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Canadian Intellectual Property Office

CA 3102765 A1 2019/12/12

(21) 3 102 765

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2019/06/04
(87) Date publication PCT/PCT Publication Date: 2019/12/12
(85) Entrée phase nationale/National Entry: 2020/12/04
(86) N° demande PCT/PCT Application No.: US 2019/035467
(87) N° publication PCT/PCT Publication No.: 2019/236636
(30) Priorités/Priorities: 2018/06/04 (US62/680,002); 2018/10/19 (US62/748,361); 2018/11/03 (US PCT/US2018/059094); 2019/03/27 (US62/825,006); 2019/05/08 (US62/845,290)

(51) Cl.Int./Int.Cl. *A61K 31/13* (2006.01), *A61K 31/785* (2006.01), *A61P 13/12* (2006.01)

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(74) Agent: SMART & BIGGAR LLP

(54) Titre : METHODE DE TRAITEMENT DE TROUBLES DE L'EQUILIBRE ACIDO-BASIQUE
(54) Title: METHOD OF TREATING ACID-BASE DISORDERS

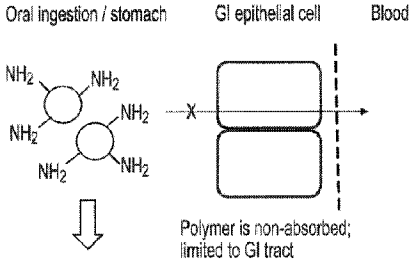

FIG. 1A

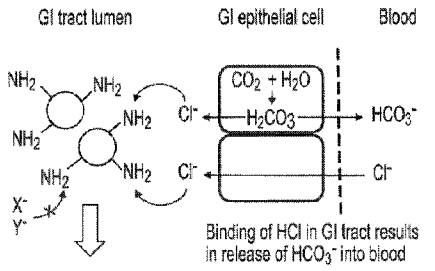

FIG. 1B

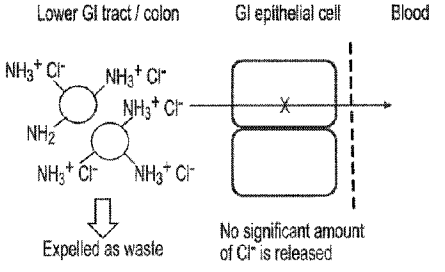

FIG. 1C

(57) Abrégé/Abstract:
The present disclosure provides, inter alia, pharmaceutical compositions for and methods of treating an animal, including a human, and methods of preparing such compositions. In certain embodiments, the pharmaceutical compositions contain nonabsorbable compositions and may be used, for example, to treat diseases or other metabolic conditions in which removal of protons, the conjugate base of a strong acid and/or a strong acid from the gastrointestinal tract would provide physiological benefits such as normalizing serum bicarbonate concentrations and the blood pH in an animal, including a human. In certain embodiments, compositions for and methods of improving the quality of life and/or physical function score of such patients are also provided. In certain embodiments, compositions for and methods of slowing the progression of kidney disease in such patients are also provided.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 December 2019 (12.12.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/236636 A1

(51) International Patent Classification:
A61K 31/13 (2006.01) *A61P 13/12* (2006.01)
A61K 31/785 (2006.01)

(21) International Application Number:
PCT/US2019/035467

(22) International Filing Date:
04 June 2019 (04.06.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/680,002	04 June 2018 (04.06.2018)	US
62/748,361	19 October 2018 (19.10.2018)	US
PCT/US2018/059094	03 November 2018 (03.11.2018)	US
62/825,006	27 March 2019 (27.03.2019)	US
62/845,290	08 May 2019 (08.05.2019)	US

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(54) Title: METHOD OF TREATING ACID-BASE DISORDERS

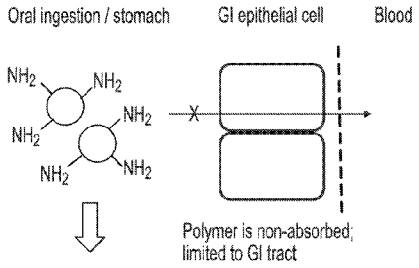

FIG. 1A

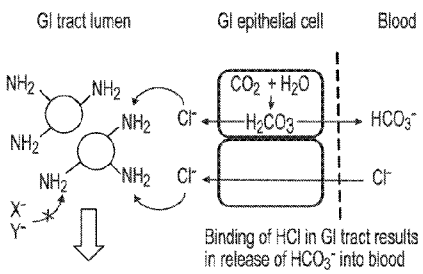

FIG. 1B

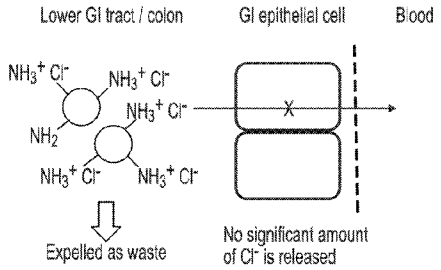

FIG. 1C

(57) Abstract: The present disclosure provides, *inter alia*, pharmaceutical compositions for and methods of treating an animal, including a human, and methods of preparing such compositions. In certain embodiments, the pharmaceutical compositions contain nonabsorbable compositions and may be used, for example, to treat diseases or other metabolic conditions in which removal of protons, the conjugate base of a strong acid and/or a strong acid from the gastrointestinal tract would provide physiological benefits such as normalizing serum bicarbonate concentrations and the blood pH in an animal, including a human. In certain embodiments, compositions for and methods of improving the quality of life and/or physical function score of such patients are also provided. In certain embodiments, compositions for and methods of slowing the progression of kidney disease in such patients are also provided.

WO 2019/236636 A1

[Continued on next page]

WO 2019/236636 A1

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 302

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JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 302

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

METHOD OF TREATING ACID-BASE DISORDERS

[0001] The present application claims benefit of U.S. Provisional Patent Application Serial No. 62/680,002, filed on June 4, 2018, U.S. Provisional Patent Application Serial No. 62/748,361, filed on October 19, 2018, PCT application, PCT/US18/59094, filed on November 3, 2018, U.S. Provisional Patent Application Serial No. 62/825,006, filed on March 27, 2019, and U.S. Provisional Patent Application Serial No. 62/845,290, filed on May 8, 2019, each of which is incorporated by reference in its entirety.

[0002] The present invention generally relates to methods of treating acid-base disorders that may be used, for example, in the treatment of metabolic acidosis. Metabolic acidosis is the result of metabolic and dietary processes that in various disease states create a condition in which non-volatile acids accumulate in the body, causing a net addition of protons (H^+) or the loss of bicarbonate (HCO_3^-). Metabolic acidosis occurs when the body accumulates acid from metabolic and dietary processes and the excess acid is not completely removed from the body by the kidneys. Chronic kidney disease is often accompanied by metabolic acidosis due to the reduced capacity of the kidney to excrete hydrogen ions secondary to an inability to reclaim filtered bicarbonate (HCO_3^-), synthesize ammonia (ammoniagenesis), and excrete titratable acids. Clinical practice guidelines recommend initiation of alkali therapy in patients with non-dialysis-dependent chronic kidney disease (CKD) when the serum bicarbonate level is <22 mEq/L to prevent or treat complications of metabolic acidosis. (Clinical practice guidelines for nutrition in chronic renal failure, K/DOQI, National Kidney Foundation, Am. J. Kidney Dis. 2000; 35:S1-140; Raphael, KL, Zhang, Y, Wei, G, et al. 2013, Serum bicarbonate and mortality in adults in NHANES III, Nephrol. Dial. Transplant 28: 1207-1213). These complications include malnutrition and growth retardation in children, exacerbation of bone disease, increased muscle degradation, reduced albumin synthesis, and increased inflammation. (Leman, J, Litzow, JR, Lennon, EJ. 1966. The effects of chronic acid loads in normal man: further evidence for the participation of bone mineral in the defense against chronic metabolic acidosis, J. Clin. Invest. 45: 1608-1614; Franch HA, Mitch WE, 1998, Catabolism in uremia: the impact of metabolic acidosis, J. Am. Soc. Nephrol. 9: S78-81; Ballmer, PE, McNurlan, MA, Hulter, HN, et

al., 1995, Chronic metabolic acidosis decreases albumin synthesis and induces negative nitrogen balance in humans, J. Clin. Invest. 95: 39-45; Farwell, WR, Taylor, EN, 2010, Serum anion gap, bicarbonate and biomarkers of inflammation in healthy individuals in a national survey, CMAJ 182:137-141). Overt metabolic acidosis is present in a large proportion of patients when the estimated glomerular filtration rate is below 30 ml/min/1.73m^2. (KDOQI bone guidelines: American Journal of Kidney Diseases (2003) 42:S1-S201. (suppl); Widmer B, Gerhardt RE, Harrington JT, Cohen JJ, Serum electrolyte and acid base composition: The influence of graded degrees of chronic renal failure, Arch Intern Med 139:1099-1102, 1979; Dobre M, Yang, W, Chen J, et. al., Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: a report from the chronic renal insufficiency cohort (CRIC) study. Am. J. Kidney Dis. 62: 670-678, 2013; Yaqoob, MM. Acidosis and progression of chronic kidney disease. Curr. Opin. Nephrol. Hypertens. 19: 489-492, 2010).

[0003] Metabolic acidosis, regardless of etiology, lowers extracellular fluid bicarbonate and, thus, decreases extracellular pH. The relationship between serum pH and serum bicarbonate is described by the Henderson-Hasselbalch equation

$$pH = pK' + \log [HCO_3^-]/[(0.03X\ P_aCO_2)]$$

where 0.03 is the physical solubility coefficient for CO_2, $[HCO_3^-]$ and P_aCO_2 are the concentrations of bicarbonate and the partial pressure of carbon dioxide, respectively.

[0004] There are several laboratory tests that can be used to define metabolic acidosis. The tests fundamentally measure either bicarbonate (HCO_3^-) or proton (H^+) concentration in various biological samples, including venous or arterial blood. These tests can measure either bicarbonate (HCO_3^-) or proton (H^+) concentration by enzymatic methodology, by ion selective electrodes or by blood gas analysis. In both the enzymatic and ion selective electrode methods, bicarbonate is "measured." Using blood gas analysis, bicarbonate level can be calculated using the Henderson-Hasselbalch equation.

[0005] Arterial blood gas (ABG) analysis is commonly performed for clinical evaluation, but the procedure has certain limitations in the form of reduced patient acceptability because of painful procedure and the potential to cause

complications such as arterial injury, thrombosis with distal ischaemia, haemorrhage, aneurysm formation, median nerve damage and reflex sympathetic dystrophy. Venous blood gas (VBG) analysis is a relatively safer procedure as fewer punctures are required thus reducing the risk of needle stick injury to the health care workers. Therefore, as set out below, when the invention requires assessment of metabolic acidosis, it is preferred to complete this assessment using VBG analysis. Any measurements specified herein are preferably achieved by VBG analysis where possible, for example measurements of blood or serum bicarbonate levels.

[0006] The most useful measurements for the determination of acidosis rely on a measurement of the venous plasma bicarbonate (or total carbon dioxide [tCO_2]), or arterial plasma bicarbonate (or total carbon dioxide [tCO_2]), serum electrolytes Cl^-, K^+, and Na^+, and a determination of the anion gap. In the clinical laboratory, measurement of venous plasma or serum electrolytes includes an estimation of the tCO_2. This measurement reflects the sum of circulating CO_2 [i.e., the total CO_2 represented by bicarbonate (HCO_3^-), carbonic acid, (H_2CO_3) and dissolved CO_2 (0.03 X PCO_2)]. tCO_2 can also be related to HCO_3^- by using a simplified and standardized form of the Henderson-Hasselbalch equation: $tCO_2 = HCO_3^- + 0.03\ PCO_2$, where PCO_2 is the measured partial pressure of CO_2. Since HCO_3^- concentration is greater than 90% of the tCO_2, and there are small amounts of H_2CO_3, then venous tCO_2 is often used as a reasonable approximation of the venous HCO_3^- concentration in the blood. Especially during chronic kidney disease, an abnormal plasma HCO_3^- value <22 mEq/L generally indicates metabolic acidosis.

[0007] Changes in serum Cl^- concentration can provide additional insights into possible acid-base disorders, particularly when they are disproportionate to changes in serum Na^+ concentration. When this occurs, the changes in serum Cl^- concentration are typically associated with reciprocal changes in serum bicarbonate. Thus, in metabolic acidosis with normal anion gap, serum Cl^- increases >105 mEq/L as serum bicarbonate decreases <22 mEq/L.

[0008] Calculation of the anion gap [defined as the serum $Na^+ – (Cl^- + HCO_3^-)$] is an important aspect of the diagnosis of metabolic acidosis. Metabolic acidosis may be present with a normal or an elevated anion gap. However, an elevated anion gap commonly signifies the presence of metabolic acidosis,

regardless of the change in serum HCO_3^-. An anion gap greater than 20 mEq/L (normal anion gap is 8 to 12 mEq/L) is a typical feature of metabolic acidosis.

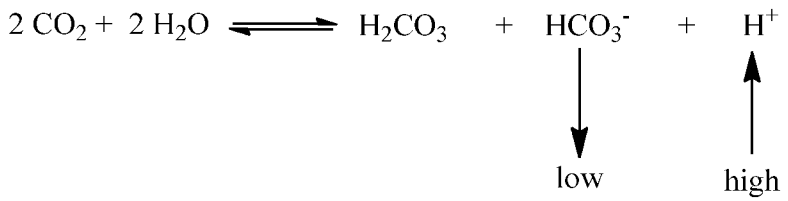
[0009] Arterial blood gases are used to identify the type of an acid-base disorder and to determine if there are mixed disturbances. In general, the result of arterial blood gas measures should be coordinated with history, physical exam and the routine laboratory data listed above. An arterial blood gas measures the arterial carbon dioxide tension (P_aCO_2), acidity (pH), and the oxygen tension (P_aO_2). The HCO_3^- concentration is calculated from the pH and the P_aCO_2. Hallmarks of metabolic acidosis are a pH <7.35, P_aCO_2 <35 mm Hg and HCO_3^- <22 mEq/L. The value of P_aO_2 (normal 80-95 mmHg) is not used in making the diagnosis of metabolic acidosis but may be helpful in determining the cause. Acid-base disturbance are first classified as respiratory or metabolic. Respiratory disturbances are those caused by abnormal pulmonary elimination of CO_2, producing an excess (acidosis) or deficit (alkalosis) of CO_2 (carbon dioxide) in the extracellular fluid. In respiratory acid-base disorders, changes in serum bicarbonate (HCO_3^-) are initially a direct consequence of the change in PCO_2 with a greater increase in PCO_2 resulting in an increase in HCO_3^-. (Adrogue HJ, Madias NE, 2003, Respiratory acidosis, respiratory alkalosis, and mixed disorders, in Johnson RJ, Feehally J (eds): Comprehensive Clinical Nephrology. London, CV Mosby, pp. 167-182). Metabolic disturbances are those caused by excessive intake of, or metabolic production or losses of, nonvolatile acids or bases in the extracellular fluid. These changes are reflected by changes in the concentration of bicarbonate anion (HCO_3^-) in the blood; adaptation in this case involves both buffering (immediate), respiratory (hours to days) and renal (days) mechanisms. (DuBose TD, MacDonald GA: renal tubular acidosis, 2002, in DuBose TD, Hamm LL (eds): Acid-base and electrolyte disorders: A companion to Brenners and Rector's the Kidney, Philadelphia, WB Saunders, pp. 189-206).

[0010] The overall hydrogen ion concentration in the blood is defined by the ratio of two quantities, the serum HCO_3^- content (regulated by the kidneys) and the PCO_2 content (regulated by the lungs) and is expressed as follows:

$$[H^+] \propto (PCO_2/[HCO_3^-])$$

[0011] The consequence of an increase in the overall hydrogen ion concentration is a decline in the major extracellular buffer, bicarbonate. Normal

blood pH is between 7.38 and 7.42, corresponding to a hydrogen ion (H^+) concentration of 42 to 38 nmol/L (Goldberg M: Approach to Acid-Base Disorders. 2005. In Greenberg A, Cheung AK (eds) Primer on Kidney Diseases, National Kidney Foundation, Philadelphia, Elsevier-Saunders, pp. 104-109.). Bicarbonate (HCO_3^-) is an anion that acts to buffer against pH disturbances in the body, and normal levels of plasma bicarbonate range from 22-26 mEq/L (Szerlip HM: Metabolic Acidosis, 2005, in Greenberg A, Cheung AK (eds) Primer on Kidney Diseases, National Kidney Foundation, Philadelphia, Elsevier-Saunders, pp. 74-89.). Acidosis is the process which causes a reduction in blood pH (acidemia) and reflects the accumulation of hydrogen ion (H^+) and its consequent buffering by bicarbonate ion (HCO_3^-) resulting in a decrease in serum bicarbonate. Metabolic acidosis can be represented as follows:



(Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. Am. J. Kidney Dis. 2000; 35:S1-140). Using this balance equation, the loss of one HCO_3^- is equivalent to the addition of one H^+ and conversely, the gain of one HCO_3^- is equivalent to the loss of one H^+. Thus, changes in blood pH, particularly increases in H^+ (lower pH, acidosis) can be corrected by increasing serum HCO_3^- or, equivalently, by decreasing serum H^+.

