minus the baseline value.

10.2.3 Responder

A responder is defined as a subject who, at a specified point in time, had a change from baseline in serum bicarbonate ≥ 4 mEq/L or had a serum bicarbonate in the normal range (22 - 29 mEq/L), as measured onsite using an i-STAT point-of-care device.

10.2.4 Study Day

In Study TRCA-301E, Study Day, which follows the CDISC SDTM standard, is defined as (Assessment date – date of first study drug dosing in the parent Study TRCA-301) + 1.

10.2.5 Age

Age (years) will be calculated as the number of years between date of birth and date of informed consent in the parent Study TRCA-301, expressed as an integer.

10.2.6 Estimated Glomerular Filtration Rate

The eGFR value will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula from serum creatinine. The primary analysis for change in eGFR will be based on serum creatinine reported by the central laboratory. Because of the potential for changes in muscle mass related to bicarbonate correction, eGFR calculated from serum cystatin C levels (at the Week 52/ET Visit) will also be evaluated as an exploratory analysis.

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 × minimum (Serum cystatin C/0.8,1)$^{-0.499}$ × maximum (Serum cystatin C/0.8,1)$^{-1.328}$ × 0.996^{Age} × 0.932 [if female].

10.2.7 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).

10.2.8 Multiple Records at a Time Point

For analysis purposes, the mean value of multiple measurements collected from subjects in the same position (i.e., supine, standing, etc.) at a visit will be used for that time point. Summary of the vital sign parameters will be presented by treatment and time point, regardless of the subjects' position (e.g., supine, sitting) during recording of the vital signs. All collected measurements and the mean values will be listed.

10.2.9 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as all AEs with an onset date or worsening in severity on or after the date of the first dose of study drug in the parent Study TRCA-301 (also in Section 11.3.1). Related AEs are those reported by the investigator as having a relationship to study drug that is "related", "probable" or "possible." TEAEs with onset date or worsening in severity after the enrollment in Study TRCA-301E (i.e., Week 12 Visit) will be identified as TRCA-301E TEAEs. Ongoing AEs with an onset date during Study TRCA-301 that were ongoing when the subject enrolled in the extension study were reported as TEAEs in Study TRCA-301.

10.2.10 Prior and Concomitant Medications

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 date of the first dose of study drug in the parent Study TRCA-301. Concomitant medications are defined as all prescription and over-the-counter medications that are used concurrently with study drug and through the post-treatment follow-up. A prior medication can also be a CM (see also Section 11.3.2) if it continued after the first dose of study drug in the parent Study TRCA-301. Medications with start date after the enrollment in Study TRCA-301E (Week 12 Visit) will be identified as CMs that were started in the extension study.

Ongoing CMs with a start date during or prior to the first dose of study drug in the parent Study TRCA-301 and that were ongoing when the subject enrolled into TRCA-301E will be reported as CMs for both studies.

10.2.11 Alkali Therapy

Oral alkali therapies are medications containing bicarbonate or bicarbonate equivalents, such as sodium bicarbonate, potassium citrate or sodium citrate. Baseline alkali therapies are those medications that were used at the start of study treatment in the parent Study TRCA-301. Alkali dose change information was collected on the CRF at each visit. These data will be used for analyses to determine if a dose change occurred. Given that oral alkali treatment was algorithmically stopped and re-started in Study TRCA-301E, the number (%) of subjects who changed their oral alkali treatment, as well as reasons for such change, will be summarized by scheduled time point. The dose changes will be indicated in the medication listing.

10.2.12 Acid Reducing Drug

An acid reducing drug is defined as a CM (Section 10.2.10) with coded text of Anatomic Therapeutic Chemical (ATC) class level 2 being “DRUGS FOR ACID RELATED DISORDERS” using the World Health Organization Drug Dictionary (WHO DD).

10.2.13 Calcium Supplement Medication

Calcium supplement medications will be determined by the medical monitor through his/her review of the medication data. Calcium supplement medications will be flagged in the medication listing.

10.2.14 Antihypertensive Medication

Antihypertensive medications will be determined by the medical monitor through his/her review of the medication data. Antihypertensive medications will be flagged in the medication listing.

10.2.15 Diuretic Medication

The concomitant use of loop and thiazide-type diuretics (i.e., potassium-wasting diuretics) will be summarized. Examples of loop diuretics include furosemide, piretanide, bumetanide and torasemide. Examples of thiazide-type diuretics include chlorothiazide (e.g., Diuril®), chlorthalidone, hydrochlorothiazide (e.g., Microzide®), indapamide and metolazone. Combination drugs that include a loop or thiazide diuretic will be include in the above counts. A newly added diuretic is one of these medications started during Study TRCA-301E. A subject will be considered to have received both types of diuretics if both medications started during TRCA-301E.

Potassium-sparing diuretics include spironolactone, eplerenone and amiloride.

10.2.16 KDQOL Physical Functioning Survey

The KDQOL is a validated, kidney disease-specific measure of health-related quality of life (Hays 1997). This instrument includes the 36-item Short Form Health Survey (SF-36) as a generic chronic disease core, as well as items relevant to patients with kidney disease, such as symptoms, burden of illness, social interaction, staff encouragement, and patient satisfaction. For studies TRCA-301 and TRCA-301E, Item 3 of the KDQOL, also known as the SF-36 Physical Function subscale, was selected to measure physical functioning and is referenced herein as the KDQOL Physical Functioning Survey.

10.2.17 Repeated Chair Stand Test

The repeated chair stand test was used as a measure of lower extremity muscle strength. It is among the group of measures (gait speed, chair stand, and balance tests) comprising the Short Physical Performance Battery, which has been used as a predictive tool for possible disability and for monitoring physical functioning in older people (Guralnik 1995).

10.2.18 Hemolysis

Serum potassium results will be excluded from data analysis, if the test sample was hemolyzed. Hemolyzed results are defined as values > 50 mg/dL hemoglobin based on the LIH assay and these will be considered a "fail" for potassium.

10.3 Analysis Windows

Clinic 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 (Section 10.2.4). 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 scheduled time point (or target Study Day). Analysis visit windows are presented in Table 2 by type of assessments and/or measurements. For summary tables that present data for Week 52/ET, the data will include the last measurement or assessment that was collected at that visit.

Table 2 Analysis Visit Windows

Scheduled Time Point	Target Study Day	Analysis Visit Windows (Study Day)					
		Bicarbonate, Serum Chemistry, Vital Signs	Haematology, Urinalysis Spot Urine	Repeated Chair Stand Test, KDQOL Physical Functioning Survey	ECG	Physical Examination, Body Weight	Serum Cystatin C, Biomarkers, 24-hour Urine Parameters
Screening 1	-14	low to -8	-	-	-	-	-
Screening 2	-7	-7 to -1	-	-	-	-	-
Day 1	1	1 to 4	-14 to 1	-14 to 1	-14 to 1	-14 to 1	-14 to 1
Week 1	8	5 to 11	2 to 24	-	-	-	-
Week 2	15	12 to 22	-	-	2 to 28	-	-
Week 4	29	23 to 36	-	-	-	2 to 42	-
Week 6	43	37 to 50	25 to 63	-	29 to 63	-	-
Week 8	57	51 to 64	-	-	-	43 to 70	-

Table 2 Analysis Visit Windows

Scheduled Time Point	Target Study Day	Analysis Visit Windows (Study Day)					
		Bicarbonate, Serum Chemistry, Vital Signs	Haematology, Urinalysis Spot Urine	Repeated Chair Stand Test, KDQOL Physical Functioning Survey	ECG	Physical Examination, Body Weight	Serum Cystatin C, Biomarkers, 24-hour Urine Parameters
Week 10	71	65 to 78	-	-	-	-	-
Week 12	85	79 to 92	64 to 91	2 to 91	64 to 91	71 to 91	2 to 91
Week 14	99	93 to 106	-	-	-	-	-
Week 16	113	107 to 127	-	-	-	-	-
Week 20	141	128 to 155	92 to 168	-	-	-	-
Week 24	169	156 to 183	-	-	92 to 203	-	-
Week 28	197	184 to 218	169 to 238	-	-	92 to 280	-
Week 34	239	219 to 260	-	-	204 to 301	-	-
Week 40	281	261 to 302	239 to 322	92 to 322	-	-	-
Week 46	323	303 to 344	-	-		-	-
Week 52	365	345 to 368	323 to 371	323 to 371	302 to 367	281 to 371	92 to 371
Week 53	372	369 to 375	-	-	-	-	-
Week 54	379	≥376	≥372	-	≥368	≥372	-

ECG = electrocardiogram; ET = early termination; KDQOL = kidney disease quality of life
Note: ET Visit is not shown. The summary for the visit will include the last measurement or assessment collected.

