# SUPPLEMENTAL MATERIAL

## Randomized Controlled Trial of TRC101 to Increase Serum Bicarbonate in Chronic Kidney Disease Patients

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# APPENDIX

## Exclusion Criteria and Concomitant Medications

Patients were excluded from the study if they had any level of low serum bicarbonate at screening or day -1 that, in the opinion of the investigator, required emergency intervention. Additional exclusion criteria comprised: dialysis or acute kidney injury in the past 3 months; serum potassium values of < 3.8 mEq/L or > 5.9 mEq/L at screening; Type 1 diabetes; severe comorbid conditions (other than CKD) such as congestive heart failure with maximum New York Heart Association (NYHA) Class III or IV symptoms, unstable angina or acute coronary syndrome, dementia, hypertensive emergency, transient ischemic attack, stroke, or use of home oxygen during the 6 months prior to screening; chronic obstructive pulmonary disease; heart or kidney transplant or anticipated need for transplant or dialysis during study participation; hospitalization during the 3 months prior to screening; and history of bariatric surgery or history or current diagnosis of diabetic gastroparesis, bowel obstruction, swallowing disorders, severe gastrointestinal disorders or major gastrointestinal surgery. Additional exclusions included active gastric/duodenal ulcers; severe recurrent diarrhea or constipation; liver enzyme or total bilirubin values >3X the upper limit of normal; active cancer or history of cancer in the past 2 years; body mass index ≥40 kg/m$^2$; any investigational medication during the month preceding day 1 of the study; history of alcoholism or drug abuse; inability to consume the study drug or the study-specific diet. In addition, patients were excluded from participation in the study if they had a change in the dose of any of the following drugs in the 21 days prior to Day 1 of the study, or anticipated a need for a dose modification for these drugs or drug classes: diuretics, non-ophthalmic carbonic anhydrase inhibitors, oral diabetes drugs, antihypertensive drugs, antacids, H2-blockers or proton pump inhibitors. Diuretics administered daily at a stable dose were permitted. Use of any of the following drugs in the 14 days prior to Day 1 of the study, or an anticipated need for these drugs or drug classes during the study, resulted in exclusion from the study: insulin, non-daily or "as needed" diuretics, herbal products, dietary supplements, multivitamins, naturopathic remedies, sodium bicarbonate, potassium citrate, sodium citrate or other alkali therapy. Patients using any of the following drugs in the 7 days prior to day 1 of the study, or an anticipated need for these drugs or drug classes during the study, were excluded: nonsteroidal anti-inflammatory drugs (NSAIDs); fiber supplements; laxatives; calcium and

magnesium supplements; or electrolyte binders and other binder drugs. Patients with a known allergy to microcrystalline cellulose (used as placebo) were also excluded from the study.

**Randomization and Blinding**

The randomization allocation sequence was generated by a contract research organization (EndPoint) and was integrated into a central interactive web-based system to obtain the randomized treatment assignments. The placebo used in this study (microcrystalline cellulose, NF grade) was not identical in appearance to TRC101. Further, although it was suspended in the same volume of water, the amount of TRC101 in an administered dose (1.5, 3, 4.5, 6 g) differed among the four active treatment arms of the study. Because of these factors, designated staff at the clinical research unit were unblinded with respect to treatment assignments of study patients. These individuals were: (1) the designated unblinded research pharmacist(s) responsible for dispensing study drug and (2) the study personnel responsible for supervising the suspension and administration of the study drug. These individuals had no other responsibilities for the study. The investigator, patients, clinical research unit staff (including all those involved in collection of safety and efficacy information) except as described above, and most contract research organization staff (including the medical monitor and all personnel responsible for monitoring study records other than those assigned to review drug accountability records) remained blinded to the patient's treatment assignment throughout the study. The sponsor and the study biostatistician were blinded from the beginning of the study until the first 60 patients (see study design section) completed the study. A pre-specified blinding plan detailed the blinding procedures.

**Assays**

Serum bicarbonate concentrations used for efficacy analyses were measured with the enzymatic assay method and performed by local laboratories (Forrester RL, Wataji LJ, Silverman DA, Pierre KJ: Enzymatic method for determination of $CO_2$ in serum. *Clin Chem* 22(2): 243 – 245, 1976). Strict procedures were in place for handling of specimens, including minimization of exposure of samples to air. The time during which serum sample tubes were uncapped prior to analysis was captured in the study database.