[0012] In order to maintain extracellular pH within the normal range, the daily production of acid must be excreted from the body. Acid production in the body results from the metabolism of dietary carbohydrates, fats and amino acids. Complete oxidation of these metabolic substrates produces water and CO_2. The carbon dioxide generated by this oxidation (~20,000 mmol/day) is efficiently exhaled by the lungs, and represents the volatile acid component of acid-base balance.

[0013] In contrast, nonvolatile acids (~50-100 mEq/day) are produced by the metabolism of sulfate- and phosphate-containing amino acids and nucleic acids. Additional nonvolatile acids (lactic acid, butyric acid, acetic acid, other organic acids) arise from the incomplete oxidation of fats and carbohydrates, and from

carbohydrate metabolism in the colon, where bacteria residing in the colon lumen convert the substrates into small organic acids that are then absorbed into the bloodstream. The impact of short chain fatty acids on acidosis is somewhat minimized by anabolism, for example into long-chain fatty acids, or catabolism to water and CO_2.

[0014] The kidneys maintain pH balance in the blood through two mechanisms: reclaiming filtered HCO_3^- to prevent overall bicarbonate depletion and the elimination of nonvolatile acids in the urine. Both mechanisms are necessary to prevent bicarbonate depletion and acidosis.

[0015] In the first mechanism, the kidneys reclaim HCO_3^- that is filtered by the glomerulus. This reclamation occurs in the proximal tubule and accounts for ~4500 mEq/day of reclaimed HCO_3^-. This mechanism prevents HCO_3^- from being lost in the urine, thus preventing metabolic acidosis. In the second mechanism, the kidneys eliminate enough H^+ to equal the daily nonvolatile acid production through metabolism and oxidation of protein, fats and carbohydrates. Elimination of this acid load is accomplished by two distinct routes in the kidney, comprising active secretion of H^+ ion and ammoniagenesis. The net result of these two interconnected processes is the elimination of the 50-100 mEq/day of nonvolatile acid generated by normal metabolism.

[0016] Thus, normal renal function is needed to maintain acid-base balance. During chronic kidney disease, filtration and reclamation of HCO_3^- is impaired as is generation and secretion of ammonia. These deficits rapidly lead to chronic metabolic acidosis which is, itself, a potent antecedent to end-stage renal disease. With continued acid production from metabolism, a reduction in acid elimination will disturb the H^+/HCO_3^- balance such that blood pH falls below the normal value of pH = 7.38 -7.42.

[0017] Treatment of metabolic acidosis by alkali therapy is usually indicated to raise and maintain the plasma pH to greater than 7.20. Sodium bicarbonate ($NaHCO_3$) is the agent most commonly used to correct metabolic acidosis. $NaHCO_3$ can be administered intravenously to raise the serum HCO_3^- level adequately to increase the pH to greater than 7.20. Further correction depends on the individual situation and may not be indicated if the underlying process is treatable

or the patient is asymptomatic. This is especially true in certain forms of metabolic acidosis. For example, in high-anion gap (AG) acidosis secondary to accumulation of organic acids, lactic acid, and ketones, the cognate anions are eventually metabolized to HCO_3^-. When the underlying disorder is treated, the serum pH corrects; thus, caution should be exercised in these patients when providing alkali to raise the pH much higher than 7.20, to prevent an increase in bicarbonate above the normal range (> 26 mEq/L).

[0018] Citrate is an appropriate alkali therapy to be given orally or IV, either as the potassium or sodium salt, as it is metabolized by the liver and results in the formation of three moles of bicarbonate for each mole of citrate. Potassium citrate administered IV should be used cautiously in the presence of renal impairment and closely monitored to avoid hyperkalemia.

[0019] Intravenous sodium bicarbonate ($NaHCO_3$) solution can be administered if the metabolic acidosis is severe or if correction is unlikely to occur without exogenous alkali administration. Oral alkali administration is the preferred route of therapy in persons with chronic metabolic acidosis. The most common alkali forms for oral therapy include $NaHCO_3$ tablets where 1 g of $NaHCO_3$ is equal to 11.9 mEq of HCO_3^-. However, the oral form of $NaHCO_3$ is not approved for medical use and the package insert of the intravenous sodium bicarbonate solution includes the following contraindications, warnings and precautions (Hospira label for NDC 0409-3486-16):

> **Contraindications**: Sodium Bicarbonate Injection, USP is contraindicated in patients who are losing chloride by vomiting or from continuous gastrointestinal suction, and in patients receiving diuretics known to produce a hypochloremic alkalosis.
> **Warnings**: Solutions containing sodium ions should be used with great care, if at all, in patients with congestive heart failure, severe renal insufficiency and in clinical states in which there exists edema with sodium retention. In patients with diminished renal function, administration of solutions containing sodium ions may result in sodium retention. The intravenous administration of these solutions can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema.

Precautions: [...] The potentially large loads of sodium given with bicarbonate require that caution be exercise in the use of sodium bicarbonate in patients with congestive heart failure or other edematous or sodium-retaining states, as well as in patients with oliguria or anuria.

[0020] Acid-base disorders are common in chronic kidney disease and heart failure patients. Chronic kidney disease (CKD) progressively impairs renal excretion of the approximately 1 mmol/kg body weight of hydrogen ions generated in healthy adults (Yaqoob, MM. 2010, Acidosis and progression of chronic kidney disease, Curr. Opin. Nephrol. Hyperten. 19:489-492.). Metabolic acidosis, resulting from the accumulation of acid (H^+) or depletion of base (HCO_3^-) in the body, is a common complication of patients with CKD, particularly when the glomerular filtration rate (GFR, a measure of renal function) falls below 30 ml/min/1.73m^2. Metabolic acidosis has profound long term effects on protein and muscle metabolism, bone turnover and the development of renal osteodystrophy. In addition, metabolic acidosis influences a variety of paracrine and endocrine functions, again with long term consequences such as increased inflammatory mediators, reduced leptin, insulin resistance, and increased corticosteroid and parathyroid hormone production (Mitch WE, 1997, Influence of metabolic acidosis on nutrition, Am. J. Kidney Dis. 29:46-48.). The net effect of sustained metabolic acidosis in the CKD patient is loss of bone and muscle mass, a negative nitrogen balance, and the acceleration of chronic renal failure due to hormonal and cellular abnormalities (De Brito-Ashurst I, Varagunam M, Raftery MJ, et al, 2009, Bicarbonate supplementation slows progression of CKD and improves nutritional status, J. Am. Soc. Nephrol. 20: 2075-2084). Conversely, the potential concerns with alkali therapy in CKD patients include expansion of extracellular fluid volume associated with sodium ingestion, resulting in the development or aggravation of hypertension, facilitation of vascular calcification, and the decompensation of existing heart failure. CKD patients of moderate degree (GFR at 20-25% of normal) first develop hyperchloremic acidosis with a normal anion gap due to the inability to reclaim filtered bicarbonate and excrete proton and ammonium cations. As they progress toward the advanced stages of CKD the anion gap increases, reflective of the continuing degradation of the kidney's ability to excrete the anions that were associated with the unexcreted protons. Serum bicarbonate in these patients rarely goes below 15 mmol/L with a maximum elevated

anion gap of approximately 20 mmol/L. The non-metabolizable anions that accumulate in CKD are buffered by alkaline salts from bone (Lemann J Jr, Bushinsky DA, Hamm LL Bone buffering of acid and base in humans. Am. J. Physiol Renal Physiol. 2003 Nov, 285(5):F811-32).

[0021] The majority of patients with chronic kidney disease have underlying diabetes (diabetic nephropathy) and hypertension, leading to deterioration of renal function. In almost all patients with hypertension a high sodium intake will worsen the hypertension. Accordingly, kidney, heart failure, diabetes and hypertensive guidelines strictly limit sodium intake in these patients to less than 1.5 g or 65 mEq per day (HFSA 2010 guidelines, Lindenfeld 2010, J Cardiac Failure V16 No 6 P475). Chronic anti-hypertensive therapies often induce sodium excretion (diuretics) or modify the kidney's ability to excrete sodium and water (such as, for example, Renin Angiotensin Aldosterone System inhibiting "RAASi" drugs). However, as kidney function deteriorates, diuretics become less effective due to an inability of the tubule to respond. The RAASi drugs induce life-threatening hyperkalemia as they inhibit renal potassium excretion. Given the additional sodium load, chronically treating metabolic acidosis patients with amounts of sodium-containing base that often exceed the total daily recommended sodium intake is not a reasonable practice. As a consequence, oral sodium bicarbonate is not commonly prescribed chronically in these diabetic nephropathy patients. Potassium bicarbonate is also not acceptable as patients with CKD are unable to readily excrete potassium, leading to severe hyperkalemia.

[0022] Despite these shortcomings, the role of oral sodium bicarbonate has been studied in the small subpopulation of non-hypertensive CKD patients. As part of the Kidney Research National Dialogue, alkali therapy was identified as having the potential to slow the progression of CKD, as well as to correct metabolic acidosis. The annual age-related decline in glomerular filtration rate (GFR) after the age of 40 is 0.75-1.0 ml/min/1.73m^2 in normal individuals. In CKD patients with fast progression, a steeper decline of >4 ml/min/1.73m^2 annually can be seen. Glomerular filtration rate or estimated glomerular filtration rate is typically used to characterize kidney function and the stage of chronic kidney disease. The five stages of chronic kidney disease and the GFR for each stage is as follows:

Stage 1 with normal or high GFR (GFR > 90 mL/min/1.73 m^2)

Stage 2 Mild CKD (GFR = 60-89 mL/min/1.73 m^2)

Stage 3A Moderate CKD (GFR = 45-59 mL/min/1.73 m^2)

Stage 3B Moderate CKD (GFR = 30-44 mL/min/1.73 m^2)

Stage 4 Severe CKD (GFR = 15-29 mL/min/1.73 m^2)

Stage 5 End Stage CKD (GFR <15 mL/min/1.73 m^2).

[0023] In one outcome study, De Brito-Ashurst et al showed that bicarbonate supplementation preserves renal function in CKD (De Brito-Ashurst I, Varagunam M, Raftery MJ, et al, 2009, Bicarbonate supplementation slows progression of CKD and improves nutritional status, J. Am. Soc. Nephrol. 20: 2075-2084). The study randomly assigned 134 adult patients with CKD (creatinine clearance [CrCl] 15 to 30 ml/min per 1.73 m^2) and serum bicarbonate 16 to 20 mmol/L to either supplementation with oral sodium bicarbonate or standard of care for 2 years. The average dose of bicarbonate in this study was 1.82 g/day, which provides 22 mEq of bicarbonate per day. The primary end points were rate of CrCl decline, the proportion of patients with rapid decline of CrCl (>3ml/min per 1.73 m^2/yr), and end-stage renal disease ("ESRD") (CrCl <10 ml/min). Compared with the control group, decline in CrCl was slower with bicarbonate supplementation (decrease of 1.88 ml/min per 1.73 m^2 for patients receiving bicarbonate versus a decrease of 5.93 ml/min per 1.73 m^2 for control group; P<0.0001). Patients supplemented with bicarbonate were significantly less likely to experience rapid progression (9% versus 45%; relative risk 0.15; 95% confidence interval 0.06 to 0.40; P < 0.0001). Similarly, fewer patients supplemented with bicarbonate developed ESRD (6.5% versus 33%; relative risk 0.13; 95% confidence interval 0.04 to 0.40; P < 0.001).

[0024] Hyperphosphatemia is a common co-morbidity in patients with CKD, particularly in those with advanced or end-stage renal disease. Sevelamer hydrochloride is a commonly used ion-exchange resin that reduces serum phosphate concentration. However, reported drawbacks of this agent include metabolic acidosis apparently due to the net absorption of HCl in the process of binding phosphate in the small intestine. Several studies in patients with CKD and hyperphosphatemia who received hemodialysis or peritoneal dialysis found decreases in serum bicarbonate concentrations with the use of Sevelamer

hydrochloride (Brezina, 2004 Kidney Int. V66 S90 (2004) S39-S45; Fan, 2009 Nephrol Dial Transplant (2009) 24:3794).

[0025] Among the various aspects of the present disclosure, the following is a useful guide for one method for treating metabolic acidosis (without wishing to be bound by theory). When an H^+ is pumped into the stomach a HCO_3^- enters the systemic circulation and raises the serum bicarbonate concentration. The initial binding of gastric H^+ to a nonabsorbable composition as described herein results in HCO_3^- entering the systemic circulation and raising the serum bicarbonate concentration. The more H^+ bound the greater the increase in systemic HCO_3^-. The binding of Cl^- the nonabsorbable composition prevents subsequent exchange of luminal Cl^- for HCO_3^- which would counteract the initial rise in HCO_3^-. The analogous clinical situation to administering the composition is vomiting. Administration of the composition is essentially causing the loss of gastric HCl as in vomiting. If a person vomits they lose gastric HCl and have an increase in serum bicarbonate. The increase in serum bicarbonate persists only if they are not given a lot of oral Cl^-, for example as NaCl, which would allow subsequent exchange of intestinal Cl^- for HCO_3^- and dissipate the increase in serum bicarbonate concentration. The disclosure is not limited by these requirements, and instead they are set out in full below.

[0026] Among the various aspects of the present disclosure may be noted a method of treating an individual afflicted with a chronic acid/base disorder characterized by a baseline serum bicarbonate value of less than 22 mEq/l. The method comprises oral administration of a pharmaceutical composition comprising a nonabsorbable composition having the capacity to bind a target species selected from the group consisting of protons, a conjugate base of a strong acid, and a strong acid as it transits the digestive system and increase the individual's serum bicarbonate value to at least 24 mEq/l but less than 30 mEq/l.

[0027] Among the various aspects of the present disclosure may be noted a method of treating an individual afflicted with a chronic acid/base disorder characterized by a baseline serum bicarbonate value of less than 22 mEq/l. The method comprises oral administration of a pharmaceutical composition comprising a nonabsorbable composition having the capacity to bind a target species selected from the group consisting of protons, a conjugate base of a strong acid, and a strong

acid as it transits the digestive system and increase the individual's serum bicarbonate value to at least 24 mEq/l but not greater than 29 mEq/l.

[0028] Another aspect of the present disclosure is a method of treating an individual afflicted with an acid-base disorder characterized by a baseline serum bicarbonate value of less than 22 mEq/l, the method comprising oral administration of a daily dose of a pharmaceutical composition having the capacity to remove at least 5 meq of a target species as it transits the digestive system to increase the individual's serum bicarbonate value to at least 24 mEq/l but not greater than 29 mEq/l from baseline within a treatment period not greater than 1 month. The target species is selected from the group consisting of protons, strong acids, and conjugate bases of strong acids.

[0029] Another aspect of the present disclosure is a composition for use in a method of treating metabolic acidosis in an adult human patient by increasing that patient's serum bicarbonate value by at least 1 mEq/L over 15 days of treatment (*i.e.*, within 15 days of treatment), said composition being a nonabsorbable composition having the capacity to remove protons from the patient. In this aspect, the composition may be administered orally, and so would be an orally administered nonabsorbable composition as defined herein.

[0030] In certain embodiments, the orally administered nonabsorbable composition comprises cations (such as Na^+, K^+, Mg^{2+}, Ca^{2+} Li^+, or a combination thereof) that are exchanged for protons as the nonabsorbable composition transits the digestive system, and the protons are then excreted from the body along with the nonabsorbable composition upon defecation. The net effect is reduction in protons in the body, in exchange for an increase in one or more cations. In this embodiment, the pharmaceutical composition may also optionally comprise a pharmaceutically acceptable carrier, diluent or excipient, or a combination thereof that does not significantly interfere with the proton-binding characteristics of the nonabsorbable composition *in vivo*. Optionally, the pharmaceutical composition may also comprise an additional therapeutic agent.