11 STATISTICAL AND ANALYSIS ISSUES

11.1 Adjustments for Covariates

The Baseline Bicarbonate and the Baseline eGFR, as continuous covariates, will be included in a statistical model, such as a mixed-model for repeated measures (MMRM) for analysis of change from baseline in serum bicarbonate. Other baseline values of continuous variables will be included in the analysis of covariance (ANCOVA) models (Section 14.4) as covariates.

Baseline Bicarbonate group (≤ 18 versus > 18 mEq/L) was a stratification variable for randomization in the parent Study TRCA-301 and will be used as a subgroup (Section 11.9) to evaluate safety and durability of effect in Study TRCA-301E. Other baseline characteristics, such as age group (< 65 versus ≥ 65 years), sex, Screening eGFR group (< 30 versus ≥ 30 mL/min/1.73m^2), baseline alkali therapy (Yes versus No) and geographic region (Europe versus United States [USA]) may also be used as subgroups (Section 11.9).

11.2 Handling Dropouts or Missing Data

11.2.1 General Considerations

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 20 (e.g., have assessments through Week 20) would have their early termination assessments mapped to the next scheduled visit (i.e., Week 24) based on the analysis window (Section 10.3). A summary including data collected at the Week 52/ET Visit will be presented.

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 "possible", for analysis purposes. In the subject listing, both collected and imputed values will be presented.

11.2.2 Evaluating Missing Data

11.2.2.1 Missing Data in Serum Bicarbonate

If serum bicarbonate data are missing from either treatment group, such data will be considered to be missing at random. Missing data will not be imputed for the analysis of change from baseline in serum bicarbonate. Serum bicarbonate data will be examined by treatment group and scheduled time point. In order to evaluate the potential effect of missing data on the durability of effect, sensitivity analyses (Section 14.8.1) for responders and change from baseline in serum bicarbonate will be performed using multiple imputation models under a missing not at random (MNAR) assumption for the TRCA-301E MITT Analysis Set.

11.2.2.2 Missing Data in KDQOL Physical Functioning Survey and Repeated Chair Stand Test

The reasons for missing time to complete repeated chair stand test results may include, but are not limited to: a) the subject was weak and thus unable to stand up from the chair once; b) the subject could stand up from the chair once, but was unable to do so five times as required for the repeated chair stand test; c) the subject was physically unable to perform the test, for example

due to below the knee amputation of both lower extremities; and d) the subject missed a visit. The reasons for missing data will be examined by treatment group and scheduled time point.

For both analysis of the KDQOL Physical Functioning Survey and the repeated chair stand test, for subjects with no data after the Week 40 Visit, the Week 40 Visit value will be used in the analysis.

For the purposes of the main analysis of change from baseline in time to complete the repeated chair stand test, the missing chair stand time for subjects who were unable to perform the chair stand test due to reasons (a) or (b) will be set to 60 seconds, which is the maximum time period allowed for the test. The change from baseline value will be calculated after the imputed values at baseline and/or post baseline time point. The rank-based ANCOVA model will be used for this analysis, by ranking the change from baseline values within each scheduled time point.

A sensitivity analysis (Section 14.8.2) will be performed that excludes subjects who were unable to perform the chair stand test. For subjects with no data after the Week 40 Visit, the Week 40 Visit value will be used in the analysis.

11.3 Handling of Safety Data

11.3.1 Adverse Events

All AE verbatim terms reported on the electronic CRFs 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 in the parent Study TRCA-301, Study Day 1. In Study TRCA-301E, TEAEs are defined as those AEs with an onset or worsening in severity after the date of Week 12 Visit. 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 Study Day 1 (or after the date of Week 12 Visit, for TRCA-301E TEAE).
- Day and month are missing, and the year is equal to or after the year of the first date of study drug dosing (or after the date of Week 12 Visit, for TRCA-301E TEAE);

- Day is missing, and the year is after the year of the first date of study drug dosing (or after year of the date of Week 12 Visit, for TRCA-301E TEAE);
- 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 after the date of Week 12 Visit, for TRCA-301E TEAE); or
- Year is missing.

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

11.3.2 Prior and Concomitant Medications

All medication verbatim terms reported on the electronic CRFs will be mapped according to the WHO DD (Enhanced version, March 1, 2017, B2 format). The medication verbatim terms will be mapped to ATC class and preferred names. Prior and concomitant medications are defined in Section 10.2.10. Two CM flags will be used to identify medications taken in the parent Study TRCA-301 and/or in TRCA-301E (Table 3).

Table 3 Concomitant Medications in TRCA-301 and/or TRCA-301E

Study	Definition of Concomitant Medication
TRCA-301	The CM was given anytime between the date of first study drug dosing in TRCA-301 and the date of last visit in TRCA-301 (either Week 12/ET or Week 14, whichever is the last)
TRCA-301E	The CM was given anytime between date after the Week 12 Visit in TRCA-301E and the date of last visit in TRCA-301E (either Week 52/ET or Week 54, whichever is the last)

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 CM 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.

11.4 Interim Analyses and Data Monitoring

No interim analyses are planned.

11.5 Multicenter Considerations

A total of 25 study centers in Europe and 12 centers in the USA participated in Study TRCA-301, while 22 centers in Europe and 7 centers in the USA participated in Study TRCA-301E. Data from all study centers will be pooled for safety and efficacy analyses, as well as for summaries. Because the number of subjects at each center is small, no analyses will be performed by study center. Geographic region (i.e., Europe and USA) will be used for subgroup analyses.

11.6 Multiple Comparisons, Multiplicity

In order to control family-wise error rate, formal statistical testing for the durability of effect endpoints (described in the protocol as secondary endpoints) will be performed sequentially:

1. A formal comparison between the TRC101 and the placebo groups will be performed using Fisher's exact test for the proportion of responders at the Week 52 Visit.
2. Only when comparison No. 1 is statistically significant at the two-sided 0.05 level, will a formal test for the change from baseline in serum bicarbonate at the Week 52 Visit be performed. A MMRM model will be used to compare the group least squares (LS) means of change from baseline in serum bicarbonate at Week 52.
3. Only when both comparisons No. 1 and No. 2 are statistically significant at the two-sided 0.05 level, will a formal test for the change from baseline in the total score of the KDQOL Physical Functioning Survey at the Week 52 Visit be performed. A rank-based ANCOVA model will be used to compare the group means of change in the total score of the KDQOL Physical Functioning Survey at Week 52.
4. Only when all aforementioned comparisons are statistically significant at the two-sided 0.05 level, will a formal test for the change from baseline in the duration of the repeated chair stand test at the Week 52 Visit be performed. A rank-based ANCOVA model will be used to compare the group means of change in the duration of the repeated chair stand test at Week 52.

11.7 Use of an "Efficacy Subset" of Subjects

TRCA-301E PP Analysis Set will be used for supportive analyses for the primary durability of effect endpoints as outlined in Section 14.1.1.

11.8 Active-Control Studies

There was no active control group. The placebo group will serve as a comparator in this study.

11.9 Examination of Subgroups

Subjects will be categorized into the following subgroups for the purposes of evaluating the safety and the durability of TRC101 effect. All subgroup analyses will be performed using data collected at Week 52.

The subgroup analyses below will be performed for the responder analysis (Section 14.2) and the analysis of change from baseline in serum bicarbonate (Sections 14.3):

- Baseline 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 (Europe versus USA)
- Acid reducing drug (Section 10.2.13) (Yes versus No)

The subgroup analyses below will be performed for the change from baseline in total score of KDQOL Physical Functioning Survey and change from baseline in time to complete the repeated chair stand test:

- Baseline Bicarbonate (≤ 18 versus > 18 mEq/L)
- Age (< 65 versus ≥ 65 years)
- Sex (Male versus Female)
- Baseline Score (above versus below median) for the respective test, KDQOL Physical Functioning Survey or repeated chair stand.

The subgroup analyses below will be performed for the proportion of subjects with hyperkalemia AEs (Section 19.4):

- Baseline Bicarbonate (≤ 18 versus > 18 mEq/L)
- Screening eGFR (< 30 versus ≥ 30 mL/min/1.73m^2)
- Baseline potassium level (below normal range, within normal range, above normal range)
- Diabetes mellitus (Yes versus No)

- Concomitant angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) use (Section 19.1) (Yes versus No)
- Concomitant use of potassium-wasting diuretic (Section 10.2.15) (Yes versus No)
- Concomitant use of potassium-sparing diuretic (Section 19.2) (Yes versus No)
- Concomitant use of ACEi or ARB plus potassium-sparing diuretic (Yes versus No)
- Mean daily dose of the study drug (< mean daily dose versus ≥ mean daily dose) (for events occurring in the TRC101 group only)

12 STUDY PATIENTS

12.1 Subject Disposition

12.1.1 Overall Summary

Enrollment and disposition will be summarized by treatment group and overall. The subject disposition summary will include:

- Number of subjects randomized in Study TRCA-301
- Number (%) of subjects in the Phase 3 Safety Analysis Set
- Number of subjects who completed the 12-week Treatment Period in Study TRCA-301
- Number of subjects who discontinued early from Study TRCA-301
    - The primary reason for early discontinuation
- Number of subjects who enrolled in Study TRCA-301E
- Number (%) of subjects in the TRCA-301E Safety Analysis Set
- Number (%) of subjects in the TRCA-301E MITT Analysis Set
- Number (%) of subjects in the TRCA-301E PP Analysis Set
- Number of subjects who completed the 40-week Treatment Period in Study TRCA-301E
- Number of subjects who completed Study TRCA-301E (i.e., completed the Week 54 Visit)
- Number of subjects who discontinued early from Study TRCA-301E
    - The primary reason for early discontinuation

A listing of disposition will be provided for all randomized subjects. Those subjects who did not enroll in the extension study will be noted with asterisk (*). The dates of last treatment, completed/discontinued study and last contact for these subjects occurred in Study TRCA-301.