**Schedule of Assessments, Procedures and Monitoring for Study TRCA-101**

During screening, essential elements of the enrollment process were completed, including obtaining informed consent, evaluating eligibility criteria, recording demographics and complete medical history including bowel habits, collecting prior and concomitant medication information, recording vital signs, performing a physical examination (including weight and height), conducting ECGs, conducting serum pregnancy test (if applicable), and collecting blood and urine samples for analysis. Patients who met enrollment criteria were invited back to the sites for confirmatory serum bicarbonate and eGFR measurements on Day -1, and those who continued to meet eligibility criteria were randomized into the study and admitted to the clinical research unit. Additional assessments on Day -1 included baseline physical examination (including weight), baseline ECG, fasting serum chemistry (including pregnancy test when applicable), bowel movement diary, and recording any AEs and concomitant medications.

Eligible patients admitted to the clinical research unit on day -1 were placed on a study diet controlled for anions, cations and acid/base content, which was provided by the clinical site. For all patients, this diet also specified caloric and protein content in accordance with standard of care for CKD patients and prior diet; the diet was consistent during the study treatment period.

During the 14-day treatment period, patients remained in the clinical research unit where vital signs, monitoring of bowel movements, and adverse event and concomitant medication collection was performed daily. Fasting serum chemistry tests, including serum bicarbonate determination, were also performed each day. Periodic testing of liver function, lipid panel, coagulation, hematology, spot urine and urinalysis was conducted on days 1, 3, 8 and 15 of the treatment period.

Enrolled patients were randomized on Day -1 and dosing was initiated in the morning on Day 1 (next day) in accordance with the randomization assignment. The first dose of study drug was taken with breakfast. One hour prior to administration of the study drug, venous blood was drawn for a pre-dose serum bicarbonate (to determine the baseline value, which was the mean of Day -1 and Day 1 pre-dose serum bicarbonate values) and safety laboratory measurements. Patients remained in the clinical research unit and continued dosing with study drug for 14 days.

Safety and efficacy assessments (i.e., serum bicarbonate levels) were performed at pre-specified time points throughout the study. On Day 15, patients were discharged from the clinical research unit. Patients who completed the treatment period entered the follow-up period, consisting of a discharge assessment on day 15 and up to four clinic visits at Days 17, 21, 24 and 28.

Follow up evaluation (TRC101 off-treatment period) comprised outpatient visits beginning on the day of study completion (Day 15), and on Day 17, 21 and 28 thereafter. Fasting serum chemistry, including serum bicarbonate assessments were on Days 15, 17, 21, 24 and 28; similarly, adverse events and concomitant medication collection and bowel movements were monitored at each follow-up visit. Vital signs were measured at Days 15, 17 and 21. Physical examination (including weight), ECG, liver function tests, coagulation, hematology, spot urine and urinalysis, and serum pregnancy test (if applicable) were completed only on Day 21 of the follow up period.

Safety assessments included: adverse events, vital signs (blood pressure, heart rate, temperature and respiratory rate); physical examination (including body weight); fasting serum chemistry (serum bicarbonate, blood urea nitrogen [BUN], calcium, chloride, creatinine [including eGFR], glucose, magnesium, phosphate, potassium and sodium), lipid panel (high density lipoprotein [HDL], low density lipoprotein [LDL], total cholesterol, triglycerides), liver function tests (LFTs; alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin [total and direct]); coagulation (prothrombin time, international normalized ratio [INR]; for patients receiving vitamin K antagonists or factor Xa inhibitors only); hematology (red blood cell count, white blood cell count, hemoglobin, hematocrit, platelet count); spot urine (albumin, chloride, creatinine, potassium, sodium); urinalysis (bilirubin, blood, glucose, ketones, leukocytes, pH, protein, nitrites, urobilinogen); bowel movement diary; and electrocardiograms (ECGs). HbA1c was assessed to determine eligibility only.

The source data was 100% verified during site monitoring visits.