[0031] In certain embodiments, the orally administered nonabsorbable composition comprises anions that are exchanged for chloride ions and if the anion comprised by the orally administered nonabsorbable composition is a stronger base

(*e.g.*, OH^-) than the removed base (*e.g.*, Cl^-, HSO_4^-, or SO_4^{2-}), the net effect is the removal of a strong acid from the body (*e.g.*, HCl or H_2SO_4) in exchange for a weak acid (*e.g.*, H_2O). In this embodiment, the pharmaceutical composition may also optionally comprise a pharmaceutically acceptable carrier, diluent or excipient, or a combination thereof that does not significantly interfere with the chloride-binding characteristics of the nonabsorbable composition *in vivo*. Optionally, the pharmaceutical composition may also comprise an additional therapeutic agent.

[0032] In certain embodiments, the orally administered nonabsorbable composition is a neutral composition having the capacity to bind and remove a strong acid, such as HCl or H_2SO_4, from the body upon oral administration. The nonabsorbable composition may, but does not necessarily, introduce (*i.e.*, by ion exchange) counterbalancing cations or anions in the process of removing the acid. In this embodiment, binding of both ionic species of HCl (H^+ and Cl^-) may be achieved through favorable surface energy of the bulk material, which can include hydrogen bonding and other interactions as well as ionic interactions. Complexation of HCl can occur on functional groups that are dehydrated and upon administration in an acidic aqueous medium, result in the hydrochloride salt of the functional group.

[0033] Among the various aspects of the present disclosure may further be noted a method of treating an individual afflicted with a chronic acid/base disorder comprising oral administration of a pharmaceutical composition containing a nonabsorbable composition having the capacity to bind protons and chloride ions as it transits the digestive system and remove the bound protons and chloride ions from the individual's digestive system via defecation. In each of these embodiments, the pharmaceutical composition may also optionally comprise a pharmaceutically acceptable carrier, diluent or excipient, or a combination thereof that does not significantly interfere with the chloride-binding characteristics of the nonabsorbable composition *in vivo*. Optionally, the pharmaceutical composition may also comprise an additional therapeutic agent.

[0034] In one embodiment, any of the methods of treating an individual afflicted with an acid-base disorder disclosed in this application comprise: i) the individual having a diet regimen, or ii) the method including, specifying, prescribing or recommending a diet regimen. In one embodiment, said diet regimen is an alkaline diet regimen. In one embodiment, said diet regimen is a conventional low-

protein diet regimen (< 0.6 g/kg per day). In one embodiment, said diet regimen is a very low-protein diet regimen (0.3-0.4 g/kg per day). In one embodiment, said diet regimen is a vegetarian diet regimen. In one embodiment, said diet regimen is a vegetarian diet regimen supplemented with either essential amino acids or a mixture of essential amino acids and nitrogen-free ketoanalogues (keto diet regimen). In one embodiment, said diet regimen is ketoanalogue-supplemented vegetarian very low-protein diet. In one embodiment, said diet regimen is a vegan diet regimen. In one embodiment, said diet regimen is a casein diet regimen. In one embodiment, said diet regimen is an adenine-containing diet regimen. In one embodiment, said diet regimen comprises one or more base-producing vegetables (e.g. carrots, cauliflower, eggplant, lettuce, potatoes, spinach, tomatoes, or zucchini, or a combination thereof). In one embodiment, said diet regimen comprises one or more base-producing fruits (e.g. apple, apricot, oranges, peaches, pears, raisins, or strawberries, or a combination thereof). In one embodiment, said diet regimen does not comprise acid-producing meat.

[0035] In one embodiment the diet commences one year before administering the nonabsorbable composition. In another embodiment the diet commences six months before administering the nonabsorbable composition. In another embodiment the diet commences one month before administering the nonabsorbable composition. In another embodiment the diet regimen commences when the administering of the nonabsorbable composition commences. In another embodiment the diet commences one month after administering the nonabsorbable composition. In another embodiment the diet commences six months after administering the nonabsorbable composition. In another embodiment the diet commences one year after administering the nonabsorbable composition.

[0036] Among the various aspects of the present disclosure may further be noted a method of improving the quality of life of a patient afflicted with chronic kidney disease and an acid-base disorder characterized by a baseline serum bicarbonate value of ≤22 mEq/L. The method comprises oral administration of a pharmaceutical composition capable of increasing and maintaining the patient's serum bicarbonate above 20 mEq/L for a period of at least twelve weeks, the pharmaceutical composition having the capacity to bind a target species selected

from the group consisting of protons, strong acids, and conjugate bases of strong acids.

[0037] Among the various aspects of the present disclosure may further be noted a method of treating an individual afflicted with chronic kidney disease, the method comprising administering a composition described herein.

[0038] In one embodiment, the rate of progression of the individual's chronic kidney disease is decreased. In this embodiment, the rate of progression may decrease for at least about 1 month, at least about 4 months, at least about 6 months, or at least about 12 months. As shown in Figure 35, the rate of progression of chronic kidney disease is decreased to such an extent that the Death/Dialysis/≥50% eGFR decline (DD50) is reduced to 4% for populations treated with veverimer (TRC101) relative to 10.8% for populations treated with placebo.

[0039] Among the various aspects of the present disclosure may further be noted a method of decreasing the rate of progression of chronic kidney disease in an individual, the method comprising administering a composition described herein.

[0040] In one embodiment, the individual is afflicted with metabolic acidosis. The metabolic acidosis may be eubicarbonatemic metabolic acidosis. The metabolic acidosis may be characterized by a blood serum or blood plasma bicarbonate value not in excess of about 25 mEq/l, 24 mEq/l, or 23 mEq/l. The metabolic acidosis may be characterized by a blood serum or blood plasma bicarbonate value of less than about 22 mEq/l.

[0041] In another embodiment, the rate of decrease in the progression of chronic kidney disease is measurable by a decreased rate of change in eGFR.

[0042] In another embodiment, the decreased rate of change in eGFR occurs to the extent that eGFR stops decreasing.

[0043] In another embodiment, the decreased rate of change in eGFR occurs to the extent that there is an improvement in eGFR.

[0044] In another embodiment, the delay in the progression of chronic kidney disease includes the individual's stage of chronic kidney disease remaining constant. The patient may remain at stage 1, 2, 3A, 3B, 4 or 5 of chronic kidney disease. In this embodiment, the patient may remain at the claimed stage of chronic

kidney disease for at least about 1 month, at least about 4 months, at least about 6 months, or at least about 12 months.

[0045] In any of the aspects disclosed herein, the blood pressure of the patient after treatment is unchanged relative to the blood pressure of the patient before treatment.

[0046] In any of the aspects disclosed herein, the blood pressure of the patient during treatment is unchanged relative to the blood pressure of the patient before treatment.

[0047] In any of the aspects disclosed herein, there is not a significant change in the blood pressue of the patient after treatment relative to the blood pressure of the patient before treatment.

[0048] In any of the aspects disclosed herein, there is not a significant change in the blood pressue of the patient during treatment relative to the blood pressure of the patient before treatment.

[0049] In any of the aspects disclosed herein the method or composition does not adversely affect blood pressure of treated patient or individual.

[0050] In another embodiment, a method of improving the quality of life of a patient afflicted with chronic kidney disease and an acid-base disorder is provided. This method comprises oral administration of a pharmaceutical composition having: (a) the capacity to selectively bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay, wherein the improvement in quality of life is statistically significant compared to a placebo control group for a period of at least twelve weeks as assessed by a Quality of Life (QoL) questionnaire.

[0051] Another embodiment provides a method of improving quality of life of a patient afflicted with chronic kidney disease and an acid-base disorder, wherein the patient has a baseline serum bicarbonate value of ≤22 mEq/L. This method comprises orally administering to the patient an effective amount of TRC101 once daily for a period of time sufficient to statistically significantly increase the patient's quality of life compared to a placebo control.

[0052] A further embodiment provides a method of improving quality of life of a patient afflicted with metabolic acidosis disease. This method comprises administering to the patient a daily dose of a nonabsorbed crosslinked amine polymer, which daily dose: (a) is sufficient to increase the patient's serum bicarbonate concentration by at least 1 mEq/L; (b) results in a sustained serum bicarbonate increase of at least 1 mEq/L over a period of at least twelve weeks; and (c) is sufficient to improve the patient's quality of life compared to a placebo control group over the period, wherein the improvement in quality of life is statistically significant.

[0053] Another embodiment provides a pharmaceutical composition for improving the quality of life of a human patient afflicted with chronic kidney disease and an acid-base disorder, the patient having a baseline serum bicarbonate level of ≤22 mEq/L prior to treatment. This composition is a nonabsorbable composition having the capacity to: (a) remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) improve the patient's quality of life compared to a placebo control in a statistically significant manner over at least a twelve-week period.

[0054] A further embodiment is a pharmaceutical composition for improving the quality of life of a human patient suffering from a disease or disorder by increasing that patient's serum bicarbonate value by at least 1 mEq/L over at least twelve weeks of treatment. In this embodiment, the composition: (a) is a nonabsorbable composition having the capacity to remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (b) is characterized by a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (c) has the capacity to improve the patient's quality of life compared to a placebo control in a statistically significant manner over at least the twelve-week period.

[0055] Another embodiment is a pharmaceutical composition for improving the quality of life of a human patient suffering from metabolic acidosis disease, wherein: (a) an effective amount of the pharmaceutical composition is administered to the patient per day over at least a twelve-week period; (b) the pharmaceutical composition is nonabsorbable with the capacity to remove from the patient a target species selected from the group consisting of protons, strong acids, and conjugate

bases of strong acids; (c) the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (d) the improvement in quality of life compared to a placebo control is statistically significant over the twelve-week period.

[0056] A further embodiment is a method of improving the physical function of a patient afflicted with chronic kidney disease and an acid-base disorder characterized by a baseline serum bicarbonate value of ≤22 mEq/L. In this embodiment, the method comprises oral administration of a pharmaceutical composition capable of increasing and maintaining the patient's serum bicarbonate above 20 mEq/L for a period of at least twelve weeks, the pharmaceutical composition having the capacity to bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids.

[0057] A further embodiment is a method of improving the physical function of a patient afflicted with chronic kidney disease and an acid-base disorder. This method comprises oral administration of a pharmaceutical composition having: (a) the capacity to selectively bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay, wherein the improvement in physical function is statistically significant compared to a placebo control group at least twelve weeks after initiation of treatment as assessed by the patient's answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF).

[0058] Another embodiment is a method of improving the physical function of a patient afflicted with chronic kidney disease and an acid-base disorder, wherein the patient has a baseline serum bicarbonate value of ≤22 mEq/L. This method comprises orally administering to the patient an effective amount of TRC101 once daily for a period of time sufficient to statistically significantly increase the patient's physical function score based on answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF) compared to the patient's baseline physical function score.

[0059] A further embodiment is a method of improving the physical function of a patient afflicted with metabolic acidosis disease. This method

comprises administering to the patient a daily dose of a nonabsorbed crosslinked amine polymer, which daily dose: (a) is sufficient to increase the patient's serum bicarbonate concentration by at least 1 mEq/L; (b) results in a sustained serum bicarbonate increase of at least 1 mEq/L over a period of at least twelve weeks; and (c) is sufficient to improve the physical function score of the patient compared to a placebo control group at the end of the period, wherein the improvement in the physical function score is statistically significant.

[0060] Yet another embodiment is pharmaceutical composition for improving the physical function score of a human patient afflicted with chronic kidney disease and an acid-base disorder, the patient having a baseline serum bicarbonate level of ≤22 mEq/L prior to treatment. In this embodiment, the composition is a nonabsorbable composition having the capacity to: (a) remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) improve the patient's physical function score based on answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF) compared to a placebo control in a statistically significant manner at the end of at least a twelve-week period.

[0061] A further embodiment is a pharmaceutical composition for improving the physical function score of a human patient suffering from a disease or disorder by increasing that patient's serum bicarbonate value by at least 1 mEq/L over at least twelve weeks of treatment. In this embodiment, the composition: (a) is a nonabsorbable composition having the capacity to remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (b) is characterized by a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (c) has the capacity to improve the patient's physical function score based on answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF) compared to a placebo control in a statistically significant manner at the end of an at least the twelve-week period.

[0062] Another embodiment is a pharmaceutical composition for improving the physical function score of a human patient suffering from metabolic acidosis disease, wherein: (a) an effective amount of the pharmaceutical composition is administered to the patient per day over at least a twelve-week period; (b) the

pharmaceutical composition is nonabsorbable with the capacity to remove from the patient a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (c) the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (d) the improvement in physical function score is a statistically significant improvement over a baseline physical function score based on answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF) compared to a placebo control at the end of the at least twelve-week period.

[0063] A further embodiment is a method of slowing the progression of kidney disease in a patient afflicted with chronic kidney disease and an acid-base disorder characterized by a baseline serum bicarbonate value of ≤22 mEq/L. In this embodiment, the method comprises oral administration of a pharmaceutical composition capable of increasing and maintaining the patient's serum bicarbonate above 20 mEq/L for a period of at least twelve weeks, the pharmaceutical composition having the capacity to bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids.

[0064] Another embodiment is a method of slowing the progression of kidney disease in a patient afflicted with chronic kidney disease and an acid-base disorder, wherein the patient has a baseline serum bicarbonate value of ≤22 mEq/L. This method comprises orally administering to the patient an effective amount of TRC101 once daily for a period of time sufficient to increase the patient's serum bicarbonate by at least 1 mEq/L.

[0065] Another embodiment is a method of slowing the progression of kidney disease in a patient afflicted with chronic kidney disease and metabolic acidosis disease. This method comprises administering to the patient a daily dose of a nonabsorbed crosslinked amine polymer, which daily dose: (a) is sufficient to increase the patient's serum bicarbonate concentration by at least 1 mEq/L; (b) results in a sustained serum bicarbonate increase of at least 1 mEq/L over a period of at least twelve weeks; and (c) is sufficient to slow the progression of kidney disease.

[0066] A further embodiment is a pharmaceutical composition for slowing the progression of kidney disease in a human patient afflicted with chronic kidney disease and an acid-base disorder, the patient having a baseline serum bicarbonate level of ≤22 mEq/L prior to treatment. In this embodiment, the composition is a nonabsorbable composition having the capacity to: (a) remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) slow the progression of kidney disease in a human patient over at least a twelve-week period.

[0067] A further embodiment is a pharmaceutical composition for slowing the progression of kidney disease in a human patient afflicted with chronic kidney disease and an acid-base disorder by increasing that patient's serum bicarbonate value by at least 1 mEq/L over at least twelve weeks of treatment. In this embodiment, the composition: (a) is a nonabsorbable composition having the capacity to remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (b) is characterized by a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (c) has the capacity to slow the progression of kidney disease over at least the twelve-week period.

[0068] Another embodiment is a pharmaceutical composition for slowing the progression of kidney disease in a human patient also suffering from metabolic acidosis disease, wherein: (a) an effective amount of the pharmaceutical composition is administered to the patient per day over at least a twelve-week period; (b) the pharmaceutical composition is nonabsorbable with the capacity to remove from the patient a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (c) the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (d) the progression of kidney disease in the patient is slowed over the twelve-week period compared to a placebo control group not receiving the pharmaceutical composition.

[0069] Another embodiment is a pharmaceutical composition for use in a method of treating an acid-base disorder in a patient, wherein the method of treatment improves the quality of life of the patient.

[0070] Yet another embodiment is a pharmaceutical composition for use in a method of treating an acid-base disorder in a patient, wherein the method of treatment improves the physical function of the patient.

[0071] In one embodiment, the present invention is directed to a nonabsorbable composition for use in a method of treating an acid-base disorder, wherein the patient's physical function increases and the patient's baseline serum bicarbonate value does not increase, or does not significantly increase or does not increase in proportion to the improvement in the patient's physical function.

[0072] Suprisingly in the extended phase III clinical study TRCA-301E a direct proportionality between baseline serum bicarbonate value and physical function was not always observed. Without wishing to be bound by theory, one or both of the two following mechanisms may allow the physical function to increase independently of baseline serum bicarbonate values.

[0073] The first mechanism proposed is that an increase in blood bicarbonate arising from treatment may be offset by an increased protein intake and consequent increase in acid production.

[0074] More specifically, patients with improved physical function may have increased their protein intake in response to increased muscle mass. This hypothesis is supported by the higher excretion of urea nitrogen in a 24 hour urine collection at the end of the study compared to baseline. Any increase in protein intake may have resulted in increased acid production, which would have consequently masked the bicarbonate response to treatment.

[0075] The second mechanism proposed is that the improvement in physical function occurs due to treatment neutralizing retained acid that was stimulating muscle catabolism. The reduction in muscle catabolism is thought to occur before blood bicarbonate levels increase.