12.1.2 Examination of Time to Early Discontinuation of the Study

Time to premature discontinuation will be examined using the Kaplan-Meier method. Percentage, along with the 95% confidence interval (CI) of the percentage, of subjects who discontinued at specified time intervals will be provided. The p-value from the log-rank test comparing the distributions of two treatment groups of early termination will be reported. A Kaplan-Meier plot of the time to premature discontinuation will be provided. This analysis will include all subjects who were randomized into Study TRCA-301. Subjects who completed Study TRCA-301 and did not enroll in the extension study will be censored at their last visit in the parent study. Similarly, subjects who completed Study TRCA-301E will be censored at their last visit in the extension study. The duration is between Day 1 (in the parent Study TRCA-301) to the date of last visit in Study TRCA-301 if a subject did not enroll in the extension study or to the date of last visit in Study TRCA-301E if a subject enrolled in the extension study. The incidence rate of early discontinuation will be calculated as 100% × number of discontinuations / total person-year in the study. Total person-year is the sum of individual subject's duration (year) in the study.

12.2 Protocol Deviations

Protocol deviations that occurred during Study TRCA-301E (i.e., after the Week 12 Visit through Week 54 Visit) will be classified by deviation type (e.g., important or minor) and category (e.g., eligibility criteria, out of window visit, SAE reporting, missed or out of window procedures, etc.). All deviations will be identified and adjudicated prior to database lock. Important protocol deviations are defined per ICH guidance. They are described in detail in the Protocol Deviation Adjudication Memo. Protocol deviation categories include:

- Investigational product
- Informed consent
- Key eligibility criteria
- SAE reporting

- Out of window procedure
- Procedure - missed or not interpretable
- Out of window visit
- Missed visit
- Restricted medications
- Blinding
- Other

The important deviations that occurred during Study TRCA-301E will be presented in a subject listing and summarized by deviation category and treatment group.

12.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group for subjects who enrolled in Study TRCA-301E. Demographic characteristics will include age, age group (< 65 or ≥ 65 years), sex, race, ethnicity and geographic region (Europe or USA). The following baseline characteristics will be summarized: baseline oral alkali therapy use (Yes or No), baseline weight, height, body mass index (BMI), baseline systolic blood pressure (mmHg) and baseline systolic blood pressure group (≤ 135 or > 135 mmHg). Selected baseline laboratory test results will be summarized: Screening eGFR, Screening eGFR group (< 30 or ≥ 30 mL/min/1.72m^2), Baseline eGFR, baseline serum creatinine, Baseline Bicarbonate, Baseline Bicarbonate group (≤ 18 or > 18 mEq/L), baseline serum potassium, baseline potassium group (below, within, or above the limits of normal), baseline spot urine ACR, baseline spot urine ACR group (< 30, ≥ 30 and ≤ 300, > 300 mg/g), baseline 24-hour urine ACR, and baseline 24-hour urine ACR group (< 30, ≥ 30 and ≤ 300, > 300 mg/g). All of the above information will be listed by subject.

12.4 Medical History

General medical history terms will be mapped to preferred terms (PTs) and system organ classes (SOCs) using MedDRA® version 20.0. Additional medical history that may have come to light in the extension study was captured in an additional medical history electronic CRF. General medical history, selected medical history terms, selected signs and symptoms experienced recurrently or continuously during the 3 months prior to Screening in the parent Study TRCA-301, as well as

primary cause of CKD will be summarized by treatment group for subjects who enrolled in Study TRCA-301E. All medical histories will be listed.

13 STUDY DRUG AND OTHER MEDICATIONS

The following data analyses will be performed for the 54-week study duration.

13.1 Study Drug Exposure, Compliance, and Titration

13.1.1 Study Drug Exposure

Study drug exposure during the 40-week Treatment Period in Study TRCA-301E will be descriptively summarized by the total number of packets dispensed, total number of packets consumed, total number of doses taken, total TRC101 dose (g) consumed, mean daily TRC101 dose (g), study drug dosing compliance (%), and duration (days) of exposure. Number (%) subjects taking study drug at different dose levels at any time during the study will be summarized by the number of study drug packets prescribed.

The total number of packets consumed is defined as the total number of packets dispensed – the total number of unused packets returned. Due to study drug titration, the assigned number of packets per day for a subject could change from one time interval to another. The total number of packets expected to be taken is the sum of the number of prescribed number of packets in all time intervals. The total number of doses taken is the sum of dosing days in all time intervals. The total TRC101 dose (g) consumed is derived as 3 g × the total number of packets consumed. The TRC101 mean daily dose is derived as the total TRC101 dose (g) / the total number of doses taken. The duration of study drug exposure in Study TRCA-301E is defined as the number of days on treatment from the date of the Week 12 Visit to the date of last dose. A by-subject listing of exposure will be provided.

13.1.2 Study Drug Compliance

Study drug compliance during the 40-week Treatment Period in Study TRCA-301E (expressed in percentage) is defined as the total number of packets consumed divided by the total number of packets expected to be taken. A subject who completes the 40-week Treatment Period without

dose interruption is expected to take study drug for a total of 280 days. Without dose titration and at 6 g TRC101/day, the total number of packets expected to be taken is 560 packets = 280 days × 2 (i.e., 6 g per day divided by 3 g per packet). Depending on dose titration, the total number of expected packets varies by subject.

13.1.3 Dose Titration

Titration of study drug will be summarized by type (i.e., titration, up-titration, down-titration, dose interruption) and reason for each type of dose change during Study TRCA-301E (i.e., from the Week 12 Visit through the Week 52 Visit). Specifically, the number (%) of subjects with the following information will be summarized by treatment group:

- without any titration
- with any titration
- with an up-titration from
    - 0 to 1 packet
    - 1 to 2 packets
    - 2 to 3 packets
- reason for up-titration
- with a down-titration from
    - 2 to 1 packet
    - 3 to 2 packets
- reason for down-titration
- with a dose interruption from
    - 1 to 0 packets
    - 2 to 0 packets
    - 3 to 0 packets
- reason for dose interruption
- with only up-titration
- with only down-titration
- with both up and down titrations

- with
    - 0 titrations
    - 1 titration
    - 2 titrations
    - 3 titrations
    - 4 titrations
    - 5 or more titrations

13.2 Prior and Concomitant Medications

Prior and concomitant medications (Section 11.3.2) will be summarized for the 42-week TRCA-301E Study Period (i.e., 40-week Treatment Period and 2-week Follow-up Period) 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 preferred name within each ATC class.

13.3 Restricted Medications

The concomitant use of restricted medications during the 42-week TRCA-301E Study Period, as defined in the Study TRCA-301E Protocol Section 5.9 Table 1, will be summarized and listed separately, using the same dictionary mapping as described above. Oral alkali therapy (Section 10.2.11) during the 42-week TRCA-301E Study Period will be summarized by category (stopped dosing or new/dose change) and by timepoint, with reasons for stopping or re-starting oral alkali also summarized.

13.4 Medications Used for Certain Analyses

13.4.1 Calcium Supplements and Selected Antihypertensive Medications

Calcium supplements (Section 10.2.13) used during the 42-week TRCA-301E Study Period will be summarized by category (stopped dosing or new/dose change).a Summary of new/dose changed antihypertensive medications will also be provided by treatment group using WHO DD ATC class and preferred name.

13.4.2 Diuretics

Prior use (i.e., before the first dose of study drug in the parent Study TRCA-301) and new use of loop and thiazide diuretics (Section 10.2.15) during the TRCA-301E 42-week Study Period will be summarized by treatment group. Number (%) of subjects who used loop diuretics, thiazide-type diuretics or both will be presented. The medication listing will flag the two types of diuretics.

14 EFFICACY ANALYSES

All efficacy analyses will be performed using the TRCA-301E MITT Analysis Set. The analyses of the main durability of effect endpoints (Section 14.1.1) will also be performed using the TRCA-301E PP Analysis Set. The change from baseline values will be calculated as described in Section 10.2.2. Baseline values are defined in Section 10.2.1.

14.1 Endpoints, Analyses, and Analysis Variables

14.1.1 Main Durability of Effect Endpoints

The main durability of effect endpoints were defined as secondary endpoints in the Study TRCA-301E protocol.