**Dietary Control During Treatment Period**

During the treatment period, patients were given a study diet controlled for protein and caloric content, as well as anions, cations and fiber, in accordance with dietary recommendations for CKD patients (KDOQI, 2003). Four detailed meal plans were developed that specified the foods (including measured quantities) provided at breakfast, lunch, dinner and two light snacks each day (Supplemental Table 1). Care was taken to ensure the diet closely approximated the patients' typical diet so that perturbations in serum bicarbonate related to a sudden change in diet would be minimized. The dietary sources of protein were predominantly plant-based, with animal-sourced protein (pork, fish) served once per day on two of the four meal plans. The study sites rotated among the four daily meal plans over the course of the treatment period.

The potential kidney acid load was assessed for each of the four meal plans to ensure that the study diet was neither acidic nor basic; potential kidney acid load values for the four daily meal plans ranged from –1.7 mEq/day to +1.9 mEq/day and averaged 0.8 mEq/day. The potential kidney acid load was calculated as follows (Scialla JJ, Anderson CAM: Dietary acid load: a novel nutritional target in chronic kidney disease? *Adv Chronic Kidney Dis* 20(2): 141 – 149, 2013):

Potential kidney acid load (mEq/d) = (0.49 * protein [g/d]) + (0.037 * phosphorus [mg/d]) – (0.021 * potassium [mg/d]) – (0.026 * magnesium [mg/d]) – 0.013 * (calcium [mg/d])

Analysis of the mean serum bicarbonate level in the placebo group over the course of the treatment (i.e., patients in unit) and follow-up (i.e., patients back home) periods suggests that the study diet was similar to the patients' home diet in terms of acid load, and so had no impact on serum bicarbonate. The mean (± standard deviation) serum bicarbonate level in the patients who received placebo was 17.6 (± 1.4) mEq/L at baseline and varied from this level during the 14-day treatment period and the 14-day follow-up period only within a narrow range (i.e., from 17.3 [± 1.8] mEq/L to 18.5 [± 2.4] mEq/L).

**Additional Statistical Methods for TRCA-101 Study**

The safety analysis set was defined as all patients who received any amount of study drug (TRC101 or placebo) and was used for evaluation of safety, based on actual treatment received. The efficacy analysis set was defined as all randomized patients who received study drug (TRC101 or placebo) and had both baseline and at least one post-baseline serum bicarbonate value.

The following were reported by time point and dose group: the least squares (LS) mean of change from baseline in serum bicarbonate of each of the TRC101 groups (and combined TRC101 group); standard error of LS mean; two-sided 95% confidence interval (CI) of the LS mean; LS mean difference between individual TRC101 groups (or combined TRC101 group) and placebo; standard error of LS mean difference; and 95% CI of the LS mean difference. The p-values from the mixed model for comparing LS mean change from baseline in serum bicarbonate $\neq 0$ within each dose group, difference in LS means of the change from baseline in serum bicarbonate between individual (or combined) TRC101 groups and placebo was provided by time point.

Descriptive statistics for serum bicarbonate at baseline and at each scheduled post-baseline time point, along with CFB in serum bicarbonate, was summarized by time point. Within-group analysis of serum bicarbonate included within individual treatment group paired comparisons between baseline bicarbonate and each post-baseline time point bicarbonate (days 2 through 15) while on TRC101, as well as paired comparisons between baseline serum bicarbonate and each post-baseline time point within the combined TRC101 dose group. Between-group analysis of serum bicarbonate CFB included comparisons between each of the TRC101 dose groups and placebo over time while on study drug, as well as between the TRC101 combined group (i.e., all TRC101 dose groups averaged) and placebo.

**Interim Analysis**

An interim analysis was performed to provide an initial descriptive summary of serum bicarbonate results. The sponsor received tables summarizing mean serum bicarbonate levels over time by coded treatment group after 30 patients had completed the study and the sponsor

was unblinded after 60 patients completed the study. There were no stopping rules associated with this interim analysis.

**Supplemental Table 1. Composition of Study TRCA-101 Treatment Period Diet and Calculated Potential Kidney Acid Load**

| Parameter | Calories | Protein (g) | Ca (mg) | Mg (mg) | P (mg) | K (mg) | Na (mg) | Fiber (g) | Potential Kidney Acid Load (mEq/day) |
|---|---|---|---|---|---|---|---|---|---|
| Mean | 2209.3 | 52.3 | 810 | 232.5 | 1008.1 | 2171.4 | 2249.5 | 27.0 | 0.8 |
| Range | 2129 – 2246 | 50.6 – 53.4 | 778 – 849 | 210 – 266 | 972 – 1060 | 2048 – 2277 | 2076 – 2370 | 22.9 – 32.1 | –1.7 – +1.9 |