[0076] More specifically, when the patient's kidneys deteriorate they retain the acid that would normally be excreted. This retained acid may then be buffered by muscle catabolism to maintain a normal blood pH and serum bicarbonate level. An increase in muscle catabolism would contribute to a loss of physical function. Thus muscle catabolism and loss of physical function can occur in the setting of a normal or near normal blood pH and serum bicarbonate.

[0077] When the patient is treated, the retained acid is neutralized by the increased bicarbonate entering the blood. This removal of retained acid may reduce the stimulus for muscle catabolism and consequently improve physical function. It is thought that this reduction in the stimulus of muscle catabolism may occur before an increase in blood bicarbonate. Thus an improvement in physical function may be observed before an increase in blood bicarbonate.

[0078] Therefore in one embodiment, the present disclosure sets out a treatment which does not increase serum blood bicarbonate in proportion to the improvement in the patient's physical function. Therefore, disclosed are methods of treating an acid-base disorder in a patient in need thereof by administering a nonabsorbable composition, wherein the patient's physical function increases and the patient's baseline serum bicarbonate value does not increase, or does not significantly increase or does not increase in proportion to the improvement in the patient's physical function.

[0079] In one embodiment, the physical function of the patient improves and the patient's baseline serum bicarbonate value does not increase. In one embodiment, the physical function of the patient improves and the patient's baseline serum bicarbonate value does not significantly increase. In one embodiment, the improvement in physical function of the patient is not proportional to the increase in the patient's baseline serum bicarbonate value. In one embodiment, the improvement in physical function of the patient is independent of the increase in the patient's baseline serum bicarbonate value. In one embodiment, the improvement in physical function of the patient occurs before an increase in the patient's baseline serum bicarbonate value is observed.

[0080] In one embodiment, the quality of life of the patient improves and the patient's baseline serum bicarbonate value does not increase. In one embodiment, the quality of life of the patient improves and the patient's baseline serum bicarbonate value does not significantly increase. In one embodiment, the improvement in quality of life of the patient is not proportional to the increase in the patient's baseline serum bicarbonate value. In one embodiment, the improvement in quality of life of the patient is independent of the increase in the patient's baseline serum bicarbonate value. In one embodiment, the improvement in quality of life of

the patient occurs before an increase in the patient's baseline serum bicarbonate value is observed.

[0081] De Brito-Ashurst *et al.* is one of six published prospective randomized, controlled clinical studies of alkali supplementation and dietary intervention, which demonstrate that increasing serum bicarbonate levels results in improved renal outcomes associated with chronic metabolic acidosis. The five other studies are: Garneata L, Stancu A, Dragomir D, *et al.*, 2016, Ketoanalogue-Supplemented Vegetarian Very Low-Protein Diet and CKD Progression, J. Am. Soc. Nephrol. 27: 2164-2176; Phisitkul S, Khanna A, Simoni J, *et al.*, 2010, Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR, Kidney International 77: 617-623; Goraya N, Simoni J, Jo C, Wesson D, 2013, A comparison of treating metabolic acidosis in CKD stage 4 hypertensive kidney disease with fruits and vegetables or sodium bicarbonate, Clin. J. Am. Soc. Nephrol. 8: 371-381; Goraya N, Simoni J, Jo C, Wesson D, 2014, Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate, Kidney International 86: 1031-1038; and Mahajan A, Simoni J, Sheather S, *et al.*, 2010, Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy, Kidney International 78: 303-309.

[0082] Garneata *et al.* assessed the effects of a ketoanalogue-supplemented vegetarian very low protein diet (0.3 g/kg/day) in diet-compliant patients to those of a usual mixed-source low protein diet (0.6 g/kg/day). Baseline serum bicarbonate was similar in the two treatment groups (16.7-16.8 mEq/L), however the end of study serum bicarbonate value was significantly higher in the vegetarian very low protein diet group than the usual mixed-source low protein diet group. Efficacy of the vegetarian very low protein diet to reduce incidence of renal events was most noted in patients with initial eGFR <20 mL/min.1.73m^2.

[0083] In those embodiments in which the nonabsorbable composition binds chloride ions, it is generally preferred that the nonabsorbable composition selectively bind chloride ions relative to other physiologically significant competing anions such as bicarbonate equivalent anions, phosphate anions, and the conjugate bases of bile and fatty acids that are present in the GI tract. Stated differently, it is

generally preferred that the nonabsorbable composition remove more chloride ions than any other competing anion in the GI tract.

[0084] In those embodiments in which the nonabsorbable composition binds protons, it is generally preferred that the nonabsorbable composition bind protons without delivering sodium, potassium, calcium, magnesium, and/or other electrolytes in exchange for the protons in an amount that is physiologically detrimental. As a result, treatment with the nonabsorbable composition will not significantly contribute to edema, hypertension, hyperkalemia, hypercalcemia or a similar disorder associated with an elevated load of sodium, potassium, calcium or other electrolyte. Similarly, in those embodiments in which the nonabsorbable composition binds protons, it is generally preferred that the nonabsorbable composition bind protons without removing an amount of sodium, potassium, calcium, magnesium and/or other electrolytes along with the protons. As a result, treatment with the nonabsorbable composition will not significantly contribute to hypotension, hypokalemia, hypocalcemia or other disorder associated with a depressed serum concentration of sodium, potassium, calcium, magnesium or other electrolyte.

[0085] In certain embodiments, the polymers preferably bind and maintain their ability to bind proton and anions at the physiological conditions found along the gastrointestinal (GI) lumen. These conditions can change according to dietary intake (see, for example, Fordtran J, Locklear T. Ionic constituents and osmolality of gastric and small-intestinal fluids after eating. Digest Dis Sci. 1966;11(7):503-21) and location along the GI tract (Binder, H et al. Chapters 41-45 in “Medical Physiology”, 2nd Edition, Elsevier [2011]. Boron and Boulpaep [Ed.]). Rapid binding of proton and chloride in the stomach and small intestine is desirable. High binding levels and selectivity for chloride later in the GI tract (lower small intestine and large intestine) is also desirable. In general, the polymers also preferably have a pK_a such that the majority of amines are protonated under the various pH and electrolyte conditions encountered along the GI tract and are thereby capable of removing proton, along with an appropriate counter anion (preferably chloride), from the body into the feces.

[0086] Since the stomach is an abundant source of HCl, and the stomach is the first site of potential HCl binding (after the mouth), and since residence time in the stomach is short (gastric residence half-life of approximately 90 minutes),

compared to the rest of the GI tract (small intestine transit time of approximately 4 hours; whole gut transit time of 2-3 days; Read, NW et al. Gastroenterology [1980] 79:1276), it is desirable for the polymer of the present disclosure to demonstrate rapid kinetics of proton and chloride binding in the lumen of this organ, as well as in in vitro conditions designed to mimic the stomach lumen (e.g. SGF). Phosphate is a potential interfering anion for chloride binding in the stomach and small intestine, where phosphate is mostly absorbed (Cross, HS et al Miner Electrolyte Metab [1990] 16:115-24). Therefore rapid and preferential binding of chloride over phosphate is desirable in the small intestine and in in vitro conditions designed to mimic the small intestine lumen (e.g. SIB). Since the transit time of the colon is slow (2-3 days) relative to the small intestine, and since conditions in the colon will not be encountered by an orally administered polymer until after stomach and small intestine conditions have been encountered, kinetics of chloride binding by a polymer of the present disclosure do not have to be as rapid in the colon or in in vitro conditions designed to mimic the late small intestine/colon. It is, however, important that chloride binding and selectivity over other interfering anions is high, for example, at 24 and/or 48 hours or longer.

[0087] Other aspects and features will be in part apparent and in part pointed out hereinafter.

[0088] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

[0089] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color

drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0090] The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

[0091] Fig. 1A-1C is a flow chart schematically depicting the mechanism of action of the polymer when passing through the gastrointestinal tract of an individual from oral ingestion/stomach (Fig. 1A), to the upper GI tract (FIG. 1B) to the lower GI tract/colon (Fig. 1C).

[0092] Fig. 2 is a graph of the effect of TRC101 on serum bicarbonate in a rat model of adenine-induced nephropathy and metabolic acidosis in Part 1 of the study described in Example 1.

[0093] Figs. 3A, 3B and 3C are graphs of the effect of TRC101 on fecal excretion of chloride (Fig. 3A), sulfate (Fig. 3B), and phosphate (Fig. 3C) in a rat model of adenine-induced nephropathy and metabolic acidosis in Part 1 of the study described in Example 1.

[0094] Fig. 4 is a graph of the effect of TRC101 on serum bicarbonate in a rat model of adenine-induced nephropathy and metabolic acidosis in Part 2 of the study described in Example 1.

[0095] Figs. 5A, 5B and 5C are graphs of the effect of TRC101 on fecal excretion of chloride (Fig. 5A), sulfate (Fig. 5B), and phosphate (Fig. 5C) in a rat model of adenine-induced nephropathy and metabolic acidosis in Part 2 of the study described in Example 1.

[0096] Figs. 6A, 6B and 6C are graphs of the *in vivo* chloride (Fig. 6A), sulfate (Fig. 6B) and phosphate (Fig. 6C) binding capacities of TRC101 and bixalomer in a pig with normal renal function in the study described in Example 2.

[0097] Fig. 7 is a line graph showing the mean change in serum bicarbonate (SBC) from baseline (BL) and standard error (SE) by treatment group over time in a human study as described more fully in Example 3 (Part 1).

[0098] Fig. 8 is a bar graph showing the least squares mean (LS Mean) change from baseline (CFB) to end of treatment in serum bicarbonate (SBC) by treatment group in a human study as described more fully in Example 3 (Part 1). Single asterisk (" * ") indicates statistically significant difference ($p<0.5$) and double asterisk (" ** ") indicates highly statistically significant difference ($p<0.0001$).

[0099] Fig. 9 is a bar graph showing the effect on serum bicarbonate (SBC) levels and standard error (SE) at days 8 and 15 resulting from treatment (Tx = treatment) and upon withdrawal of TRC101 in a human study as described more fully in Example 3 (Part 1).

[00100] Fig. 10 is a line graph showing the mean change in serum bicarbonate (SBC) and standard error (SE) for the four TRC101 active arms and the two placebo arms (pooled) of the study described more fully in Example 3 (Parts 1 and 2).

[00101] Fig. 11 is a bar graph showing the least squares mean (LS Mean) change from baseline (CFB) in serum bicarbonate (SBC) by treatment group over time for the four TRC101 active arms and the two placebo arms (pooled) of the study described more fully in Example 3 (Parts 1 and 2). Single asterisk (" * ") indicates statistically significant difference ($p<0.5$) and double asterisk (" ** ") indicates highly statistically significant difference ($p<0.0001$).

[00102] Fig. 12 is a bar graph showing the treatment effect on serum bicarbonate (SBC) levels and standard error (SE) at days 8 and 15 resulting from treatment (Tx = treatment) with and upon withdrawal of TRC101 in a human study as described more fully in Example 3 (Parts 1 and 2).

[00103] Figs. 13A, 13B, 13C and 13D are graphs showing the changes in serum bicarbonate (Fig. 13A), serum chloride (Fig. 13B), serum sodium (Fig. 13C) and serum potassium (Fig. 13D) for the four TRC101 active arms (combined) vs the two placebo arms (pooled) over time for the study described more fully in Example 3 (Parts 1 and 2).

[00104] Fig. 14 is a graph showing the changes in the calculated anion gap for the four TRC101 active arms (combined) vs the two placebo arms (pooled) over time for the study described more fully in Example 3 (Parts 1 and 2).

[00105] Fig. 15 is a dataset analysis diagram and timeline, as described in greater detail in Example 4.

[00106] Fig. 16 is a population analysis flow chart, as described in greater detail in Example 4.

[00107] Fig. 17 is an illustration of the subpopulation used in the Cox Regression Analysis, as described in greater detail in Example 4.

[00108] Fig. 18 is an analysis diagram and timeline for the clinical trial as described in more detail in Example 5.

[00109] Fig. 19A is a graph showing the composite primary endpoint at the end of the treatment period for the clinical study described in more detail in Example 5.

[00110] Fig. 19B is a graph showing the achievement of serum bicarbonate thresholds at various time points for the clinical study described in more detail in Example 5.

[00111] Fig. 19C is a graph showing the change from baseline in serum bicarbonate over time at various time points for the clinical study described in more detail in Example 5.

[00112] Figs. 20A-20B are graphs showing that TRC101-treated subjects experienced a statistically significant improvement in quality of life, particularly, in physical function, based on results from Question #3 of the KDQOL-SF survey for the clinical study described in more detail in Example 5.

[00113] Fig. 21 is a copy of Question #3 of the KDQOL-SF survey for the clinical study described in Example 5. The score conversion is as follows: 1 (limited a lot) = 0; 2 (limited a little) = 50; 3 (not limited) = 100. Total score = sum of all 10, divided by 10.

[00114] Fig. 22A is a copy of the Single Chair Stand and Repeated Chair Stand protocols, including the scoring criteria (Fig. 22B), as described in more detail in Example 5.

[00115] Fig. 23 is table showing the analysis from baseline in total score in kidney disease and quality of life (Question 3) at week 12, as described in more detail in Example 5.

[00116] Fig. 24 is a table showing the analysis from baseline in time (seconds) of completing repeated chair stand at the end of week 12, as described in more detail in Example 5.

[00117] Fig. 25 is a diagram showing the overall design of the Retrospective Model, as described in more detail in Example 4.

[00118] Fig. 26 is a graph showing the time to first occurrence of DD40 endpoint, as described in more detail in Example 4.

[00119] Fig. 27 is a table showing the differences in outcome of TRC101 treated patients against placebo treated patients in the combined TRCA-301 and TRCA-301E 52 week study, as described in more detail in Example 6.

[00120] Fig. 28 is a graph showing SBC durability effect for TRC101-treated patients against placebo treated patients at the end of the TRCA-301 and TRCA-301E 52 week study, as described in more detail in Example 6.

[00121] Fig. 29 is a graph showing the mean change from baseline in serum bicarbonate level for TRC101 treated patients and placebo treated patients at various time points across the combined TRCA-301 and TRCA-301E 52 week study, as described in more detail in Example 6.

[00122] Fig. 30 is a graph showing the mean change from baseline in KDQOL-Physical Functioning Domain for TRC101 treated patients and placebo treated patients across the TRCA-301 and TRCA-301E 52 week study, as described in more detail in Example 6. The number N at each data point was: Verimer (N) 114, 109 and 113; and Placebo (N) 82, 76 and 78. The p values at each of 12 weeks, 40 weeks, and 52 weeks since randomization were $p = 0.0396$, $p = 0.0177$, and $p < 0.0001$, respectively.

[00123] Fig. 31 is a graph showing the mean change from baseline in time to perform the repeated chair stand test for TRC101 treated patients and placebo treated patients at various time points in the TRCA-301 and TRCA-301E 52 week study, as described in more detail in Example 6. The number N at each data point was: Verimer (N) 114, 106 and 112; and Placebo (N) 81, 76 and 77. The p values at each of 12 weeks, 40 weeks, and 52 weeks since randomization were $p = 0.0017$, $p < 0.0001$, and $p < 0.0001$, respectively.

[00124] Fig. 32 is a table showing the difference between active vs placebo for adverse effects occurring at ≥2% of the proportions of patients affected for TRC101-treated patients and placebo-treated patients in the TRCA-301 and TRCA-301E 52 week study, as described in more detail in Example 6.

[00125] Fig. 33 is a table showing the adverse events occurring at ≥5% of the study populations and the proportions of TRC101-treated patients and placebo-treated patients in the TRCA-301 and TRCA-301E 52 week study, as described in more detail in Example 6.

[00126] Fig. 34 is a table summarizing the number of withdrawals in both TRC101-treated patients and placebo-treated patients across the TRCA-301 and the TRCA-301E studies, as described in more detail in Example 6.

[00127] Fig. 35 is a table showing the incidences of death, dialysis, ≥50% eGFR decline and DD50 across the TRCA-301 and the TRCA-301E study for TRC101-treated patients and placebo-treated patients, without annualising the incidence rate.

[00128] Fig. 36 is a table showing the annualised incidence rate of death, death/dialysis and DD50 across the TRCA-301 and the TRCA-301E study for TRC101-treated patients and placebo-treated patients.