1. Responder at the end of treatment (Week 52 Visit).
2. Change from baseline in serum bicarbonate at the end of treatment (Week 52 Visit)
3. Change from baseline in the total score of the KDQOL Physical Functioning Survey at the end of treatment (Week 52 Visit)
4. Change from baseline in the duration of the repeated chair stand test at the end of treatment (Week 52 Visit)

14.1.2 Additional Durability of Effect Analyses

Additional durability of effect analyses will be performed by scheduled time point (Table 1):

1. Responder (number and percentage of subjects) at each visit
2. Change from baseline in serum bicarbonate at each visit
3. Individual components of response at each visit
    - Number and percentage of subjects having a change from baseline in serum bicarbonate ≥ 4 mEq/L
    - Number and percentage of subjects having a serum bicarbonate in the normal range (22 to 29 mEq/L)
4. Categorical change from baseline in serum bicarbonate (number and percentage of subjects) at each visit

- ≥ 2 mEq/L
- ≥ 3 mEq/L
- ≥ 4 mEq/L
- ≥ 5 mEq/L
- ≥ 6 mEq/L
- ≥ 7 mEq/L

5. Change from baseline in the total score of the KDQOL Physical Functioning Survey at Week 12 and Week 40
6. Change from baseline in the duration of the repeated chair stand test at Week 12 and Week 40

In addition, the distribution and mean (SD) number of visits when the responder definition (change from baseline in serum bicarbonate ≥ 4 mEq/L or to a level within the normal range [22 to 29 mEq/L]) was met will be summarized by treatment group.

14.1.3 Exploratory Analyses

14.1.3.1 Individual Items from KDQOL Physical Functioning Survey

The change from baseline in individual items (i.e., items a – j) of the KDQOL Physical Functioning Survey will be analyzed at the Weeks 12, 40 and 52.

14.1.3.2 Biomarkers

The change from baseline in the following biomarkers will be analyzed at the end of treatment (Week 52 Visit).

- Parathyroid hormone
- Serum prealbumin
- 25-hydroxyvitamin D
- Urinary biomarkers of bone resorption
  a. N-terminal telopeptide (NTX)
  b. C-terminal telopeptide (CTX)
- Serum biomarkers of bone resorption
  a. Tartrate-resistant acid phosphatase 5b (TRAP 5b)
  b. Bone-specific alkaline phosphatase (BSAP)
  c. Procollagen 1 N-terminal propeptide (P1NP)
- Serum osteocalcin
- 24-Hour urine biomarkers
  a. Endothelin-1

b. Aldosterone
c. Angiotensinogen
d. Endothelin-1 to creatinine ratio
e. Aldosterone to creatinine ratio
f. Angiotensinogen to creatinine ratio

14.1.3.3 Offset of Treatment Effect

Offset of treatment effect will be assessed using the serum bicarbonate data collected during the 2-week post treatment period (i.e., Follow-up Period), when subjects will not receive study drug. The following analyses will be performed at Weeks 53 and 54:

1. Responder
2. Change from baseline in serum bicarbonate
3. Change from the last on treatment serum bicarbonate value

14.1.4 Efficacy Variables

14.1.4.1 Change from Baseline in Serum Bicarbonate

Serum bicarbonate values will be measured onsite using an i-STAT point-of-care device. Change from baseline in serum bicarbonate is defined in Section 10.2.2. A positive change will indicate an increase in serum bicarbonate relative to baseline. The analysis methods for change from baseline in serum bicarbonate are described in Sections 14.3 and 14.6.

14.1.4.2 Categorical Change in Serum Bicarbonate

Binary indicator variables will be used to identify the percentage of patients with increases in post-baseline serum bicarbonate levels at each scheduled time point. The components of the response are:

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

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

- an increase in serum bicarbonate from baseline ≥ 2 mEq/L
- an increase in serum bicarbonate from baseline ≥ 3 mEq/L
- an increase in serum bicarbonate from baseline ≥ 4 mEq/L
- an increase in serum bicarbonate from baseline ≥ 5 mEq/L
- an increase in serum bicarbonate from baseline ≥ 6 mEq/L

- an increase in serum bicarbonate from baseline ≥ 7 mEq/L

The analysis method for the above categorical variables is described in Section 14.6.2.

14.1.4.3 Other Change from Baseline Variables

The following change from baseline variables will be calculated as the measured value subsequent to the first dose of study drug in the parent Study TRCA-301 minus the baseline value:

- Change from baseline in the total score of the KDQOL Physical Functioning Survey (measured at Weeks 12, 40 and 52)
- Change from baseline in the repeated chair stand test duration (measured at Weeks 12, 40 and 52)
- Change from baseline in biomarkers (measured at Week 52)

The analysis methods for the above change from baseline variables are described in Sections 14.4 and 14.6.

Due to the fact that the change from baseline in the individual items of the KDQOL Physical Functioning Survey (i.e., items a – j) (measured at Weeks 12, 40 and 52) are discrete in nature, they will be summarized using counts and percentages.

14.2 Responder Analysis Method

14.2.1 Reporting Results

The number and proportions (expressed as percentages) of responders (Section 10.2.2) at each scheduled time point and at the Week 52 Visit will be calculated. These proportions, along with their exact (Clopper-Pearson) 95% CIs, will be summarized by treatment group and scheduled time point. In addition, the difference in proportion between TRC101 and placebo subjects and its exact 95% CI and the p-value from Fisher's exact test comparing the TRC101 group and the placebo group will be reported by scheduled time point (i.e., on or after Week 14).

14.2.2 Statistical Hypotheses

The primary null hypothesis is that the proportion of subjects who are responders at the Week 52 Visit is the same in the TRC101 and placebo groups: the TRC101 proportion (π_{TRC101}) = the placebo proportion ($\pi_{Placebo}$). The alternative hypothesis is that the proportion of subjects who are

responders at the Week 52 Visit differs in the TRC101 and the placebo groups: the TRC101 proportion (π_{TRC101}) ≠ the placebo proportion ($\pi_{placebo}$).

14.2.3 Statistical Testing

Testing for the difference (TRC101 – placebo) in proportion (≠ 0) at the Week 52 Visit will be conducted using the Fisher's exact test. Durability of effect of TRC101 will be declared when the difference in proportions of responders between TRC101 and placebo at the Week 52 Visit is statistically significant at a two-sided alpha level of 0.05.

14.2.4 Evaluating Interactions

As an exploratory analysis, the interactions between treatment and the following terms will be evaluated using logistic regression models for the responder analysis at the Week 52 Visit.

- Baseline 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)
- Baseline alkali use (Yes versus No)
- Geographic region (Europe versus USA)
- Acid reducing drug (Section 10.2.12) (Yes versus No)

A logistic regression model will include responder (Yes or No) as the dependent variable, treatment, and treatment × subgroup variable interaction term as independent variables. The p-value for testing the treatment × subgroup variable interaction term will be reported.

A forest plot will be generated to include the main analysis and the above subgroups. The p-values of interactions between the treatment and the above subgroups will be presented on the forest plot.

14.3 Analysis Method for Change from Baseline in Serum Bicarbonate

14.3.1 Mixed-effect Model for Repeated Measures

The MMRM model will include the change from baseline in serum bicarbonate as the dependent variable; treatment, scheduled time point (i.e., Week 1 through Week 52), and treatment by scheduled time point interaction as fixed effects; subject as a random effect; and the Baseline eGFR and the Baseline 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)

14.3.2 Reporting Results

The LS mean of the change from baseline in serum bicarbonate, standard error (SE) of the LS mean, and two-sided 95% CI of the LS mean from the mixed model will be reported by treatment and scheduled time point. The LS mean difference of the change from baseline in serum 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-values of the LS mean difference from the mixed model will be provided by scheduled time point.

In addition, descriptive statistics for serum bicarbonate at baseline and at each scheduled post-baseline time point, along with change from baseline in serum bicarbonate, will be summarized by

treatment and scheduled time point. Graphic presentation of serum bicarbonate change over the 52-week period will be plotted:

- LS mean (95% CI of LS mean) of serum bicarbonate by treatment group, including Week 1 through Week 52
- LS mean (95% CI of LS mean) of change from baseline in serum bicarbonate by treatment group, including Week 1 through Week 52
- Arithmetic mean ± SE (from descriptive statistics) of serum bicarbonate by treatment group, including scheduled time points of Screening 1, Screening 2, and Day 1 pre-dose, through Week 54.
- Arithmetic mean ± SE of change from baseline in serum bicarbonate by treatment group, including scheduled time points from baseline to Week 54.