Ca = calcium; K = potassium; Mg = magnesium; Na = sodium; P = phosphate

## Supplemental Table 2. Change from Baseline in Serum Bicarbonate (mEq/L) at Day 2

| | Pooled Placebo (N = 31) | TRC101 1.5 g Twice Daily (N = 25) | TRC101 6 g Once Daily (N = 28) | TRC101 3 g Twice Daily (N = 25) | TRC101 4.5 g Twice Daily (N = 26) | TRC101 Combined (N=104) |
|---|---|---|---|---|---|---|
| **Baseline** | | | | | | |
| Mean (95% CI) | 17.6 (17.1, 18.2) | 18.0 (17.6, 18.4) | 17.7 (17.3, 18.1) | 17.8 (17.3, 18.3) | 17.5 (17.0, 18.0) | 17.7 (17.5, 18.0) |
| SD of Mean | 0.3 | 0.2 | 0.2 | 0.2 | 0.3 | 0.1 |
| Median (IQR) | 17.6 (1.4) | 17.9 (1.3) | 17.7 (1.4) | 17.8 (1.7) | 17.7 (1.3) | 17.8 (1.5) |
| Min, Max | 14.1, 19.9 | 15.6, 20.4 | 15.8, 19.7 | 15.4, 19.9 | 14.5, 19.2 | 14.5, 20.4 |
| **Day 2** | | | | | | |
| Mean (95% CI) | 17.4 (16.8, 18.1) | 18.6 (18.0, 19.1) | 18.7 (18.1, 19.4) | 18.8 (18.2, 19.4) | 18.6 (18.0, 19.2) | 18.7 (18.4, 19.0) |
| SD of Mean | 0.3 | 0.3 | 0.3 | 0.3 | 0.3 | 0.1 |
| Median (IQR) | 17.3 (2.5) | 18.7 (1.6) | 18.5 (2.7) | 19.0 (2.1) | 18.8 (2.1) | 18.7 (2.1) |
| Min, Max | 12.3, 20.2 | 15.5, 20.2 | 14.7, 21.5 | 15.9, 21.9 | 15.9, 20.8 | 14.7, 21.9 |
| **Day 2 Change from Baseline (CFB)** | | | | | | |
| Mean (95% CI) | -0.2 (-0.7, 0.3) | 0.5 (0.0, 1.1) | 1.0 (0.3, 1.7) | 1.0 (0.4, 1.6) | 1.1 0.5, 1.7) | 0.9 (0.6, 1.2) |
| SD of Mean | 0.2 | 0.3 | 0.3 | 0.3 | 0.3 | 0.1 |
| Median (IQR) | 0.2 (2.2) | 0.4 (1.5) | 1.3 (1.8) | 1.0 (2.3) | 1.4 (1.2) | 1.0 (2.0) |
| Min, Max | -3.3, 2.4 | -2.2, 4.5 | -3.0, 4.4 | -1.3, 4.3 | -1.9, 3.7 | -3.0, 4.5 |
| | | | | | | |
| Within Group CFB | | | | | | |
| LS Mean (SEM) | -0.2 (0.4) | 0.7 (0.4) | 1.0 (0.4) | 1.1 (0.4) | 1.0 (0.4) | 0.9 (0.2) |
| 95% CI of LS Mean | -0.9, 0.5 | -0.1, 1.5 | 0.2, 1.7 | 0.3, 1.9 | 0.2, 1.8 | 0.5, 1.3 |
| p-value | 0.52 | 0.10 | 0.01 | 0.008 | 0.01 | <0.001 |
| | | | | | | |
| Between Group CFB Difference (TRC101 Treated – Pooled Placebo) | | | | | | |
| LS Mean (SEM) | NA | 0.9 (0.5) | 1.2 (0.5) | 1.3 (0.5) | 1.2 (0.5) | 1.2 (0.4) |
| 95% CI of LS Mean | NA | -0.2, 2.0 | 0.2, 2.3 | 0.2, 2.4 | 0.2, 2.3 | 0.4, 2.0 |
| p-value | NA | 0.09 | 0.02 | 0.02 | 0.02 | 0.005 |
| | | | | | | |
| Between Group CFB Difference (TRC101 3 g twice daily – TRC101 6 g once daily) | | | | | | |
| LS Mean (SEM) | NA | NA | 0.1 (0.6) | NA | NA | NA |
| 95% CI of LS Mean | NA | NA | -1.0, 1.2 | NA | NA | NA |
| p-value | NA | NA | 0.87 | NA | NA | NA |