[00129] Fig. 37 is a plot showing the change in the individual items of the kidney disease and quality of life – physical functioning domain. Patients treated with TRC101 reported greatest improvement in tasks requiring lower body strength. Compared with placebo, TRC101 significantly improved the daily activities of climbing a flight of stairs ($p<0{\cdot}0001$); walking (one block [$p<0{\cdot}01$], several blocks [$p<0{\cdot}001$], and more than a mile [$p=0{\cdot}03$]); bending, kneeling, or stooping ($p=0{\cdot}01$); and lifting or carrying groceries ($p=0{\cdot}049$). Changes in the limitations related to vigorous activities such as participating in strenuous sports, moderate activities such as moving a table, climbing several flights of stairs, and bathing and dressing did not differ in the two treatment groups. The p values for select items were as follows: for item (c) $p = 0.0488$, for item (e) $p < 0.0001$, for item (f) $p = 0.0113$, for item (g) $p = 0.0001$, for item (h) $p = 0.0003$, for item (i) $p = 0.0020$. In each pair of bars, the bar to the left represents the placebo group, and the bar to the right represents the veverimer treated group.

[00130] Fig. 38A-38B is a plot showing that of the 217 patients randomised (124 to veverimer and 93 to placebo) in the TRCA-301 study, 196 (114 veverimer and 82 placebo) continued on their blinded randomised treatment assignment into the TRCA-301E study. The groups were well balanced with respect to demographics, common comorbidities, CKD etiology, common concomitant medication use, and baseline kidney function and electrolytes.

[00131] Fig. 39 is a table showing the adverse events experienced by patients.

[00132] Fig. 40A-40B is a table showing that the study drug dose was algorithmically titrated by the interactive response technology system in the range from 0-9 grams/day (or equivalent number of placebo packets) to a target bicarbonate level of 22-29 mmol/L based on the bicarbonate measurement at each visit.

[00133] Fig. 41 is a table showing the restricted concomitant medications throughout the TRCA-301 and TRCA-301E studies.

[00134] Fig. 42 is a table showing the baseline characteristics of patients randomized in the TRCA-301 study who did not enroll in the TRCA-301E study.

[00135] Fig. 43 is a table showing the outcome events in the combined TRCA-301 and TRCA-301E 52 week treatment period.

[00136] Fig. 44 is a diagram of patient flow through the combined TRCA-301 and TRCA-301E studies.

[00137] Fig. 45 is a Kaplan-Meier plot of time to first occurance of death, renal replacement therapy or ≥50% decline in eGFR across the TRCA-301 and TRCA-301E studies.

[00138] Fig. 46 is a box plot for serum potassium by treatment group across the TRCA-301 and TRCA-301E studies.

[00139] Fig. 47 is is a box plot for serum chloride by treatment group across the TRCA-301 and TRCA-301E studies.

[00140] Fig. 48 is a box plot for serum sodium by treatment group across the TRCA-301 and TRCA-301E studies.

[00141] Figure 49 is a schematic showing the design of the TRCA-301 and TRCA-301 studies.

[00142] Figure 50 is a further graph showing SBC durability effect for TRC101-treated patients against placebo treated patients at the end of the TRCA-301 and TRCA-301E 52 week study, as described in more detail in Example 6.

[00143] Figure 51 is a further graph showing the mean change from baseline in serum bicarbonate level for TRC101 treated patients and placebo treated patients at various time points across the combined TRCA-301 and TRCA-301E 52 week study, as described in more detail in Example 6.

[00144] Figure 52A-52B is a further table showing change from baseline in laboratory parameters and blood pressure after 52 weeks of treatment.

[00145] Figure 53 is a further copy of Question #3 of the KDQOL-SF survey for the clinical study described in Example 5.

DETAILED DESCRIPTION OF THE INVENTION

ABBREVIATIONS AND DEFINITIONS

[00146] The following definitions and methods are provided to better define the present invention and to guide those of ordinary skill in the art in the practice of the present invention. Unless otherwise noted, terms are to be understood according to conventional usage by those of ordinary skill in the relevant art.

[00147] The term "absorption capacity" as used herein in connection with a polymer and a swelling agent (or in the case of a mixture of swelling agents, the mixture of swelling agents) is the amount of the swelling agent (or such mixture) absorbed during a period of at least 16 hours at room temperature by a given amount of a dry polymer (*e.g.*, in the form of a dry bead) immersed in an excess amount of the swelling agent (or such mixture).

[00148] The term “acid neutralizing agent” as used herein takes its normal meaning in the art. Therefore an “acid neutralizing agent” may be a composition or compound or mixture of compounds. An “acid neutralizing agent” may also be absorbable or nonabsorbable. In one embodiment, the “acid neutralizing agent” is

absorbable. An "acid neutralizing agent" will react with a target species in use. For example, an "acid neutralizing agent" may react with a target species to raise pH, for example in an acidic environment. An "acid neutralizing agent" may react with a target species to reduce the rate of a decrease in pH, for example where the pH of the system is changing, for example in a patient whose acid load has increased. An "acid neutralizing agent" may also react with a target species to buffer against a change in pH, for example such that there is no change in pH but acid has been neutralised to prevent a decrease in pH. An "acid neutralizing agent" may react with acid to remove protons but is not required to raise the pH to neutral. An "acid neutralizing agent" may react with ingested acid to reduce acid load. An "acid neutralizing agent" may possess the capacity to react with clinically significant quantities of one or more target species: (i) protons, (ii) the conjugate base(s) of one or more strong acids (*e.g.*, bisulfate (HSO_4^-), (iii) the conjugate acid(s) of one or more bases (*e.g.*, hydrogen carbonate (HCO_3^-)) and/or (iii) one or more strong acids (*e.g.*, HCl and/or H_2SO_4).

[00149] The term "acrylamide" denotes a moiety having the structural formula H_2C=CH-C(O)NR-*, where * denotes the point of attachment of the moiety to the remainder of the molecule and R is hydrogen, hydrocarbyl, or substituted hydrocarbyl.

[00150] The term "acrylic" denotes a moiety having the structural formula H_2C=CH-C(O)O-*, where * denotes the point of attachment of the moiety to the remainder of the molecule.

[00151] The term "adult" refers to an individual over 18 years of age.

[00152] The term "alicyclic", "alicyclo" or "alicyclyl" means a saturated monocyclic group of 3 to 8 carbon atoms and includes cyclopentyl, cyclohexyl, cycloheptyl, and the like.

[00153] The term "aliphatic" denotes saturated and non-aromatic unsaturated hydrocarbyl moieties having, for example, one to about twenty carbon atoms or, in specific embodiments, one to about twelve carbon atoms, one to about ten carbon atoms, one to about eight carbon atoms, or even one to about four carbon atoms. The aliphatic groups include, for example, alkyl moieties such as

methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like, and alkenyl moieties of comparable chain length.

[00154] The term “alkanol” denotes an alkyl moiety that has been substituted with at least one hydroxyl group. In some embodiments, alkanol groups are “lower alkanol” groups comprising one to six carbon atoms, one of which is attached to an oxygen atom. In other embodiments, lower alkanol groups comprise one to three carbon atoms.

[00155] The term "alkenyl group" encompasses linear or branched carbon radicals having at least one carbon-carbon double bond. The term "alkenyl group" can encompass conjugated and non-conjugated carbon-carbon double bonds or combinations thereof. An alkenyl group, for example and without being limited thereto, can encompass two to about twenty carbon atoms or, in a particular embodiment, two to about twelve carbon atoms. In certain embodiments, alkenyl groups are "lower alkenyl" groups having two to about four carbon atoms. Examples of alkenyl groups include, but are not limited thereto, ethenyl, propenyl, allyl, vinyl, butenyl and 4-methylbutenyl. The terms "alkenyl group" and "lower alkenyl group", encompass groups having "cis" or "trans" orientations, or alternatively, "E" or "Z" orientations.

[00156] The term "alkyl group" as used, either alone or within other terms such as "haloalkyl group," “aminoalkyl group” and "alkylamino group", encompasses saturated linear or branched carbon radicals having, for example, one to about twenty carbon atoms or, in specific embodiments, one to about twelve carbon atoms. In other embodiments, alkyl groups are "lower alkyl" groups having one to about six carbon atoms. Examples of such groups include, but are not limited thereto, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like. In more specific embodiments, lower alkyl groups have one to four carbon atoms.

[00157] The term "alkylamino group" refers to amino groups directly attached to the remainder of the molecule via the nitrogen atom of the amino group and wherein the nitrogen atom of the alkylamino group is substituted by one or two alkyl groups. In some embodiments, alkylamino groups are "lower alkylamino" groups having one or two alkyl groups of one to six carbon atoms, attached to a

nitrogen atom. In other embodiments, lower alkylamino groups have one to three carbon atoms. Suitable "alkylamino" groups may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino, pentamethyleneamine and the like.

[00158] The term “allyl” denotes a moiety having the structural formula $H_2C=CH-CH_2-*$, where * denotes the point of attachment of the moiety to the remainder of the molecule and the point of attachment is to a heteroatom or an aromatic moiety.

[00159] The term “allylamine” denotes a moiety having the structural formula $H_2C=CH-CH_2N(X_8)(X_9)$, wherein X_8 and X_9 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl, or X_8 and X_9 taken together form a substituted or unsubstituted alicyclic, aryl, or heterocyclic moiety, each as defined in connection with such term, typically having from 3 to 8 atoms in the ring.

[00160] The term “amine” or "amino" as used alone or as part of another group, represents a group of formula $-N(X_8)(X_9)$, wherein X_8 and X_9 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl, heteroaryl, or heterocyclo, or X_8 and X_9 taken together form a substituted or unsubstituted alicyclic, aryl, or heterocyclic moiety, each as defined in connection with such term, typically having from 3 to 8 atoms in the ring.

[00161] The term "aminoalkyl group" encompasses linear or branched alkyl groups having one to about ten carbon atoms, any one of which may be substituted with one or more amino groups, directly attached to the remainder of the molecule via an atom other than a nitrogen atom of the amine group(s). In some embodiments, the aminoalkyl groups are "lower aminoalkyl" groups having one to six carbon atoms and one or more amino groups. Examples of such groups include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl.

[00162] The terms “anion exchange material” and “cation exchange material” take their normal meaning in the art. For example, the terms “anion exchange material” and “cation exchange material” refer to materials that exchange anions and cations, respectively. Anion and cation exchange materials are typically water-insoluble substances which can exchange some of their cations or anions, respectively, for similarly charged anions or cations contained in a medium with

which they are in contact. Anion exchange materials may contain positively charged groups, which are fixed to the backbone materials and allow passage of anions but reject cations. A non-exhaustive list of such positively charged groups includes: amino group, alkyl substituted phosphine, and alkyl substituted sulphides. A non-exhaustive list of cation or anion exchange materials includes: clays (e.g., bentonite, kaolinite, and illite), vermiculite, zeolites (e.g., analcite, chabazite, sodalite, and clinoptilolite), synthetic zeolites, polybasic acid salts, hydrous oxides, metal ferrocyanides, and heteropolyacids. Cation exchange materials can contain negatively charged groups fixed to the backbone material, which allow the passage of cations but reject anions. A non-exhaustive list of such negatively charged groups includes: sulphate, carboxylate, phosphate, and benzoate.

[00163] The term "aromatic group" or "aryl group" means an aromatic group having one or more rings wherein such rings may be attached together in a pendent manner or may be fused. In particular embodiments, an aromatic group is one, two or three rings. Monocyclic aromatic groups may contain 5 to 10 carbon atoms, typically 5 to 7 carbon atoms, and more typically 5 to 6 carbon atoms in the ring. Typical polycyclic aromatic groups have two or three rings. Polycyclic aromatic groups having two rings typically have 8 to 12 carbon atoms, preferably 8 to 10 carbon atoms in the rings. Examples of aromatic groups include, but are not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

[00164] The term “bead” is used to describe a crosslinked polymer that is substantially spherical in shape.

[00165] The term “bicarbonate equivalent” is used to describe an organic acid or anion that yields bicarbonate when metabolized. Citrate and succinate are exemplary bicarbonate equivalents.

[00166] The term "binds" as used herein in connection with a polymer and one or more ions, that is, a cation (e.g. “proton-binding” polymer) and an anion, is an "ion-binding" polymer and/or when it associates with the ion, generally though not necessarily in a non-covalent manner, with sufficient association strength that at least a portion of the ion remains bound under the in vitro or in vivo conditions in

which the polymer is used for sufficient time to effect a removal of the ion from solution or from the body.

[00167] The term “ceramic material” takes its normal meaning in the art. In certain embodiments, the term “ceramic material” refers to an inorganic, nonmetallic, solid material comprising metal, nonmetal or metalloid atoms primarily held in ionic and covalent bonds. A non-exhaustive list of examples of ceramic materials includes: barium titanate, bismuth strontium calcium copper oxide, boron oxide, earthenware, ferrite, lanthanum carbonate, lead zirconate, titanate, magnesium diboride, porcelain, sialon, silicon carbide, silicon nitride, titanium carbide, yttrium barium copper oxide, zinc oxide, zirconium dioxide, and partially stabilised zirconia. In certain embodiments, the term “clinically significant increase” as used herein in connection with a treatment refers to a treatment that improves or provides a worthwhile change in an individual from a dysfunctional state back to a relatively normal functioning state, or moves the measurement of that state in the direction of normal functioning, or at least a marked improvement to untreated. A number of methods can be used to calculate clinical significance. A non-exhaustive list of methods for calculating clinical significance includes: Jacobson-Truax, Gulliksen-Lord-Novick, Edwards-Nunnally, Hageman-Arrindell, and Hierarchical Linear Modeling (HLM).

[00168] The term “crosslink density” denotes the average number of connections of the amine containing repeat unit to the rest of the polymer. The number of connections can be 2, 3, 4 and higher. Repeat units in linear, non-crosslinked polymers are incorporated via 2 connections. To form an insoluble gel, the number of connections should be greater than 2. Low crosslinking density materials such as Sevelamer have on average about 2.1 connections between repeat units. More crosslinked systems such as bixalomer have on average about 4.6 connections between the amine-containing repeat units. “Crosslinking density” represents a semi-quantitative measure based on the ratios of the starting materials used. Limitations include the fact that it does not account for different crosslinking and polymerization methods. For example, small molecule amine systems require higher amounts of crosslinker as the crosslinker also serves as the monomer to form the polymer backbone whereas for radical polymerizations the polymer chain is formed independent from the crosslinking reaction. This can lead to inherently higher

crosslinking densities under this definition for the substitution polymerization/small molecule amines as compared to radical polymerization crosslinked materials.

[00169] The term "crosslinker" as used, either alone or within other terms, encompasses hydrocarbyl or substituted hydrocarbyl, linear or branched molecules capable of reacting with any of the described monomers, or the infinite polymer network, as described in Formula 1, more than one time. The reactive group in the crosslinker can include, but is not limited to alkyl halide, epoxide, phosgene, anhydride, carbamate, carbonate, isocyanate, thioisocyanate, esters, activated esters, carboxylic acids and derivatives, sulfonates and derivatives, acyl halides, aziridines, α,β-unsaturated carbonyls, ketones, aldehydes, pentafluoroaryl groups, vinyl, allyl, acrylate, methacrylate, acrylamide, methacrylamide, styrenic, acrylonitriles and combinations thereof. In one exemplary embodiment, the crosslinker's reactive group will include alkyl halide, epoxide, anhydrides, isocyanates, allyl, vinyl, acrylamide, and combinations thereof. In one such embodiment, the crosslinker's reactive group will be alkyl halide, epoxide, or allyl.

[00170] The term "diallylamine" denotes an amino moiety having two allyl groups.

[00171] The terms "dry bead" and "dry polymer" refer to beads or polymers that contain no more than 5% by weight of a non-polymer swelling agent or solvent. Often the swelling agent/solvent is water remaining at the end of a purification. This is generally removed by lyophilization or oven drying before storage or further crosslinking of a preformed amine polymer. The amount of swelling agent/solvent can be measured by heating (*e.g.*, heating to 100-200°C) and measuring the resulting change in weight. This is referred to a "loss on drying" or "LOD."

[00172] The term "estimated glomerular filtration rate" or eGFR refers to an estimate of the glomerular filtration rate and is estimated from the serum level of an endogenous filtration marker. Creatinine is a commonly used endogenous filtration marker in clinical practice and several equations have been proposed for estimating the glomerular filtration rate. As used herein, all eGFR values may be determined according to the CKD-EPI equation (Levey et al., A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med. 2009; 150:604-612):

$GFR = 41 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$ [if female] * 1.159 [if black]

wherein Scr is serum creatinine (mg/dL), 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 Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

[00173] The term “ethereal” denotes a moiety having an oxygen bound to two separate carbon atoms as depicted the structural formula *-H_xC-O-CH_x-*, where * denotes the point of attachment to the remainder of the moiety and x independently equals 0, 1, 2, or 3.

[00174] The term “gel” is used to describe a crosslinked polymer that has an irregular shape.

[00175] The term “glomerular filtration rate” or GFR is the volume of fluid filtered from the renal (kidney) glomerular capillaries into the Bowman's capsule per unit time. GFR cannot be measured directly; instead, it is measured indirectly (mGFR) as the clearance of an exogenous filtration marker (e.g., inulin, iothalamate, iohexol, etc.) or estimated (eGFR) using an endogenous filtration marker.