14.3.3 Using Ranked-Based Models

After fitting the MMRM model, the distribution of residuals within each treatment group at a given time point will be tested for normality using the Anderson-Darling test. If the distribution of residuals in both treatment groups at a given time point is normal ($p > 0.05$), then the original values (i.e., the change from baseline values) will be used in the analysis. Methods described in Sections 14.3.1 will be followed. If the distribution of residuals in either treatment group at a given time point is significantly non-normal ($p < 0.05$), then a rank-based model will be used. In this case, only the P-values will be reported from the rank-based model. The LS mean, 95% CI of LS mean, LS mean of group difference, and 95% CI of LS mean of the difference from the candidate model using the original values will be presented.

14.4 Analysis Method for Other Change from Baseline Variables

14.4.1 Analysis of Covariance

Based on the exploratory analyses of residuals from the models using Study TRCA-301 KDQOL Physical Functioning Survey and repeat chair stand data, the normality assumption was violated. Therefore, the rank-based ANCOVA models will be used in data analysis of these endpoints. The rank of the change from baseline value will be the dependent variable; the treatment group will be a fixed effect; and the baseline value of the parameter being analyzed (e.g., total score of the

KDQOL Physical Functioning Survey or the duration of the repeated chair stand test), the Baseline eGFR, and the Baseline Bicarbonate will be continuous covariates.

14.4.2 Reporting Results

The p-value for testing the difference between treatment groups will be reported from the rank-based model at each scheduled post-baseline time point for each parameter. The descriptive statistics of reported values at baseline and at each scheduled post-baseline time point, along with change from baseline values, will be summarized by treatment and scheduled time point. The 95% CI of group means will also be provided.

14.5 Hypothesis and Testing for Change from Baseline Analyses

The following hypothesis and testing will only apply to the following change from baseline variables:

1. Change from baseline in serum bicarbonate at the end of treatment (Week 52 Visit)
2. Change from baseline in the total score of the KDQOL Physical Functioning Survey at the end of treatment (Week 52 Visit)
3. Change from baseline in the duration of repeated chair stand test at the end of treatment (Week 52 Visit)

14.5.1 Statistical Hypothesis

Comparing TRC101 with placebo at the Week 52 Visit, the null hypothesis is the two group means of a change from baseline variable are equal ($\mu_{TRC101} = \mu_{placebo}$). The alternative hypothesis is the two group means of a change from baseline variable are not equal ($\mu_{TRC101} \neq \mu_{placebo}$).

14.5.2 Statistical Testing

Using the above described MMRM or ANCOVA model for a change from baseline analysis, (LS) $mean_{TRC101}$ = (LS) $mean_{Placebo}$ at the Week 52 Visit will be tested for statistical significance. Gatekeeping procedures as described in Section 11.6 will be used in the following sequence:

1. Responder (Week 52 Visit)
2. Change from baseline in serum bicarbonate at the end of treatment (Week 52 Visit)
3. Change from baseline in the total score of the KDQOL Physical Functioning Survey at the end of treatment (Week 52 Visit)
4. Change from baseline in the duration of the repeated chair stand test at the end of treatment (Week 52 Visit)

For a given change from baseline endpoint above, the durability of effect will be declared if the current and all previous hypotheses are rejected. A subsequent formal testing will not be performed if any of the current or previous tests is not rejected.

14.6 Categorical Analysis Methods

14.6.1 Individual Components of the Response

In addition to the responder analysis (Section 14.2), the two individual components of the response (1) having a change from baseline in serum bicarbonate ≥ 4 mEq/L and (2) having a serum bicarbonate in the normal range (22 to 29 mEq/L) will also be assessed. The proportion (expressed as percentages) of subjects with an individual component at each scheduled time point will be reported as described in Section 14.2.1.

14.6.2 Categorical Change in Serum Bicarbonate

The proportions (expressed as percentages) of subjects with increases in their serum bicarbonate by ≥ 2, ≥ 3, ≥ 4, ≥ 5, ≥ 6 and ≥ 7 mEq/L at each scheduled time point will be reported as described in Section 14.2.1.

14.6.3 Individual Items of the KDQOL Physical Functioning Survey

Since the change from baseline in individual items of the KDQOL Physical Functioning Survey is categorical in nature, Cochran-Mantel-Haenszel (CMH) statistics will be used. Number (%) of subjects in each category will also be displayed by scheduled time point and item.

14.7 Analysis of Offset of Treatment Effect

The analysis of offset of treatment effect will be performed by scheduled time point (i.e., Weeks 53 and 54). The proportions (expressed as percentages) of responders will be reported as described in Section 14.2.1. Descriptive statistics of the reported and change from baseline values of serum bicarbonate will be summarized. In addition, the change from the last on-treatment serum bicarbonate value will be summarized descriptively by treatment group and scheduled time point.

14.8 Sensitivity Analyses

14.8.1 Serum Bicarbonate

In order to evaluate the potential effect of missing serum bicarbonate data, sensitivity analyses will be performed using control-based pattern imputation under the missing not at random assumption. 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; however, so does ignoring the missing data. Based on the paper by Ratitch and O'Kelly[1], which describes an implementation of the pattern-mixture model approach using a control-based pattern imputation, the imputation model for the missing observations in the TRC101 group will be constructed not from the observed data in the treatment group but rather from the observed data in the placebo group. This model will also be the imputation model that is used to impute missing observations in the placebo group.

Multiple imputation inference involves the following three steps:

1. The missing observations are filled in *m* times to generate *m* complete datasets using SAS® PROC MI based on the multiple imputation method[1]. We will set *m* to be 10.
2. The analysis methods described in Sections 14.2, 14.3 will be applied to the *m* completed datasets.
3. The results from the *m* completed datasets are combined using SAS® PROC MIANALYZE for confirmation of the analyses.

14.8.2 Time to Complete Repeated Chair Stand Test

A sensitivity analysis will be performed that excludes subjects who were unable to perform the chair stand test at baseline or either at the Week 40 or Week 52 Visit due to any reason.

15 SAFETY ANALYSES

One of the study objectives is to assess the long-term safety of TRC101. Safety will be evaluated by AEs, clinical laboratory test results, vital signs, body weight, ECG findings, and physical examination results. Two safety analysis sets will be used. The first (TRCA-301E Safety Analysis

Set [see Section 9.1]) will be used in the analyses of AEs, clinical laboratory test results, vital signs, body weight, and ECGs. The second (Phase 3 Safety Analysis Set [see Section 9.4]) will be used for time to event analyses. All descriptive statistics (described in Section 10.1) will be presented by treatment group.

15.1 Safety Variables

Safety variables include:

1. AEs, SAEs and withdrawal of study treatment due to AE
2. Having a confirmed serum bicarbonate value > 30 mEq/L
3. Laboratory test results, including
    a. Serum chemistry (Weeks 14, 16, 20, 24, 28, 34, 40, 46, 52/ET, 53, and 54)
    b. Coagulation (Weeks 14, 16, 20, 24, 28, 34, 40, 46, 52/ET, 53, and 54)
    c. Hematology (Weeks 20, 28, 40, 52/ET, 54)
    d. Urinalysis (Weeks 20, 28, 40, 52/ET, 54)
    e. Spot Urine (Weeks 20, 28, 40, 52/ET, 54)
    f. 24-hour urine (Week 52/ET Visit)
    g. Pregnancy test (Weeks 16, 20, 24, 28, 34, 40 ,46, 52/ET, 54)
    h. Cystatin C (Week 52)
4. Vital signs (Weeks 14, 16, 20, 24, 28, 34, 40, 46, 52/ET, 53, and 54)
5. Body weight (Weeks 28, 52/ET, 54)
6. 12-lead ECG rhythm and intervals (Weeks 24, 34, 52/ET, 54)

15.2 Adverse Events

TEAEs are defined in Section 11.3.1. All reported AEs (including non-TEAEs) will be listed. A separate listing will be provided for TEAEs leading to death (if any). Additionally, listings will be provided for selected TEAEs: a) gastrointestinal nonspecific inflammation and dysfunctional conditions identified by the Standardised MedDRA Queries (SMQ, Section 19.3) and b) hyperkalemia (Section 19.4). A listing of deaths and other serious adverse events will be prepared that includes deaths and SAEs that occurred in both Studies TRCA-301 and TRCA-301E. All TEAE summary tables will present the number and percentages of subjects reporting TEAEs.

15.2.1 TEAEs Occurring during Study TRCA-301E

An overall summary of TEAEs that occurred during the extension Study TRCA-301E will be presented by severity, seriousness, and relation to study drug. The denominator will be the total number of subjects from the TRCA-301E Safety Analysis Set in each treatment group. In addition, TEAEs will be summarized by MedDRA SOC and PT. Subjects can have more than one TEAE per SOC and PT. The following summaries will be presented for the TEAEs that occurred during Study TRCA-301E:

- TEAEs by SOC and PT
- TEAEs by worst severity, SOC and PT
- Related TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- TEAEs leading to death (if any) by SOC and PT
- TEAEs leading to study drug discontinuation (if any) by SOC and PT
- TEAEs leading to study drug interruption (if any) by SOC and PT

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 SOC alphabetically and by PT in descending order of the total incidence within each SOC.