Baseline serum bicarbonate is defined as an average of two serum bicarbonate values from samples collected on Day -1 and at Day 1 pre-dose. Change from baseline (CFB) is defined as post-baseline value minus baseline value. Least squares (LS) mean, standard error of LS mean (SEM), 95% CI of LS mean, and p-values are based on the mixed-effect repeated measures model with the CFB in serum bicarbonate value as the dependent variable; treatment (Pooled Placebo and TRC101 Treated), time point (Day 2), and treatment by time point as fixed effects; patient as a random effect; and baseline estimated glomerular filtration rate (eGFR) and baseline serum bicarbonate as continuous covariates. Within-patient correlations are modeled assuming a first-order autoregressive covariance structure. IQR, interquartile range; CI, confidence interval; SD, standard deviation.

## Supplemental Table 3. Change from Baseline in Serum Bicarbonate (mEq/L) at Day 3

| | Pooled Placebo (N = 31) | TRC101 1.5 g Twice Daily (N = 25) | TRC101 6 g Once Daily (N = 28) | TRC101 3 g Twice Daily (N = 25) | TRC101 4.5 g Twice Daily (N = 26) | TRC101 Combined (N=104) |
|---|---|---|---|---|---|---|
| **Baseline** | | | | | | |
| Mean (95% CI) | 17.6 (17.1, 18.2) | 18.0 (17.6, 18.4) | 17.7 (17.3, 18.1) | 17.8 (17.3, 18.3) | 17.5 (17.0, 18.0) | 17.7 (17.5, 18.0) |
| SD of Mean | 0.3 | 0.2 | 0.2 | 0.2 | 0.3 | 0.1 |
| Median (IQR) | 17.6 (1.4) | 17.9 (1.3) | 17.7 (1.4) | 17.8 (1.7) | 17.7 (1.3) | 17.8 (1.5) |
| Min, Max | 14.1, 19.9 | 15.6, 20.4 | 15.8, 19.7 | 15.4, 19.9 | 14.5, 19.2 | 14.5, 20.4 |
| **Day 3** | | | | | | |
| Mean (95% CI) | 17.9 (17.3, 18.6) | 18.9 (18.2, 19.5) | 18.9 (18.3, 19.6) | 18.9 (17.9, 19.8) | 19.3 (18.3, 20.3) | 19.0 (18.6, 19.4) |
| SD of Mean | 0.3 | 0.3 | 0.3 | 0.5 | 0.5 | 0.2 |
| Median (IQR) | 18.2 (2.7) | 19.3 (2.1) | 19.1 (2.1) | 19.3 (2.4) | 19.4 (2.4) | 19.3 (2.3) |
| Min, Max | 15.2, 22.3 | 15.7, 22.5 | 15.4, 22.0 | 14.1, 24.4 | 14.3, 24.9 | 14.1, 24.9 |
| **Day 3 Change from Baseline (CFB)** | | | | | | |
| Mean (95% CI) | 0.3 (-0.3, 0.9) | 0.9 (0.1, 1.6) | 1.2 (0.5, 1.9) | 1.1 (0.2, 2.0) | 1.8 (0.9, 2.7) | 1.2 (0.8, 1.6) |
| SD of Mean | 0.3 | 0.4 | 0.3 | 0.4 | 0.4 | 0.2 |
| Median (IQR) | 0.1 (2.7) | 0.6 (2.0) | 1.5 (2.0) | 0.9 (2.1) | 1.9 (3.0) | 1.2 (2.4) |
| Min, Max | -2.7, 5.2 | -2.4, 5.2 | -3.6, 4.1 | -3.1, 6.7 | -3.0, 7.8 | -3.6, 7.8 |
| | | | | | | |
| Within Group CFB | | | | | | |
| LS Mean (SEM) | 0.3 (0.4) | 1.0 (0.4) | 1.2 (0.4) | 1.2 (0.4) | 1.7 (0.4) | 1.3 (0.2) |
| 95% CI of LS Mean | -0.5, 1.0 | 0.2, 1.8 | 0.4, 1.9 | 0.4, 2.0 | 0.9, 2.5 | 0.9, 1.6 |
| p-value | 0.49 | 0.02 | 0.003 | 0.005 | <0.001 | <0.001 |
| | | | | | | |
| Between Group CFB Difference (TRC101 Treated – Pooled Placebo) | | | | | | |
| LS Mean (SEM) | NA | 0.7 (0.5) | 0.9 (0.5) | 0.9 (0.5) | 1.5 (0.5) | 1.0 (0.4) |
| 95% CI of LS Mean | NA | -0.3, 1.8 | -0.1, 1.9 | -0.2, 2.0 | 0.4, 2.5 | 0.2, 1.8 |
| p-value | NA | 0.18 | 0.09 | 0.10 | 0.007 | 0.02 |
| | | | | | | |
| Between Group CFB Difference (TRC101 3 g twice daily – TRC101 6 g once daily) | | | | | | |
| LS Mean (SEM) | NA | NA | 0.0 (0.6) | NA | NA | NA |
| 95% CI of LS Mean | NA | NA | -1.1, 1.1 | NA | NA | NA |
| p-value | NA | NA | 0.99 | NA | NA | NA |