[00176] The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

[00177] The term "haloalkyl group" encompasses groups wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically encompassed are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups including perhaloalkyl. A monohaloalkyl group, for example, may have either an iodo, bromo, chloro or fluoro atom within the group. Dihalo and polyhaloalkyl groups may have two or more of the same halo atoms or a combination of different halo groups. "Lower haloalkyl group" encompasses groups having 1-6 carbon atoms. In some embodiments, lower haloalkyl groups have one to three carbon atoms. Examples of haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

[00178] The term “heteroaliphatic” describes a chain of 1 to 25 carbon atoms, typically 1 to 12 carbon atoms, more typically 1 to 10 carbon atoms, and most typically 1 to 8 carbon atoms, and in some embodiments 1 to 4 carbon atoms that can be saturated or unsaturated (but not aromatic), containing one or more heteroatoms, such as halogen, oxygen, nitrogen, sulfur, phosphorus, or boron. A heteroatom atom may be a part of a pendant (or side) group attached to a chain of atoms (*e.g.*, –CH(OH)- –CH(NH_2)- where the carbon atom is a member of a chain of atoms) or it may be one of the chain atoms (*e.g.*, -ROR- or -RNHR- where each R is aliphatic). Heteroaliphatic encompasses heteroalkyl and heterocyclo but does not encompass heteroaryl.

[00179] The term “heteroalkyl” describes a fully saturated heteroaliphatic moiety.

[00180] The term “heteroaryl” means a monocyclic or bicyclic aromatic radical of 5 to 10 ring atoms, unless otherwise stated, where one or more, (in one embodiment, one, two, or three), ring atoms are heteroatom selected from N, O, or S, the remaining ring atoms being carbon. Representative examples include, but are not limited to, pyrrolyl, thienyl, thiazolyl, imidazolyl, furanyl, indolyl, isoindolyl, oxazolyl, isoxazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, tetrazolyl, and the like. As defined herein, the terms “heteroaryl” and “aryl” are mutually exclusive. “Heteroarylene” means a divalent heteroaryl radical.

[00181] The term "heteroatom" means an atom other than carbon and hydrogen. Typically, but not exclusively, heteroatoms are selected from the group consisting of halogen, sulfur, phosphorous, nitrogen, boron and oxygen atoms. Groups containing more than one heteroatom may contain different heteroatoms.

[00182] The term “heterocyclo,” “heterocyclic,” or heterocyclyl” means a saturated or unsaturated group of 4 to 8 ring atoms in which one or two ring atoms are heteroatom such as N, O, B, P and $S(O)_n$, where n is an integer from 0 to 2, the remaining ring atoms being carbon. Additionally, one or two ring carbon atoms in the heterocyclyl ring can optionally be replaced by a -C(O)- group. More specifically the term heterocyclyl includes, but is not limited to, pyrrolidino, piperidino, homopiperidino, 2-oxopyrrolidinyl, 2-oxopiperidinyl, morpholino, piperazino,

tetrahydro-pyranyl, thiomorpholino, and the like. When the heterocyclyl ring is unsaturated it can contain one or two ring double bonds provided that the ring is not aromatic. When the heterocyclyl group contains at least one nitrogen atom, it is also referred to herein as heterocycloamino and is a subset of the heterocyclyl group.

[00183] The term "hydrocarbon group" or "hydrocarbyl group" means a chain of 1 to 25 carbon atoms, typically 1 to 12 carbon atoms, more typically 1 to 10 carbon atoms, and most typically 1 to 8 carbon atoms. Hydrocarbon groups may have a linear or branched chain structure. Typical hydrocarbon groups have one or two branches, typically one branch. Typically, hydrocarbon groups are saturated. Unsaturated hydrocarbon groups may have one or more double bonds, one or more triple bonds, or combinations thereof. Typical unsaturated hydrocarbon groups have one or two double bonds or one triple bond; more typically unsaturated hydrocarbon groups have one double bond.

[00184] “Initiator” is a term used to describe a reagent that initiates a polymerization.

[00185] The term “measured glomerular filtration rate” or “mGFR” refers to a measurement of the glomerular filtration rate using any chemical (e.g., inulin, iothalamate, iohexol, etc.) that has a steady level in the blood, and is freely filtered but neither reabsorbed nor secreted by the kidneys according to standard technique.

[00186] The term “Michael acceptor” takes its normal meaning in the art. In certain embodiments the term “Michael acceptor” refers to activated olefins, such as α,β-unsaturated carbonyl compounds. A Michael acceptor can be a conjugated system with an electron withdrawing group, such as cyano, keto or ester. A non-exhaustive list of examples of Michael acceptors includes: vinyl ketones, alkyl acrylates, acrylo nitrile, and fumarates.

[00187] The term “molecular weight per nitrogen” or “MW/N” represents the calculated molecular weight in the polymer per nitrogen atom. It represents the average molecular weight to present one amine function within the crosslinked polymer. It is calculated by dividing the mass of a polymer sample by the moles of nitrogen present in the sample. “MW/N” is the inverse of theoretical capacity, and the calculations are based upon the feed ratio, assuming full reaction of crosslinker

and monomer. The lower the molecular weight per nitrogen the higher the theoretical capacity of the crosslinked polymer.

[00188] The term "neutralizing capacity" as used herein takes its normal meaning in the art. Therefore, if an acid neutralizing agent has a neutralizing capacity it is capable of reacting with an acid. For example, an acid neutralizing agent with a neutralizing capacity may be used to raise pH, for example in an acidic environment. An acid neutralizing agent with a neutralizing capacity may also be used to reduce the rate of a decrease in pH, for example where the pH of the system is changing, for example in a patient whose acid load has increased. An acid neutralizing agent with a neutralizing capacity may also be used to buffer against a change in pH, for example such that there is no change in pH but acid has been neutralised to prevent a decrease in pH.

[00189] The "neutralizing capacity" of an acid neutralizing agent may be theoretical. For example, the theoretical maximum neutralizing capacity for an acid neutralizing agent may be calculated as follows:

$$Theoretical\ maximum\ neutralizing\ capacity = \frac{1000}{Molecular\ weight\ of\ basic\ agent} \times magnitude\ of\ total\ negative\ charge\ of\ basic\ component\ of\ basic\ agent$$

[00190] For example, the molecular weight of the acid neutralizing agent $CaCO_3$ is 100 g/mol. The basic component of $CaCO_3$ is CO_3^{2-}, which has a negative charge of 2-. The magnitude of the total negative charge of the basic component of $CaCO_3$ is therefore 2. The theoretical maximum neutralizing capacity of $CaCO_3$ can therefore be calculated as follows: $\frac{1000}{100} \times 2$ = 20.0 mEq of HCl per gram of $CaCO_3$.

[00191] The "neutralizing capacity" of an acid neutralizing agent may also be determined by experimentation. There are a number of standard experiments in the art that can be used to determine the "neutralizing capacity" of an acid neutralizing agent. For example, the "neutralizing capacity" of an acid neutralizing agent may be determined by acid-base titration.

[00192] The term "nonabsorbable" as used herein takes its normal meaning in the art. Therefore, if something is nonabsorbable it is not absorbed during its passage through the human GI tract. This could be measured by any appropriate means. One option known to the skilled person would be to examine faeces to see if

the nonabsorbable material is recovered after passing through the GI tract. As a practical matter, the amount of a nonabsorbable material recovered in this scenario will never be 100% of the material administered. For example, about 90 – 99% of the material might be recovered from the faeces. Another option known to the skilled person would be to look for the presence of the material in the lymph, blood, interstitial fluid, secretions from various organs (e.g., pancreas, liver, gut, etc.) or in the body of organs (e.g., liver, kidney, lungs, etc.) as oral administration of a nonabsorbable material would not result in an increase in the amount of that material in these matrices and tissues. Nonabsorbable compositions may be particulate compositions that are essentially insoluble in the human GI tract and have a particle size that is large enough to avoid passive or active absorption through the human GI tract. As an example, nonabsorbable compositions is meant to imply that the substance does not enter the lymph, blood, interstitial fluids or organs through the main entry points of the human GI tract, namely by paracellular entry between gut epithelial cells, by endocytic uptake through gut epithelial cells, or through entry via M cells comprising the gut epithelial antigen sampling and immune surveillance system (Jung, 2000), either through active or passive transport processes. There is a known size limit for a particulate to be absorbed in the human GI tract (Jung et al., European Journal of Pharmaceutics and Biopharmaceutics 50 (2000) 147-160; Jani et al., International Journal of Pharmaceutics, 84 (1992) 245-252; and Jani et al., J. Pharm. Pharmacol. 1989, 41:809-812), so the skilled person would know that materials that, when in the GI tract, have a size of at least 1 micrometers would be nonabsorbable.

[00193] “Optional” or “optionally” means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, “heterocyclyl group optionally substituted with an alkyl group” means that the alkyl may but need not be present, and the description includes embodiments in which the heterocyclyl group is substituted with an alkyl group and embodiments in which the heterocyclyl group is not substituted with alkyl.

[00194] “Particle size” is measured by wet laser diffraction using Mie theory. Particles are dispersed in an appropriate solvent, such as water or methanol, and added to the sample chamber to achieve red channel obscuration of 10-20%.

Sonication may be performed, and a dispersing agent, such as a surfactant (e.g. Tween-80), may be added in order to disrupt weak particle-particle interactions. The refractive index setting of the particles used for size distribution calculation is selected to minimize artifacts in the results and the R parameter value, determined by the laser diffraction software. The D(0.1), D(0.5), and D(0.9) values characterizing the particle size distribution by volume-basis are recorded.

[00195] "Pharmaceutically acceptable" as used in connection with a carrier, diluent or excipient means a carrier, diluent or an excipient, respectively, that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable for veterinary use and/or human pharmaceutical use.

[00196] The term "physical function" as used herein in connection with a patient afflicted with chronic kidney disease and an acid-base disorder may be assessed using (i) the Kidney Disease and Quality of Life (KDQOL) Short Form-36, Question 3 (Physical Functioning Domain) as illustrated in Fig. 22A & 22B and Example 5, or (iii) both the KDQOL Short Form-36 Question 3 and the standardized repeated chair stand test (i.e., "i" and "ii" of this paragraph).

[00197] The term "post polymerization crosslinking" is a term that describes a reaction to an already formed bead or gel, where more crosslinking is introduced to the already formed bead or gel to create a bead or gel that has an increased amount of crosslinking.

[00198] The term "post polymerization modification" is a term that describes a modification to an already formed bead or gel, where a reaction or a treatment introduces an additional functionality. This functionality can be linked either covalently or non-covalently to the already formed bead.

[00199] The term "quaternized amine assay" ("QAA") describes a method to estimate the amount of quaternary amines present in a given crosslinked polymer sample. This assay measures chloride binding of a crosslinked polymer at a pH of 11.5. At this pH, primary, secondary and tertiary amines are not substantially protonated and do not substantially contribute to chloride binding. Therefore, any binding observed under these conditions can be attributed to the presence of permanently charged quaternary amines. The test solution used for QAA assay is

100 mM sodium chloride at a pH of 11.5. The concentration of chloride ions is similar to that in the SGF assay which is used to assess total binding capacity of crosslinked polymers. Quaternary amine content as a percentage of total amines present is calculated as follows:

$$\% \text{ Quaternary amines} = \frac{\text{Chloride bound (mmol/g) in QAA}}{\text{Chloride bound (mmol/g) in SGF}} \times 100$$

To perform the QAA assay, the free-amine polymer being tested is prepared at a concentration of 2.5 mg/ml (e.g. 25 mg dry mas) in 10 mL of QAA buffer. The mixture is incubated at 37 °C for ~16 hours with agitation on a rotisserie mixer. After incubation and mixing, 600 microliters of supernatant is removed and filtered using a 800 microliter, 0.45 micrometer pore size, 96-well poly propylene filter plate. With the samples arrayed in the filter plate and the collection plate fitted on the bottom, the unit is centrifuged at 1000Xg for 1 minute to filter the samples. After filtration into the collection plate, the respective filtrates are diluted appropriately before measuring for chloride content. The IC method (e.g. ICS-2100 Ion Chromatography, Thermo Fisher Scientific) used for the analysis of chloride content in the filtrates consists of a 15 mM KOH mobile phase, an injection volume of 5 microliters, with a run time of three minutes, a washing/rinse volume of 1000 microliters, and flow rate of 1.25 mL /min. To determine the chloride bound to the polymer, the following calculation is completed:

$$\text{Binding capacity expressed as mmol chloride/g dry polymer} = \frac{(\text{Cl start} - \text{Cl eq})}{2.5}$$

where Cl start corresponds to the starting concentration of chloride in the QAA buffer, Cl eq corresponds to the equilibrium value of chloride in the measured filtrates after exposure to the test polymer, and 2.5 is the polymer concentration in mg/ml.

[00200] The terms “short chain carboxylic acid” or “short chain fatty acid” take their normal meaning in the art. In certain embodiments, the terms “short chain carboxylic acid” or “short chain fatty acid” refer to carboxylic acids having a chain length of 0, 1, 2, 3, 4, 5 or 6 carbon atoms long. A non-exhaustive list of examples of short chain carboxylic acids includes: formic acid, acetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, and lactic acid.

[00201] "Simulated Gastric Fluid" or "SGF" Assay describes a test to determine total chloride binding capacity for a test polymer using a defined buffer that simulates the contents of gastric fluid as follows: Simulated gastric fluid (SGF) consists of 35 mM NaCl, 63 mM HCl, pH 1.2. To perform the assay, the free-amine polymer being tested is prepared at a concentration of 2.5 mg/ml (25 mg dry mass) in 10 mL of SGF buffer. The mixture is incubated at 37 °C overnight for ~12-16 hours with agitation on a rotisserie mixer. Unless another time period is otherwise stated, SGF binding data or binding capacities recited herein are determined in a time period of this duration. After incubation and mixing, the tubes containing the polymer are centrifuged for 2 minutes at 500-1000Xg to pellet the test samples. Approximately 750 microliters of supernatant are removed and filtered using an appropriate filter, for example a 0.45 micrometer pore-size syringe filter or an 800 microliter, 1 micrometer pore-size, 96-well, glass filter plate that has been fitted over a 96-well 2 mL collection plate. With the latter arrangement, multiple samples tested in SGF buffer can be prepared for analysis, including the standard controls of free amine Sevelamer, free amine bixalomer and a control tube containing blank buffer that is processed through all of the assay steps. With the samples arrayed in the filter plate and the collection plate fitted on the bottom, the unit is centrifuged at 1000Xg for 1 minute to filter the samples. In cases of small sample sets, a syringe filter may be used in lieu of the filter plate, to retrieve ~2-4 mL of filtrate into a 15 mL container. After filtration, the respective filtrates are diluted 4X with water and the chloride content of the filtrate is measured via ion chromatography (IC). The IC method (e.g. Dionex ICS-2100, Thermo Scientific) consists of an AS11 column and a 15 mM KOH mobile phase, an injection volume of 5 microliters, with a run time of 3 minutes, a washing/rinse volume of 1000 microliters, and flow rate of 1.25 mL /min. To determine the chloride bound to the polymer, the following calculation is completed:

$$\frac{(\text{Cl start} - \text{Cl eq}) \times 4}{2.5}.$$

Binding capacity expressed as mmol chloride/g polymer: where Cl start corresponds to the starting concentration of chloride in the SGF buffer, Cl eq corresponds to the equilibrium value of chloride in the diluted measured filtrates after exposure to the test polymer, 4 is the dilution factor and 2.5 is the polymer concentration in mg/ml.