15.2.2 Additional Analyses of Selected Adverse Events

Selected TEAEs below that were reported from the date of first dose of study drug in Study TRCA-301E to Week 54 in TRCA-301E will be evaluated:

- Gastrointestinal nonspecific inflammation and dysfunctional conditions that are identified using SMQ (Section 19.3)
- Hyperkalemia events (Section 19.4)

Number (%) of subjects with gastrointestinal nonspecific inflammation and dysfunctional conditions SMQ and hyperkalemia AEs will be summarized. The number (%) of events by the study drug dose level being taken on the onset date of the event will also be summarized. Placebo

is considered as a 0 g dose level. TRC101 treated subjects could be receiving a 0, 3, 6, 9 g dose level.

Hyperkalemia events will be further assessed by the association with the subgroups defined in Section 11.9.

15.3 Summary and Analyses of Death and Renal Disease Progression

Ascertainment of survival status and renal replacement therapy (RRT) status (i.e., started dialysis or received a kidney transplant) will be done at the Week 52 Visit for all subjects enrolled in the TRCA-301E study, including those who discontinued study drug treatment prior to Week 52. A subject listing will be provided.

15.3.1 Survival Analysis

Survival analysis will be performed using data from the parent Study TRCA-301 and the extension Study TRCA-301E (i.e., the Phase 3 Safety Analysis Set). Overall survival time is defined as the duration between the date of first dose of study drug in the parent Study TRCA-301 to the date of death, regardless of the cause of death. Subjects will be censored to the date that the subject was last known to be alive as determined at the last study contact. The Kaplan-Meier method will be used for the analysis of survival. Log-rank test will be used to compare the survival distributions between the treatment groups. In addition, percentage, along with their 95% CI of the percentage, of subjects who were alive at specified time intervals will be provided. A Kaplan-Meier plot of survival will be provided.

15.3.2 Time-to-Event Analyses

Two time to event analyses will be performed in a manner similar to that of the survival analysis. In the first analysis (i.e., time to death or RRT analysis), the event is defined as the first event of death or RRT. RRT is defined as either of the following:

- Initiation of chronic dialysis defined as dialysis that was ongoing at the end of the study or at last follow-up for the study
- Renal transplantation

In the second analysis (i.e., time to death, RRT or ≥ 50% decline in eGFR), the event is defined as the first occurrence of death, RRT, or ≥ 50% decline in eGFR. The eGFR decline is defined as two consecutive qualifying eGFR values ≥ 28 days apart that meet the threshold, with no intervening values that do not meet the threshold. The event onset date is the first collection date of the two qualifying values. A single qualifying value will also count: If there is at least one qualifying value < 28 days prior to the last eGFR value and the immediately preceding value represents a decline of ≥ 40%. These two values must be ≥ 7 days apart. In this case, the first of these 2 values representing a ≥ 50% decline in eGFR will be considered the start date of the event.

The time to event is defined as the duration between the date of first dose of study drug in the parent Study TRCA-301 to the date of first occurrence of the event. Subjects will be censored to the date at which the subject was last known to be

- alive and free from RRT for time to death or RRT analysis
- alive and free from RRT and event of ≥ 50% decline in eGFR for the second time to event analysis

A listing of subject status on survival, RRT, renal function decline (i.e., ≥ 50% decline in eGFR from baseline) will be provided. Kaplan-Meier plots will be provided.

15.4 Incidence of High Bicarbonate

A summary table will be provided with the number and percentage of subjects who met the high bicarbonate dose interruption criterion (confirmed > 30 mEq/L) during the 40-week Study TRCA-301E Treatment Period. The table will also include the total number of subjects and total number of occurrences of any bicarbonate value > 30 mEq/L during the Treatment Period in Study TRCA-301E.

15.5 Clinical Laboratory Evaluation

Continuous clinical laboratory test results from central laboratories (serum chemistry, hematology, spot urine, 24-hour urine and urinalysis) will be summarized using descriptive statistics at baseline and at each scheduled post-baseline time point during Study TRCA-301E. Changes from baseline will also be summarized by treatment group and scheduled time point. An additional summary will be provided for urine ACR (from a spot urine and from the 24-hour urine collection) from the

subset of subjects with a baseline value > 30 mg/g. Categorical display methods (e.g., frequencies) and plots of laboratory values over time may also be used, as appropriate. Table 4 lists all the laboratory parameters to be summarized. Box and whisker plots by treatment group and protocol scheduled time points will be provided for selected electrolytes (i.e., potassium, sodium, and chloride). The graphs will include data from all subjects from the Phase 3 Safety Analysis Set.

Descriptive statistics and out of range summaries for the eGFR derived from the central laboratory serum creatinine values will be presented separately from the chemistry test results described above.

15.5.1 Analysis of Variables Reported as Ratio to Serum Creatinine

Variables such as 24-hour urine endothelin-1-to-creatinine ratio, aldosterone-to-creatinine ratio, angiotensinogen-to-creatinine ratio, 24-hour urine ACR, and spot urine ACR will be summarized descriptively by geometric mean, 95% CI of geometric mean, minimum and maximum. The change from baseline will be reported as the geometric mean ratio (post-baseline/baseline) and 95% CI of the geometric mean ratio.

Table 4 Laboratory Parameters

Test Type	Parameter	Assessment and Summary
Whole serum bicarbonate (venous)	pH, pCO_2, pO_2 and the calculated values for HCO_3, BE, and O_2 saturation	Conducted with i-STAT: Descriptive statistics only
Venous blood gas bicarbonate – benchtop analyzer	pH, pCO_2, pO_2 and the calculated values for HCO_3, BE, and O_2 saturation if reported	Either assay to be conducted at local laboratory or study site: Descriptive statistics only
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, eGFR (derived from creatinine and cystatin C), glucose, magnesium, phosphate, potassium, sodium, serum anion gap.	Conducted at central laboratory: Descriptive statistics and categorical display (See Table 5)
Coagulation	INR	For subjects receiving vitamin K antagonists or factor Xa inhibitors only. Listing only

Table 4 Laboratory Parameters

Test Type	Parameter	Assessment and Summary
Hematology	RBC count, white blood cell count, white blood cell count differential, hemoglobin, hematocrit and platelet count, RBC indices (e.g., MCV, RDW, MCH)	Conducted at central laboratory: Descriptive statistics and categorical display (See Table 5)
Hemoglobin A1c	Glycated hemoglobin	Conducted at central laboratory: Descriptive statistics only
Urinalysis	Bilirubin, glucose, ketones, blood, leukocyte esterase, nitrites, pH, protein, urobilinogen, and urine specific gravity.	Conducted at central laboratory: Descriptive statistics only for pH and specific gravity.
Spot urine tests	Sodium, potassium, chloride, creatinine, anion gap, albumin, ACR.	Conducted at central laboratory: Descriptive statistics only.
24-hour urine collection	Volume, urea nitrogen, sulfate, uric acid, albumin, and creatinine (including ACR)	Conducted at central laboratory: Descriptive statistics only.
Pregnancy test	β-HCG	Conducted at central laboratory (serum pregnancy test). Urine dipstick at study site at the Week 12 Visit only. Listing only.

ACR = albumin-to-creatinine ratio; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BE = base excess; BUN = blood urea nitrogen; CK = creatine kinase; CK-MB = creatine kinase-muscle/brain; eGFR = estimated glomerular filtration rate; HCO_3 = bicarbonate; HDL = high-density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; pCO_2 = partial pressure of carbon dioxide; pO_2 = partial pressure of oxygen; RBC = red blood cell; RDW = red cell distribution width; β-HCG = β-human chorionic gonadotropin.

15.5.2 Out of Range Summary

The number (%) 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 treatment group and scheduled time point. For eGFR thresholds, the proportion of patients meeting the specified threshold at any post-baseline time point during the study will also be summarized by treatment group. Tricida chose these pre-specified levels (Table 5) for laboratory tests because they are more appropriate for the study population than normal ranges for healthy subjects.

Table 5 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, > 5.5, > 6.0 mEq/L results from specimens reported as hemolyzed (Section 10.2.18) will be excluded.

Laboratory Category	Test Name	Pre-Specified Level
Chemistry	Serum bicarbonate	< 10, < 12, > 30, > 32 mEq/L
Chemistry	Creatinine	2-fold increase, confirmed or at last follow up (see Section 15.3.2)
Chemistry	eGFR (based on creatinine)	≤ 10 mL/min/1.73m^2, < 15 mL/min/1.73m^2
Chemistry	Glucose	> 250 mg/dL
Hematology	Hemoglobin	< 9 g/dL
Hematology	Hematocrit	< 27%
Spot Urine and 24-hour urine collection	ACR	> 30 mg/g, > 300 mg/g

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 appropriate] the pre-specified levels as shown in the above table) will be flagged.

15.6 Vital Signs

Descriptive statistics for blood pressure (BP), heart rate (HR), respiratory rate, and temperature, including baseline values and change from baseline values, will be summarized by treatment group and scheduled 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 scheduled 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 threshold levels for vital signs are defined in Table 6.