Baseline serum bicarbonate is defined as an average of two serum bicarbonate values from samples collected on Day -1 and at Day 1 pre-dose. Change from baseline (CFB) is defined as post-baseline value minus baseline value. Least squares (LS) mean, standard error of LS mean (SEM), 95% CI of LS mean, and p-values are based on the mixed-effect repeated measures model with the CFB in serum bicarbonate value as the dependent variable; treatment (Pooled Placebo and TRC101 Treated), time point (Day 3), and treatment by time point as fixed effects; patient as a random effect; and baseline estimated glomerular filtration rate (eGFR) and baseline serum bicarbonate as continuous covariates. Within-patient correlations are modeled assuming a first-order autoregressive covariance structure. IQR, interquartile range; CI, confidence interval; SD, standard deviation.

## Supplemental Table 4. Change from Baseline in Serum Bicarbonate (mEq/L) at Day 4

| | Pooled Placebo (N = 31) | TRC101 1.5 g Twice Daily (N = 25) | TRC101 6 g Once Daily (N = 28) | TRC101 3 g Twice Daily (N = 25) | TRC101 4.5 g Twice Daily (N = 26) | TRC101 Combined (N=104) |
|---|---|---|---|---|---|---|
| **Baseline** | | | | | | |
| Mean (95% CI) | 17.6 (17.1, 18.2) | 18.0 (17.6, 18.4) | 17.7 (17.3, 18.1) | 17.8 (17.3, 18.3) | 17.5 (17.0, 18.0) | 17.7 (17.5, 18.0) |
| SD of Mean | 0.3 | 0.2 | 0.2 | 0.2 | 0.3 | 0.1 |
| Median (IQR) | 17.6 (1.4) | 17.9 (1.3) | 17.7 (1.4) | 17.8 (1.7) | 17.7 (1.3) | 17.8 (1.5) |
| Min, Max | 14.1, 19.9 | 15.6, 20.4 | 15.8, 19.7 | 15.4, 19.9 | 14.5, 19.2 | 14.5, 20.4 |
| **Day 4** | | | | | | |
| Mean (95% CI) | 17.8 (17.2, 18.5) | 19.2 (18.7, 19.8) | 19.1 (18.4, 19.8) | 19.3 (18.5, 20.0) | 19.7 (18.9, 20.4) | 19.3 (19.0, 19.7) |
| SD of Mean | 0.3 | 0.3 | 0.3 | 0.4 | 0.4 | 0.2 |
| Median (IQR) | 17.7 (2.5) | 19.1 (1.8) | 19.5 (2.4) | 19.2 (2.5) | 19.2 (2.1) | 19.2 (2.2) |
| Min, Max | 14.6, 21.2 | 17.1, 22.9 | 15.2, 22.6 | 16.1, 23.9 | 16.5, 24.4 | 15.2, 24.4 |
| **Day 4 Change from Baseline (CFB)** | | | | | | |
| Mean (95% CI) | 0.2 (-0.5, 0.9) | 1.2 (0.5, 1.9) | 1.4 (0.6, 2.1) | 1.5 (0.8, 2.2) | 2.2 (1.5, 2.9) | 1.6 (1.2, 1.9) |
| SD of Mean | 0.3 | 0.3 | 0.4 | 0.3 | 0.4 | 0.2 |
| Median (IQR) | 0.2 (2.4) | 1.2 (1.5) | 1.8 (2.2) | 1.5 (2.5) | 2.3 (2.6) | 1.6 (2.2) |
| Min, Max | -3.5, 4.1 | -2.5, 4.5 | -2.5, 5.5 | -1.5, 5.1 | -0.4, 7.3 | -2.5, 7.3 |
| | | | | | | |
| Within Group CFB | | | | | | |
| LS Mean (SEM) | 0.2 (0.4) | 1.4 (0.4) | 1.3 (0.4) | 1.6 (0.4) | 2.1 (0.4) | 1.6 (0.2) |
| 95% CI of LS Mean | -0.5, 0.9 | 0.6, 2.2 | 0.6, 2.1 | 0.8, 2.4 | 1.3, 2.9 | 1.2, 2.0 |
| p-value | 0.64 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| | | | | | | |
| Between Group CFB Difference (TRC101 Treated – Pooled Placebo) | | | | | | |
| LS Mean (SEM) | NA | 1.2 (0.5) | 1.2 (0.5) | 1.4 (0.5) | 1.9 (0.5) | 1.4 (0.4) |
| 95% CI of LS Mean | NA | 0.1, 2.3 | 0.1, 2.2 | 0.3, 2.5 | 0.9, 3.0 | 0.6, 2.2 |
| p-value | NA | 0.03 | 0.03 | 0.01 | <0.001 | <0.001 |
| | | | | | | |
| Between Group CFB Difference (TRC101 3 g twice daily – TRC101 6 g once daily) | | | | | | |
| LS Mean (SEM) | NA | NA | 0.2 (0.6) | NA | NA | NA |
| 95% CI of LS Mean | NA | NA | -0.9, 1.3 | NA | NA | NA |
| p-value | NA | NA | 0.68 | NA | NA | NA |