[00202] "Simulated Small Intestine Inorganic Buffer" or "SIB" is a test to determine the chloride and phosphate binding capacity of free amine test polymers in a selective specific interfering buffer assay (SIB). The chloride and phosphate binding capacity of free amine test polymers, along with the chloride and phosphate binding capacity of free amine Sevelamer and bixalomer control polymers, was determined using the selective specific interfering buffer assay (SIB) as follows: The buffer used for the SIB assay comprises 36 mM NaCl, 20 mM NaH_2PO_4, 50 mM 2-(N-morpholino)ethanesulfonic acid (MES) buffered to pH 5.5. The SIB buffer contains concentrations of chloride, phosphate and pH that are present in the human duodenum and upper gastrointestinal tract (Stevens T, Conwell DL, Zuccaro G, Van Lente F, Khandwala F, Purich E, et al. Electrolyte composition of endoscopically collected duodenal drainage fluid after synthetic porcine secretin stimulation in healthy subjects. Gastrointestinal endoscopy. 2004;60(3):351-5, Fordtran J, Locklear T. Ionic constituents and osmolality of gastric and small-intestinal fluids after eating. Digest Dis Sci. 1966;11(7):503-21) and is an effective measure of the selectivity of chloride binding compared to phosphate binding by a polymer. To perform the assay, the free amine polymer being tested is prepared at a concentration of 2.5 mg/ml (25 mg dry mass) in 10 mL of SIB buffer. The mixture is incubated at 37 °C for 1 hour with agitation on a rotisserie mixer. Unless another time period is otherwise stated, SIB binding data or binding capacities recited herein are determined in a time period of this duration. After incubation and mixing, the tubes containing the polymer are centrifuged for 2 minutes at 1000Xg to pellet the test samples. 750 microliter of supernatant is removed and filtered using an 800 microliter, 1 micrometer pore-size, 96-well, glass filter plate that has been fitted over a 96-well 2 mL collection plate; with this arrangement multiple samples tested in SIB buffer can be prepared for analysis, including the standard controls of free amine Sevelamer, free amine bixalomer and a control tube containing blank buffer that is processed through all of the assay steps. With the samples arrayed in the filter plate and the collection plate fitted on the bottom, the unit is centrifuged at 1000Xg for 1 minute to filter the samples. In cases of small sample sets, a syringe filter (0.45 micrometer) may be used in lieu of the filter plate, to retrieve ~2-4 mL of filtrate into a 15 mL vial. After filtration into the collection plate, the respective filtrates are diluted before measuring for chloride or phosphate content. For the measurement of chloride and phosphate, the filtrates under analysis are diluted 4X with water. The

chloride and phosphate content of the filtrate is measured via ion chromatography (IC). The IC method (e.g. Dionex ICS-2100, Thermo Scientific) consists of an AS24A column, a 45 mM KOH mobile phase, an injection volume of 5 microliters, with a run time of about 10 minutes, a washing/rinse volume of 1000 microliter, and flow rate of 0.3 mL/min. To determine the chloride bound to the polymer, the following calculation is completed:

$$\text{Binding capacity expressed as mmol chloride/g polymer} = \frac{(Cl_{start} - Cl_{final}) \times 4}{2.5}$$

where Cl_{start} corresponds to the starting concentration of chloride in the SIB buffer, Cl_{final} corresponds to the final value of chloride in the measured diluted filtrates after exposure to the test polymer, 4 is the dilution factor and 2.5 is the polymer concentration in mg/ml. To determine the phosphate bound to the polymer, the following calculation is completed:

$$\text{Binding capacity expressed as mmol phosphate/g polymer} = \frac{(P_{start} - P_{final}) \times 4}{2.5}$$

where P_{start} corresponds to the starting concentration of phosphate in the SIB buffer, P_{final} corresponds to the final value of phosphate in the measured diluted filtrates after exposure to the test polymer, 4 is the dilution factor and 2.5 is the polymer concentration in mg/ml.

[00203] In certain embodiments, the term “statistically significant” refers to the likelihood that a relationship between two or more variables is caused by something other than random chance. More precisely, the significance level, α, defined for a study is the probability of the study rejecting the null hypothesis, given that it were true, and the p-value, p, of a result is the probability of obtaining a result at least as extreme, given that the null hypothesis were true. The result is statistically significant, by the standards of the study, when $p < \alpha$. The significance level for a study is chosen before data collection, and typically set to 5%.

[00204] The term "substituted hydrocarbyl," "substituted alkyl," "substituted alkenyl," "substituted aryl," "substituted heterocyclo," or "substituted heteroaryl" as used herein denotes hydrocarbyl, alkyl, alkenyl, aryl, heterocyclo, or heteroaryl moieties which are substituted with at least one atom other than carbon and

hydrogen, including moieties in which a carbon chain atom is substituted with a hetero atom such as nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or a halogen atom. These substituents include halogen, heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, keto, acyl, acyloxy, nitro, amino, amido, nitro, cyano, thiol, ketals, acetals, esters and ethers.

[00205] "Swelling Ratio" or simply "Swelling" describes the amount of water absorbed by a given amount of polymer divided by the weight of the polymer aliquot. The Swelling Ratio is expressed as: swelling = (g swollen polymer – g dry polymer)/g dry polymer. The method used to determine the Swelling Ratio for any given polymer comprised the following:

a. 50-100 mg of dry (less than 5 wt % water content) polymer is placed into an 11 mL sealable test tube (with screw cap) of known weight (weight of tube = Weight A).

b. Deionized water (10mL) is added to the tube containing the polymer. The tube is sealed and tumbled for 16 hours (overnight) at room temperature. After incubation, the tube is centrifuged at 3000xg for 3 minutes and the supernatant is carefully removed by vacuum suction. For polymers that form a very loose sediment, another step of centrifugation is performed.

c. After step (b), the weight of swollen polymer plus tube (Weight B) is recorded.

d. Freeze at –40 ºC for 30 minutes. Lyophilize for 48 h. Weigh dried polymer and test tube (recorded as Weight C).

e. Calculate g water absorbed per g of polymer, defined as: [(Weight B-Weight A)-(Weight C - Weight A)]/(Weight C - Weight A).

[00206] A "target ion" is an ion to which the polymer binds, and usually refers to the major ions bound by the polymer, or the ions whose binding to the polymer is thought to produce the therapeutic effect of the polymer (*e.g.*, proton and chloride binding which leads to net removal of HCl).

[00207] The term "theoretical capacity" represents the calculated, expected binding of hydrochloric acid in an "SGF" assay, expressed in mmol/g. The theoretical capacity is based on the assumption that 100 % of the amines from the monomer(s) and crosslinker(s) are incorporated in the crosslinked polymer based on their respective feed ratios. Theoretical capacity is thus equal to the concentration of

amine functionalities in the polymer (mmol/g). The theoretical capacity assumes that each amine is available to bind the respective anions and cations and is not adjusted for the type of amine formed (e.g. it does not subtract capacity of quaternary amines that are not available to bind proton).

[00208] "Therapeutically effective amount" means the amount of a proton-binding crosslinked polymer that, when administered to a patient for treating a disease, is sufficient to effect such treatment for the disease. The amount constituting a "therapeutically effective amount" will vary depending on the polymer, the severity of the disease and the age, weight, etc., of the mammal to be treated.

[00209] "Treating" or "treatment" of a disease includes (i) inhibiting the disease, *i.e.*, arresting or reducing the development of the disease or its clinical symptoms; or (ii) relieving the disease, *i.e.*, causing regression of the disease or its clinical symptoms. Inhibiting the disease, for example, would include prophylaxis.

[00210] The term "triallylamine" denotes an amino moiety having three allyl groups.

[00211] The term "vinyl" denotes a moiety having the structural formula $R_xH_yC=CH-*$, where * denotes the point of attachment of the moiety to the remainder of the molecule wherein the point of attachment is a heteroatom or aryl, X and Y are independently 0, 1 or 2, such that X+Y=2, and R is hydrocarbyl or substituted hydrocarbyl.

[00212] The term "weight percent crosslinker" represents the calculated percentage, by mass, of a polymer sample that is derived from the crosslinker. Weight percent crosslinker is calculated using the feed ratio of the polymerization, and assumes full conversion of the monomer and crosslinker(s). The mass attributed to the crosslinker is equal to the expected increase of molecular weight in the infinite polymer network after reaction (*e.g.*, 1,3-dichloropropane is 113 amu, but only 42 amu are added to a polymer network after crosslinking with DCP because the chlorine atoms, as leaving groups, are not incorporated into the polymer network).

[00213] When introducing elements of the present invention or the preferred embodiments(s) thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and

"having" are intended to be inclusive and not exclusive (*i.e.*, there may be other elements in addition to the recited elements).

EMBODIMENTS

[00214] In accordance with the present disclosure, acid-base disorders may be treated using pharmaceutical compositions comprising a nonabsorbable composition having the capacity to remove clinically significant quantities of protons, the conjugate base of one or more strong acids, and/or one or more strong acids. An individual afflicted with a an acute or chronic acid/base disorder characterized by a baseline serum bicarbonate value of less than 22 mEq/l may thus be treated by oral administration of a pharmaceutical composition comprising the nonabsorbable composition which then transits the individual's digestive system, binds a target species (protons, one or more conjugate base(s) of a strong acid and/or one or more strong acid(s)) as it transits the digestive system, and removes the bound target species by normal biological function (defecation).

[00215] In general, the individual afflicted with an acute or chronic acid/base disorder may be at any stage of chronic kidney disease. For example, in one embodiment the afflicted individual has not yet reached end stage renal disease ("ESRD") sometimes also referred to as end stage chronic kidney disease and is not yet on dialysis (*i.e.*, the individual has a mGFR (or eGFR) of at least 15 mL/min/1.73 m^2). In some embodiments, the afflicted individual will be Stage 3B CKD (*i.e.*, the individual has a mGFR (or eGFR) in the range of 30-44 mL/min/1.73 m^2 for at least three months). In some embodiments, the afflicted individual will be Stage 3A CKD (*i.e.*, the individual has a mGFR (or eGFR) in the range of 45-59 mL/min/1.73 m^2 for at least three months). Thus, for example, in some embodiments the afflicted individual has a mGFR or an eGFR of less than 60 mL/min/1.73 m^2 for at least three months. By way of further example, in some embodiments the afflicted individual has a mGFR or an eGFR of less than 45 mL/min/1.73 m^2 for at least three months. By way of further example, in some embodiments the afflicted individual has a mGFR or an eGFR of less than 30 mL/min/1.73 m^2 for at least three months. By way of further example, in some embodiments the afflicted individual has a mGFR or an eGFR of 15-30, 15-45, 15-60, 30-45 or even 30-60 mL/min/1.73 m^2 for at least three months.

[00216] The baseline serum bicarbonate value may be the serum bicarbonate concentration determined at a single time point or may be the mean or median value of two or more serum bicarbonate concentrations determined at two or more time-points. For example, in one embodiment the baseline serum bicarbonate value may be the value of the serum bicarbonate concentration determined at a single time point and the baseline serum bicarbonate value is used as a basis to determine an acute acidic condition requiring immediate treatment. In another embodiment, the baseline serum bicarbonate treatment value is the mean value of the serum bicarbonate concentration for serum samples drawn at different time points (*e.g.*, different days). By way of further example, in one such embodiment the baseline serum bicarbonate treatment value is the mean value of the serum bicarbonate concentration for serum samples drawn on different days (*e.g.*, at least 2, 3, 4, 5 or more days, that may be consecutive or separated by one or more days or even weeks). By way of further example, in one such embodiment the baseline serum bicarbonate treatment value is the mean value of the serum bicarbonate concentration for serum samples drawn on two consecutive days preceding the initiation of treatment.

[00217] In one embodiment, the acid-base disorder being treated is characterized by a baseline serum bicarbonate value of less than 21 mEq/l. For example, in one such embodiment the acid-base disorder being treated is characterized by a baseline serum bicarbonate value of less than 20 mEq/l. By way of further example, in one such embodiment the acid-base disorder being treated is characterized by a baseline serum bicarbonate value of less than 19 mEq/l. By way of further example, in one such embodiment the acid-base disorder being treated is characterized by a baseline serum bicarbonate value of less than 18 mEq/l. By way of further example, in one such embodiment the acid-base disorder being treated is characterized by a baseline serum bicarbonate value of less than 17 mEq/l. By way of further example, in one such embodiment the acid-base disorder being treated is characterized by a baseline serum bicarbonate value of less than 16 mEq/l. By way of further example, in one such embodiment the acid-base disorder being treated is characterized by a baseline serum bicarbonate value of less than 15 mEq/l. By way of further example, in one such embodiment the acid-base disorder being treated is characterized by a baseline serum bicarbonate value of less than 14 mEq/l. By way

of further example, in one such embodiment the acid-base disorder being treated is characterized by a baseline serum bicarbonate value of less than 13 mEq/l. By way of further example, in one such embodiment the acid-base disorder being treated is characterized by a baseline serum bicarbonate value of less than 12 mEq/l. By way of further example, in one such embodiment the acid-base disorder being treated is characterized by a baseline serum bicarbonate value of less than 11 mEq/l. By way of further example, in one such embodiment the acid-base disorder being treated is characterized by a baseline serum bicarbonate value of less than 10 mEq/l. By way of further example, in one such embodiment the acid-base disorder being treated is characterized by a baseline serum bicarbonate value of less than 9 mEq/l.

[00218] In general, however, the acid-base disorder being treated is characterized by a baseline serum bicarbonate value of at least 9 mEq/l. For example, in one such embodiment, the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 10 mEq/l. By way of further example, in one such embodiment, the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 11 mEq/l. By way of further example, in one such embodiment, the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 12 mEq/l. By way of further example, in one such embodiment, the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 13 mEq/l. By way of further example, in one such embodiment, the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 14 mEq/l. By way of further example, in one such embodiment, the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 15 mEq/l. By way of further example, in one such embodiment, the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 16 mEq/l. By way of further example, in one such embodiment, the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 17 mEq/l. By way of further example, in one such embodiment, the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 18 mEq/l. By way of further example, in one such embodiment, the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 19 mEq/l. By way of further example, in one such embodiment, the acid-base disorder is characterized by a baseline serum

bicarbonate value of at least 20 mEq/l. By way of further example, in one such embodiment, the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 21 mEq/l.

[00219] In certain embodiments, the acid-base disorder being treated is characterized by a baseline serum bicarbonate value in the range of 9 to 21 mEq/l. For example, in one such embodiment the acid-base disorder is characterized by a baseline serum bicarbonate value in the range of 12 to 20 mEq/l. By way of further example, in one such embodiment the acid-base disorder is characterized by a baseline serum bicarbonate value in the range of 12 to 19 mEq/l. By way of further example, in one such embodiment the acid-base disorder is characterized by a baseline serum bicarbonate value in the range of 12 to 18 mEq/l. By way of further example, in one such embodiment the acid-base disorder is characterized by a baseline serum bicarbonate value in the range of 12 to 17 mEq/l. By way of further example, in one such embodiment the acid-base disorder is characterized by a baseline serum bicarbonate value in the range of 12 to 16 mEq/l. By way of further example, in one such embodiment the acid-base disorder is characterized by a baseline serum bicarbonate value in the range of 9 to 11 mEq/l. By way of further example, in one such embodiment the acid-base disorder is characterized by a baseline serum bicarbonate value in the range of 12-14. By way of further example, in one such embodiment the acid-base disorder is characterized by a baseline serum bicarbonate value in the range of 15-17. By way of further example, in one such embodiment the acid-base disorder is characterized by a baseline serum bicarbonate value in the range of 18-21.

[00220] In certain embodiments, oral administration of a pharmaceutical composition containing a nonabsorbable composition increases the individual's serum bicarbonate value from baseline to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 1 mEq/l. For example, in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 1.5 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 2 mEq/l. By way of further example in one such embodiment the

treatment the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 2.5 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least at least 3 mEq/l. By way of further example in one such embodiment the treatment increases the baseline serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 3.5 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 4 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 5 mEq/l but does not exceed 29 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 5 mEq/l but does not exceed 28 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 5 mEq/l but does not exceed 27 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 5 mEq/l but does not exceed 26 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 6 mEq/l but does not exceed 29 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 6 mEq/l but does not exceed 28 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 6 mEq/l but does not exceed 27 mEq/l. By way of further example in one such embodiment the treatment increases the

individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 6 mEq/l but does not exceed 26 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 7 mEq/l but does not exceed 29 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 7 mEq/l but does not exceed 28 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 7 mEq/l but does not exceed 27 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 7 mEq/l but does not exceed 26 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 8 mEq/l but does not exceed 29 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 8 mEq/l but does not exceed 28 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 8 mEq/l but does not exceed 27 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 8 mEq/l but does not exceed 26 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 9 mEq/l but does not exceed 29 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 9 mEq/l but does not

exceed 28 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 9 mEq/l but does not exceed 27 mEq/l. By way of further example in one such embodiment the treatment increases the individual's serum bicarbonate value to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 9 mEq/l but does not exceed 26 mEq/l. In each of the foregoing exemplary embodiments recited in this paragraph, the treatment enables the increased serum bicarbonate value to be sustained over a prolonged period of at least one week, at least one month, at least two months, at least three months, at least six months, or even at least one year.