Table 6 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/min, change 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.

15.7 Body Weight

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

15.8 12-lead Electrocardiogram

Listings will present ECG data, such as clinical interpretation of ECGs, ECG rhythm and assessments of HR, and intervals of PR, QRS, QT, and QTcF. The baseline and on-study cardiac rhythms (normal sinus rhythm, atrial fibrillation, other) will be descriptively summarized. Descriptive statistics for observed values and change from baseline at each scheduled time point will be presented for these 12-lead ECG intervals 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 scheduled time point. The pre-specified levels of ECG QTc thresholds are consistent with FDA guidance (See Table 7).

Table 7 Pre-Specified Threshold Levels for Electrocardiogram 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/min

ECG = electrocardiogram; QTcF = QT interval corrected by the method of Fridericia

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

15.9 Physical Examination

Abnormal clinically significant findings were reported as Medical History or Adverse Events depending on date of onset.

16 SUBGROUP ANALYSES

Subgroups defined in Section 11.9 will be used to explore the durability of the TRC101 effect by intrinsic and extrinsic factors or to further explore safety findings. The variables to be analyzed

for the each of the subgroups are described in Table 8. The analysis methods are described in the sections of the SAP indicated in the table.

Table 8 List of Pre-Specified Subgroup Analyses at Week 52

Type	Variable	Method Section	Subgroup
Efficacy	Responders at Week 52	14.2.1	Baseline Bicarbonate (≤ 18 vs > 18 mEq/L) Screening eGFR (< 30 vs ≥ 30 mL/min/1.73m^2) Age (< 65 vs ≥ 65 years) Sex (Male vs Female) Race (White vs Non-White) Baseline alkali use (Yes vs No) Geographic region (Europe vs USA) Acid reducing drug (Yes vs No)
Efficacy	Change from baseline in serum bicarbonate	14.3	
Efficacy	Change from baseline in total score of KDQOL Physical Functioning Survey at Week 52	14.4	Baseline Bicarbonate (≤ 18 vs > 18 mEq/L) Age (< 65 vs ≥ 65 years) Sex (Male vs Female) Baseline KDQOL Question 3 score (above vs below median baseline KDQOL Physical Functioning Survey score)
Efficacy	Time to complete repeated chair stand test at Week 52	14.4	Baseline Bicarbonate (≤ 18 vs > 18 mEq/L) Age (< 65 vs ≥ 65 years) Sex (Male vs Female) Baseline time to complete repeated chair stand test (above vs below median baseline time)
Safety	Subjects reporting hyperkalemia events	15.2.2.2	Baseline Bicarbonate (≤ 18 vs > 18 mEq/L) Screening eGFR (< 30 vs ≥ 30 mL/min/1.73m^2) Baseline potassium level (below normal range, within normal range, above normal range) Diabetes mellitus (Yes vs No) Concomitant ACEi or ARB use (Yes vs No) Concomitant use of potassium-wasting diuretic (Yes vs No) Concomitant use of potassium-sparing diuretics (Yes vs No) Concomitant use of ACEi or ARB plus potassium-sparing diuretics (Yes vs No) Mean daily dose (< median daily dose level vs ≥ median daily dose level)

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ECG = electrocardiogram; ET = early termination; KDQOL = kidney disease quality of life

17 DEVIATIONS FROM THE PROTOCOL SPECIFIED ANALYSIS

17.1 Analysis of Change from Baseline in Serum Bicarbonate

In the protocol Section 8.6.1, it stated "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." In order to fully evaluate the treatment effect, the planned analysis, uses an MMRM model that comprises serum bicarbonate data from Week 1 in the parent Study TRCA-301 through Week 52 in Study TRCA-301E. The data from the Week 14 Visit through the end of the 40-week Treatment Period will be included in the model.

18 REFERENCES

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19 APPENDICES

19.1 Anatomical Therapeutic Chemical Level 4 Terms for ACEi or ARB

The following is a list of ATC Level 4 terms for ACEi or ARB. Other ATC level 4 terms may be added upon medical review.

- ACE INHIBITORS AND CALCIUM CHANNEL BLOCKERS
- ACE INHIBITORS AND DIURETICS
- ACE INHIBITORS, PLAIN
- ANGIOTENSIN II ANTAGONISTS, PLAIN

19.2 Anatomical Therapeutic Chemical Level 4 Terms for Potassium-Sparing Diuretics

The following is a list of ATC Level 4 terms for potassium-sparing diuretics:

- aldosterone antagonists
- amiloride
- eplerenone
- spironolactone
- other potassium sparing agents

19.3 Gastrointestinal Nonspecific Inflammation and Dysfunctional Conditions (Standardised MedDRA Queries)

The table below lists the PTs for gastrointestinal nonspecific inflammation and dysfunctional conditions using SMQ.

SMQ	Preferred Term
Gastrointestinal nonspecific dysfunction	Acid peptic disease
Gastrointestinal nonspecific dysfunction	Duodenogastric reflux
Gastrointestinal nonspecific dysfunction	Dyspepsia
Gastrointestinal nonspecific dysfunction	Gastrooesophageal reflux disease
Gastrointestinal nonspecific dysfunction	Gastrooesophageal sphincter insufficiency
Gastrointestinal nonspecific dysfunction	Cardiospasm
Gastrointestinal nonspecific dysfunction	Diverticulum intestinal
Gastrointestinal nonspecific dysfunction	Dyschezia
Gastrointestinal nonspecific dysfunction	Dyskinesia oesophageal
Gastrointestinal nonspecific dysfunction	Gastric atony
Gastrointestinal nonspecific dysfunction	Gastric dilatation
Gastrointestinal nonspecific dysfunction	Gastric emptying study
Gastrointestinal nonspecific dysfunction	Gastric fluid analysis abnormal
Gastrointestinal nonspecific dysfunction	Gastric hypermotility
Gastrointestinal nonspecific dysfunction	Gastric hypertonia
Gastrointestinal nonspecific dysfunction	Gastric hypomotility
Gastrointestinal nonspecific dysfunction	Gastric pH decreased
Gastrointestinal nonspecific dysfunction	Gastric pH increased
Gastrointestinal nonspecific dysfunction	Gastrointestinal hypermotility
Gastrointestinal nonspecific dysfunction	Gastrointestinal motility disorder
Gastrointestinal nonspecific dysfunction	Impaired gastric emptying
Gastrointestinal nonspecific dysfunction	Intestinal dilatation
Gastrointestinal nonspecific dysfunction	Intestinal transit time abnormal
Gastrointestinal nonspecific dysfunction	Intestinal transit time decreased
Gastrointestinal nonspecific dysfunction	Intestinal transit time increased
Gastrointestinal nonspecific dysfunction	Myochosis

SMQ	Preferred Term
Gastrointestinal nonspecific dysfunction	Oesophageal achalasia
Gastrointestinal nonspecific dysfunction	Oesophageal dilatation
Gastrointestinal nonspecific dysfunction	Oesophageal hypomotility
Gastrointestinal nonspecific dysfunction	Oesophageal manometry
Gastrointestinal nonspecific dysfunction	Oesophageal pH increased
Gastrointestinal nonspecific dysfunction	Pancreatic enzyme abnormality
Gastrointestinal nonspecific dysfunction	Pancreatic failure
Gastrointestinal nonspecific dysfunction	Presbyoesophagus
Gastrointestinal nonspecific dysfunction	Pylorus dilatation
Gastrointestinal nonspecific dysfunction	Toxic dilatation of intestine
Gastrointestinal nonspecific inflammation	Chronic gastritis
Gastrointestinal nonspecific inflammation	Colitis
Gastrointestinal nonspecific inflammation	Duodenitis
Gastrointestinal nonspecific inflammation	Enteritis
Gastrointestinal nonspecific inflammation	Erosive duodenitis
Gastrointestinal nonspecific inflammation	Erosive oesophagitis
Gastrointestinal nonspecific inflammation	Feline oesophagus
Gastrointestinal nonspecific inflammation	Functional gastrointestinal disorder
Gastrointestinal nonspecific inflammation	Gastric mucosa erythema
Gastrointestinal nonspecific inflammation	Gastritis
Gastrointestinal nonspecific inflammation	Gastritis erosive
Gastrointestinal nonspecific inflammation	Gastroduodenitis
Gastrointestinal nonspecific inflammation	Gastrointestinal erosion
Gastrointestinal nonspecific inflammation	Gastrointestinal mucosa hyperaemia
Gastrointestinal nonspecific inflammation	Gastrointestinal mucosal exfoliation
Gastrointestinal nonspecific inflammation	Haemorrhagic erosive gastritis
Gastrointestinal nonspecific inflammation	Intestinal angioedema
Gastrointestinal nonspecific inflammation	Oesophageal mucosa erythema
Gastrointestinal nonspecific inflammation	Oesophagitis
Gastrointestinal nonspecific inflammation	Reactive gastropathy
Gastrointestinal nonspecific inflammation	Reflux gastritis
Gastrointestinal nonspecific inflammation	Remnant gastritis
Gastrointestinal nonspecific inflammation	Ulcerative gastritis
Gastrointestinal nonspecific inflammation	Allergic colitis
Gastrointestinal nonspecific inflammation	Anal inflammation
Gastrointestinal nonspecific inflammation	Colitis erosive
Gastrointestinal nonspecific inflammation	Colonoscopy abnormal
Gastrointestinal nonspecific inflammation	Diverticulitis