Baseline serum bicarbonate is defined as an average of two serum bicarbonate values from samples collected on Day -1 and at Day 1 pre-dose. Change from baseline (CFB) is defined as post-baseline value minus baseline value. Least squares (LS) mean, standard error of LS mean (SEM), 95% CI of LS mean, and p-values are based on the mixed-effect repeated measures model with the CFB in serum bicarbonate value as the dependent variable; treatment (Pooled Placebo and TRC101 Treated), time point (Day 4), and treatment by time point as fixed effects; patient as a random effect; and baseline estimated glomerular filtration rate (eGFR) and baseline serum bicarbonate as continuous covariates. Within-patient correlations are modeled assuming a first-order autoregressive covariance structure. IQR, interquartile range; CI, confidence interval; SD, standard deviation.

## Supplemental Table 5. Proportion of Patients by Serum Bicarbonate Category (Days 8 and 15)

| Patients with Post-baseline Serum Bicarbonate | Pooled Placebo N = 31 | TRC101 1.5 g Twice Daily N = 25 | TRC101 6 g Once Daily N = 28 | TRC101 3 g Twice Daily N = 25 | TRC101 4.5 g Twice Daily N = 26 | TRC101 Combined N = 104 |
|---|---|---|---|---|---|---|
| **Day 8 Serum Bicarbonate Values** | | | | | | |
| > 20 mEq/L | 5 (16%) | 9 (36%) | 16 (57%) | 7 (28%) | 12 (46%) | 44 (42%) |
| > 22 mEq/L | 2 (6%) | 2 (8%) | 5 (18%) | 5 (20%) | 6 (23%) | 18 (17%) |
| > 27 mEq/L | 0 | 0 | 0 | 0 | 0 | 0 |
| > 29 mEq/L | 0 | 0 | 0 | 0 | 0 | 0 |
| **Day 15 Serum Bicarbonate Values** | | | | | | |
| > 20 mEq/L | 2 (6%) | 16 (64%) | 17 (61%) | 14 (56%) | 19 (73%) | 66 (63%) |
| > 22 mEq/L | 0 | 10 (40%) | 9 (32%) | 7 (28%) | 10 (38%) | 36 (35%) |
| > 27 mEq/L | 0 | 0 | 0 | 0 | 0 | 0 |
| > 29 mEq/L | 0 | 0 | 0 | 0 | 0 | 0 |