SMQ	Preferred Term
Gastrointestinal nonspecific inflammation	Endoscopic ultrasound abnormal
Gastrointestinal nonspecific inflammation	Endoscopy abnormal
Gastrointestinal nonspecific inflammation	Endoscopy gastrointestinal abnormal
Gastrointestinal nonspecific inflammation	Endoscopy large bowel abnormal
Gastrointestinal nonspecific inflammation	Endoscopy upper gastrointestinal tract abnormal
Gastrointestinal nonspecific inflammation	Faecal calprotectin abnormal
Gastrointestinal nonspecific inflammation	Faecal calprotectin increased
Gastrointestinal nonspecific inflammation	Faecal elastase concentration abnormal
Gastrointestinal nonspecific inflammation	Faecal elastase concentration decreased
Gastrointestinal nonspecific inflammation	Gastric fibrosis
Gastrointestinal nonspecific inflammation	Gastrointestinal inflammation
Gastrointestinal nonspecific inflammation	Intrinsic factor antibody abnormal
Gastrointestinal nonspecific inflammation	Intrinsic factor antibody positive
Gastrointestinal nonspecific inflammation	Oesophageal irritation
Gastrointestinal nonspecific inflammation	Oesophagitis chemical
Gastrointestinal nonspecific inflammation	Oesophagogastroduodenoscopy abnormal
Gastrointestinal nonspecific inflammation	Oesophagogastroscopy abnormal
Gastrointestinal nonspecific inflammation	Oesophagoscopy abnormal
Gastrointestinal nonspecific inflammation	Pancreatitis chronic
Gastrointestinal nonspecific inflammation	Pepsinogen I decreased
Gastrointestinal nonspecific inflammation	Pepsinogen I increased
Gastrointestinal nonspecific inflammation	Proctitis
Gastrointestinal nonspecific inflammation	Proctoscopy abnormal
Gastrointestinal nonspecific inflammation	Proctosigmoidoscopy abnormal
Gastrointestinal nonspecific inflammation	Sigmoidoscopy abnormal
Gastrointestinal nonspecific inflammation	Stomach scan abnormal
Gastrointestinal nonspecific inflammation	Stool chymotrypsin abnormal
Gastrointestinal nonspecific inflammation	X-ray with contrast lower gastrointestinal tract abnormal
Gastrointestinal nonspecific symptoms and therapeutic procedures	Abdominal discomfort
Gastrointestinal nonspecific symptoms and therapeutic procedures	Abdominal distension
Gastrointestinal nonspecific symptoms and therapeutic procedures	Abdominal pain
Gastrointestinal nonspecific symptoms and therapeutic procedures	Abdominal pain lower
Gastrointestinal nonspecific symptoms and therapeutic procedures	Abdominal pain upper
Gastrointestinal nonspecific symptoms and therapeutic procedures	Abdominal symptom
Gastrointestinal nonspecific symptoms and therapeutic procedures	Abdominal tenderness
Gastrointestinal nonspecific symptoms and therapeutic procedures	Abnormal faeces
Gastrointestinal nonspecific symptoms and therapeutic procedures	Aerophagia

SMQ	Preferred Term
Gastrointestinal nonspecific symptoms and therapeutic procedures	Anorectal discomfort
Gastrointestinal nonspecific symptoms and therapeutic procedures	Bowel movement irregularity
Gastrointestinal nonspecific symptoms and therapeutic procedures	Change of bowel habit
Gastrointestinal nonspecific symptoms and therapeutic procedures	Constipation
Gastrointestinal nonspecific symptoms and therapeutic procedures	Defaecation urgency
Gastrointestinal nonspecific symptoms and therapeutic procedures	Diarrhoea
Gastrointestinal nonspecific symptoms and therapeutic procedures	Discoloured vomit
Gastrointestinal nonspecific symptoms and therapeutic procedures	Epigastric discomfort
Gastrointestinal nonspecific symptoms and therapeutic procedures	Eructation
Gastrointestinal nonspecific symptoms and therapeutic procedures	Faecal volume decreased
Gastrointestinal nonspecific symptoms and therapeutic procedures	Faecal volume increased
Gastrointestinal nonspecific symptoms and therapeutic procedures	Faeces hard
Gastrointestinal nonspecific symptoms and therapeutic procedures	Faeces soft
Gastrointestinal nonspecific symptoms and therapeutic procedures	Flatulence
Gastrointestinal nonspecific symptoms and therapeutic procedures	Frequent bowel movements
Gastrointestinal nonspecific symptoms and therapeutic procedures	Gastrointestinal pain
Gastrointestinal nonspecific symptoms and therapeutic procedures	Gastrointestinal sounds abnormal
Gastrointestinal nonspecific symptoms and therapeutic procedures	Gastrointestinal toxicity
Gastrointestinal nonspecific symptoms and therapeutic procedures	Infrequent bowel movements
Gastrointestinal nonspecific symptoms and therapeutic procedures	Nausea
Gastrointestinal nonspecific symptoms and therapeutic procedures	Non-cardiac chest pain
Gastrointestinal nonspecific symptoms and therapeutic procedures	Oesophageal discomfort
Gastrointestinal nonspecific symptoms and therapeutic procedures	Oesophageal pain
Gastrointestinal nonspecific symptoms and therapeutic procedures	Premenstrual cramps
Gastrointestinal nonspecific symptoms and therapeutic procedures	Vomiting
Gastrointestinal nonspecific symptoms and therapeutic procedures	Anorectal swelling
Gastrointestinal nonspecific symptoms and therapeutic procedures	Antacid therapy
Gastrointestinal nonspecific symptoms and therapeutic procedures	Antidiarrhoeal supportive care
Gastrointestinal nonspecific symptoms and therapeutic procedures	Antiemetic supportive care
Gastrointestinal nonspecific symptoms and therapeutic procedures	Breath odour
Gastrointestinal nonspecific symptoms and therapeutic procedures	Chest pain
Gastrointestinal nonspecific symptoms and therapeutic procedures	Colonic lavage
Gastrointestinal nonspecific symptoms and therapeutic procedures	Dysphagia
Gastrointestinal nonspecific symptoms and therapeutic procedures	Early satiety
Gastrointestinal nonspecific symptoms and therapeutic procedures	Gastritis prophylaxis
Gastrointestinal nonspecific symptoms and therapeutic procedures	Gastrointestinal disorder therapy
Gastrointestinal nonspecific symptoms and therapeutic procedures	Gastrointestinal tract irritation
Gastrointestinal nonspecific symptoms and therapeutic procedures	Gastrooesophageal reflux prophylaxis

SMQ	Preferred Term
Gastrointestinal nonspecific symptoms and therapeutic procedures	Glycogenic acanthosis
Gastrointestinal nonspecific symptoms and therapeutic procedures	Hypovolaemia
Gastrointestinal nonspecific symptoms and therapeutic procedures	Laxative supportive care
Gastrointestinal nonspecific symptoms and therapeutic procedures	Malabsorption
Gastrointestinal nonspecific symptoms and therapeutic procedures	Mucous stools
Gastrointestinal nonspecific symptoms and therapeutic procedures	Pernicious anaemia
Gastrointestinal nonspecific symptoms and therapeutic procedures	Post procedural constipation
Gastrointestinal nonspecific symptoms and therapeutic procedures	Post procedural diarrhoea
Gastrointestinal nonspecific symptoms and therapeutic procedures	Post-tussive vomiting
Gastrointestinal nonspecific symptoms and therapeutic procedures	Probiotic therapy
Gastrointestinal nonspecific symptoms and therapeutic procedures	Procedural nausea
Gastrointestinal nonspecific symptoms and therapeutic procedures	Procedural vomiting
Gastrointestinal nonspecific symptoms and therapeutic procedures	Prophylaxis against diarrhoea
Gastrointestinal nonspecific symptoms and therapeutic procedures	Prophylaxis of nausea and vomiting
Gastrointestinal nonspecific symptoms and therapeutic procedures	Regurgitation
Gastrointestinal nonspecific symptoms and therapeutic procedures	Retching
Gastrointestinal nonspecific symptoms and therapeutic procedures	Steatorrhoea
Gastrointestinal nonspecific symptoms and therapeutic procedures	Vomiting projectile

19.4 Hyperkalemia Events

There are two preferred terms for hyperkalemia:

- Blood potassium increased
- Hyperkalaemia