[00221] In certain embodiments, the treatment increases the individual's serum bicarbonate value from a baseline serum bicarbonate value in the range of 12 to 21 mEq/l to an increased value in the range of 24 mEq/l to 29 mEq/l. For example, in one such embodiment the treatment increases the individual's serum bicarbonate value from a baseline serum bicarbonate value in the range of 12 to 17 mEq/l to an increased value in the range of 24 mEq/l to 29 mEq/l. By way of further example, in one such embodiment the treatment increases the individual's serum bicarbonate value from a baseline serum bicarbonate value in the range of 12 to 14 mEq/l to an increased value in the range of 24 mEq/l to 29 mEq/l. By way of further example, in one such embodiment the treatment increases the individual's serum bicarbonate value from a baseline serum bicarbonate value in the range of 15 to 17 mEq/l to an increased value in the range of 24 mEq/l to 29 mEq/l. By way of further example, in one such embodiment the treatment increases the individual's serum bicarbonate value from a baseline serum bicarbonate value in the range of 18 to 21 mEq/l to an increased value in the range of 24 mEq/l to 29 mEq/l. In each of the foregoing embodiments recited in this paragraph, the treatment enables the increased serum bicarbonate value to be sustained over a prolonged period of at least one week, at least one month, at least two months, at least three months, at least six months, or even at least one year.

[00222] In certain embodiments, the treatment achieves a clinically significant increase is achieved within a treatment period of less than one month. For example, in one such embodiment, the treatment achieves a clinically significant

increase within a treatment period of 25 days. By way of further example, in one such embodiment the treatment achieves the clinically significant increase is achieved within a treatment period of 3 weeks. By way of further example, in one such embodiment the treatment achieves the clinically significant increase is achieved within a treatment period of 15 days. By way of further example, in one such embodiment the treatment achieves the clinically significant increase is achieved within a treatment period of 2 weeks. By way of further example, in one such embodiment the treatment achieves the clinically significant increase is achieved within a treatment period of 10 days. By way of further example, in one such embodiment the treatment achieves the clinically significant increase is achieved within a treatment period of 1 week. By way of further example, in one such embodiment the treatment achieves the clinically significant increase is achieved within a treatment period of 6 days. By way of further example, in one such embodiment the treatment achieves the clinically significant increase is achieved within a treatment period of 5 days. By way of further example, in one such embodiment the treatment achieves the clinically significant increase is achieved within a treatment period of 4 days. By way of further example, in one such embodiment the treatment achieves the clinically significant increase is achieved within a treatment period of 3 days. By way of further example, in one such embodiment the treatment achieves the clinically significant increase is achieved within a treatment period of 2 days. By way of further example, in one such embodiment the treatment achieves the clinically significant increase is achieved within a treatment period of 1 day. By way of further example, in one such embodiment the treatment achieves the clinically significant increase is achieved within a treatment period of 12 hours.

[00223] In certain embodiments, the treatment achieves a clinically significant increase without any change in the individual's diet or dietary habits relative to the period immediately preceding the initiation of treatment. For example, in one such embodiment the clinically significant increase is achieved independent of the individual's diet or dietary habits.

[00224] In certain embodiments, the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 1 month of the cessation of treatment. For example, in one such embodiment the individual's serum bicarbonate

value returns to the baseline value ± 2.5 mEq/l within 3 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 2 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 10 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 9 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 8 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 7 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 6 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 5 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 4 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 3 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 2 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 1 day of the cessation of treatment.

[00225] In certain embodiments, the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 1 month of the cessation of treatment. For example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 3 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 2 weeks of the cessation of treatment. By way of further example, in one such embodiment the

individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 10 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 9 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 8 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 7 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 6 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 5 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 4 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 3 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 2 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 1 day of the cessation of treatment.

[00226] In certain embodiments, the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 1 month of the cessation of treatment. For example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 3 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 2 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 10 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 9 days of the cessation of treatment. By way of further example, in

one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 8 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 7 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 6 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 5 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 4 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 3 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 2 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 1 day of the cessation of treatment.

[00227] In certain embodiments, the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 1 month of the cessation of treatment. For example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 3 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 2 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 10 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 9 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 8 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 7 days of the cessation of treatment.

By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 6 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 5 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 4 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 3 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 2 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 1 day of the cessation of treatment.

[00228] In certain embodiments, upon the cessation of treatment the individual's serum bicarbonate value decreases by at least 1 mEq/l within 1 month of the cessation of treatment. For example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1 mEq/l within 3 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1 mEq/l within 2 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1 mEq/l within 10 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1 mEq/l within 9 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1 mEq/l within 8 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1 mEq/l within 7 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1 mEq/l within 6 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1 mEq/l within 5 days of the cessation of treatment. By way of further example, in one such embodiment the

individual's serum bicarbonate value decreases by at least 1 mEq/l within 4 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1 mEq/l within 3 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1 mEq/l within 2 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1 mEq/l within 1 day of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1 mEq/l within 12 hours of the cessation of treatment.

[00229] In certain embodiments, upon the cessation of treatment the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 1 month of the cessation of treatment. For example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 3 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 2 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 10 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 9 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 8 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 7 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 6 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 5 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 4 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 3 days of the cessation of treatment. By way

of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 2 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 1 day of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 12 hours of the cessation of treatment.

[00230] In certain embodiments, upon the cessation of treatment the individual's serum bicarbonate value decreases by at least 2 mEq/l within 1 month of the cessation of treatment. For example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2 mEq/l within 3 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2 mEq/l within 2 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2 mEq/l within 10 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2 mEq/l within 9 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2 mEq/l within 8 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2 mEq/l within 7 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2 mEq/l within 6 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2 mEq/l within 5 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2 mEq/l within 4 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2 mEq/l within 3 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2 mEq/l within 2 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2 mEq/l within 1 day of the cessation of treatment. By way of further example, in one such embodiment the

individual's serum bicarbonate value decreases by at least 2 mEq/l within 12 hours of the cessation of treatment.

[00231] In certain embodiments, upon the cessation of treatment the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 1 month of the cessation of treatment. For example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 3 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 2 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 10 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 9 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 8 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 7 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 6 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 5 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 4 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 3 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 2 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 1 day of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 12 hours of the cessation of treatment.

[00232] In certain embodiments, upon the cessation of treatment the individual's serum bicarbonate value decreases by at least 3 mEq/l within 1 month of

the cessation of treatment. For example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3 mEq/l within 3 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3 mEq/l within 2 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3 mEq/l within 10 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3 mEq/l within 9 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3 mEq/l within 8 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3 mEq/l within 7 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3 mEq/l within 6 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3 mEq/l within 5 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3 mEq/l within 4 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3 mEq/l within 3 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3 mEq/l within 2 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3 mEq/l within 1 day of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3 mEq/l within 12 hours of the cessation of treatment.

[00233] In certain embodiments, upon the cessation of treatment the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 1 month of the cessation of treatment. For example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 3 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 2

weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 10 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 9 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 8 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 7 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 6 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 5 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 4 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 3 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 2 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 1 day of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 12 hours of the cessation of treatment.

[00234] In certain embodiments, upon the cessation of treatment the individual's serum bicarbonate value decreases by at least 4 mEq/l within 1 month of the cessation of treatment. For example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4 mEq/l within 3 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4 mEq/l within 2 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4 mEq/l within 10 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4 mEq/l within 9 days of

the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4 mEq/l within 8 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4 mEq/l within 7 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4 mEq/l within 6 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4 mEq/l within 5 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4 mEq/l within 4 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4 mEq/l within 3 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4 mEq/l within 2 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4 mEq/l within 1 day of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4 mEq/l within 12 hours of the cessation of treatment.

[00235] In certain embodiments, upon the cessation of treatment the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 1 month of the cessation of treatment. For example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 3 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 2 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 10 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 9 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 8 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value

decreases by at least 4.5 mEq/l within 7 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 6 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 5 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 4 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 3 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 2 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 1 day of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 12 hours of the cessation of treatment.

[00236] In certain embodiments, upon the cessation of treatment the individual's serum bicarbonate value decreases by at least 5 mEq/l within 1 month of the cessation of treatment. For example, in one such embodiment the individual's serum bicarbonate value decreases by at least 5 mEq/l within 3 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 5 mEq/l within 2 weeks of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 5 mEq/l within 10 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 5 mEq/l within 9 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 5 mEq/l within 8 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 5 mEq/l within 7 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 5 mEq/l within 6 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 5 mEq/l within 5 days of

the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 5 mEq/l within 4 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 5 mEq/l within 3 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 5 mEq/l within 2 days of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 5 mEq/l within 1 day of the cessation of treatment. By way of further example, in one such embodiment the individual's serum bicarbonate value decreases by at least 5 mEq/l within 12 hours of the cessation of treatment.

[00237] In one embodiment, the baseline serum bicarbonate value is the value of the serum bicarbonate concentration determined at a single time point. In another embodiment, the baseline serum bicarbonate value is the mean value of at least two serum bicarbonate concentrations determined at different time-points. For example, in one such embodiment the baseline serum bicarbonate value is the mean value of at least two serum bicarbonate concentrations for serum samples drawn on different days. By way of further example, the baseline serum bicarbonate value is the mean or median value of at least two serum bicarbonate concentrations for serum samples drawn on non-consecutive days. By way of further example, in one such method the non-consecutive days are separated by at least two days. By way of further example, in one such method the non-consecutive days are separated by at least one week. By way of further example, in one such method the non-consecutive days are separated by at least two weeks. By way of further example, in one such method the non-consecutive days are separated by at least three weeks.

[00238] In certain embodiments, the daily dose is no more than 100 g/day of the nonabsorbable composition. For example, in one such embodiment the daily dose is no more than 90 g/day of the nonabsorbable composition. By way of further example, in one such embodiment the daily dose is no more than 75 g/day of the nonabsorbable composition. By way of further example, in one such embodiment the daily dose is no more than 65 g/day of the nonabsorbable composition. By way of further example, in one such embodiment the daily dose is no more than 50 g/day of the nonabsorbable composition. By way of further example, in one such

embodiment the daily dose is no more than 40 g/day of the nonabsorbable composition. By way of further example, in one such embodiment the daily dose is no more than 30 g/day of the nonabsorbable composition. By way of further example, in one such embodiment the daily dose is no more than 25 g/day of the nonabsorbable composition. By way of further example, in one such embodiment the daily dose is no more than 20 g/day of the nonabsorbable composition. By way of further example, in one such embodiment the daily dose is no more than 15 g/day of the nonabsorbable composition. By way of further example, in one such embodiment the daily dose is no more than 10 g/day of the nonabsorbable composition. By way of further example, in one such embodiment the daily dose is no more than 5 g/day of the nonabsorbable composition.

[00239] In certain embodiments, the individual is treated with the daily dose for a period of at least one day. For example, in one such embodiment the individual is treated with the daily dose for a period of at least one week. By way of further example, in one such embodiment the individual is treated with the daily dose for a period of at least one month. By way of further example, in one such embodiment the individual is treated with the daily dose for a period of at least two months. By way of further example, in one such embodiment the individual is treated with the daily dose for a period of at least three months. By way of further example, in one such embodiment the individual is treated with the daily dose for a period of at least several months. By way of further example, in one such embodiment the individual is treated with the daily dose for a period of at least six months. By way of further example, in one such embodiment the individual is treated with the daily dose for a period of at least one year.

[00240] In certain embodiments of the method of the present disclosure, the daily dose of the nonabsorbable composition has the capacity to remove at least about 5 mEq/day of the target species. For example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 6 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 7 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 8 mEq/day of the target species. By way of further

example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 9 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 10 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 11 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 12 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 13 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 14 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 15 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 16 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 17 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 18 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 19 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 20 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 21 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 22 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 23 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 24

mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 25 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 26 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 27 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 28 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 29 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 30 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 31 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 32 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 33 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 34 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 35 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 36 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 37 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 38 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 39 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable

composition has the capacity to remove at least about 40 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 41 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 42 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 43 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 44 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 45 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 46 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 47 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 48 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 49 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition has the capacity to remove at least about 50 mEq/day of the target species.

[00241] In certain embodiments of the method of the present disclosure, the daily dose of the nonabsorbable composition removes at least about 5 mEq/day of the target species. For example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 6 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 7 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 8 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 9 mEq/day of the target species.

By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 10 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 11 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 12 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 13 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 14 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 15 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 16 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 17 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 18 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 19 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 20 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 21 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 22 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 23 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 24 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 25 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 26 mEq/day of the target

species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 27 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 28 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 29 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 30 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 31 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 32 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 33 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 34 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 35 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 36 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 37 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 38 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 39 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 40 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 41 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 42 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 43 mEq/day of the target

species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 44 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 45 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 46 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 47 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 48 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 49 mEq/day of the target species. By way of further example, in one such embodiment the daily dose of the nonabsorbable composition removes at least about 50 mEq/day of the target species.

[00242] In certain embodiments of the method of the present disclosure, the daily dose of the nonabsorbable composition removes less than 60 mEq/day of the target species. For example, in one such method the daily dose removes less than 55 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 50 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 45 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 40 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 35 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 34 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 33 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 32 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 31 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 30 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than

29 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 28 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 27 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 26 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 25 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 24 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 23 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 22 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 21 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 20 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 19 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 18 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 17 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 16 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 15 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 14 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 13 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 12 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 11 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 10 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 9 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 8 mEq/day of the target species. By way of further example, in one such embodiment the daily dose removes less than 7 mEq/day of

the target species. By way of further example, in one such embodiment the daily dose removes less than 6 mEq/day of the target species.

[00243] In certain embodiments of the method of the present disclosure, the daily dose of the nonabsorbable composition has insufficient capacity to remove more than 60 mEq/day of the target species. For example, in one such method the daily dose has insufficient capacity to remove more than 55 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 50 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 45 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 40 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 35 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 34 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 33 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 32 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 31 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 30 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 29 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 28 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 27 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 26 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 25 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 24 mEq/day of the

target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 23 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 22 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 21 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 20 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 19 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 18 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 17 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 16 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 15 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 14 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 13 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 12 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 11 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 10 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 9 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 8 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 7 mEq/day of the target species. By way of further example, in one such embodiment the daily dose has insufficient capacity to remove more than 6 mEq/day of the target species.

[00244] In certain embodiments of the method of the present disclosure, the method comprises oral administration of a pharmaceutical composition to increase the individual's serum bicarbonate levels wherein: (i) the pharmaceutical composition binds a target species in the individual's digestive system when given orally, the target species being selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (ii) the pharmaceutical composition increases the serum bicarbonate level by at least 1 mEq/l in a placebo controlled study, said increase being the difference between the cohort average serum bicarbonate level in a first cohort at the end of the study, relative to the cohort average serum bicarbonate level in a second cohort at the end of the study, wherein the first cohort's subjects receive the pharmaceutical composition and the second cohort's subjects receive a placebo, wherein the first and second cohorts each comprise at least 25 subjects, each cohort is prescribed the same diet during the study and the study lasts at least two weeks. In one embodiment, the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 100 g/day. In one embodiment, the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 50 g/day. In one embodiment, the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 30 g/day. In one embodiment, the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 25 g/day. In one embodiment, the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 20 g/day. In one embodiment, the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 15 g/day. In one embodiment, the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 10 g/day. In one embodiment, the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 5 g/day. In one embodiment, the target species is protons. In one embodiment, the target species is chloride ions. In one embodiment, the target species is a strong acid. In one embodiment, the target species is HCl. In one embodiment, the pharmaceutical composition is not absorbed when ingested.

[00245] In one embodiment, the individual or adult human patient has chronic kidney disease (CKD Stage 3 – 4; eGFR 20 – <60 mL/min/1.73m^2) and a baseline serum bicarbonate value at the start of the study between 12 and 20 mEq/L. In one embodiment, the pharmaceutical composition increases the serum

bicarbonate level of the individual or adult human patient by at least 2 mEq/l in the placebo controlled study. In one embodiment, the pharmaceutical composition increases the serum bicarbonate level of the individual or adult human patient by at least 3 mEq/l in the placebo controlled study. In one embodiment, the individual or adult human patient is not yet in need for kidney replacement therapy (dialysis or transplant). In one embodiment, the individual or adult human patient has not yet reached end stage renal disease ("ESRD").

[00246] In one embodiment, the individual or adult human patient has a mGFR of at least 15 mL/min/1.73 m^2. In one embodiment, the individual or adult human patient has an eGFR of at least 15 mL/min/1.73 m^2. In one embodiment, the individual or adult human patient has a mGFR of at least 30 mL/min/1.73 m^2. In one embodiment, the individual or adult human patient has an eGFR of at least 30 mL/min/1.73 m^2. In one embodiment, the individual or adult human patient has a mGFR of less than 45 mL/min/1.73 m^2 for at least three months. In one embodiment, the individual or adult human patient has an eGFR of less than 45 mL/min/1.73 m^2 for at least three months. In one embodiment, the individual or adult human patient has a mGFR of less than 60 mL/min/1.73 m^2 for at least three months. In one embodiment, the individual or adult human patient has an eGFR of less than 60 mL/min/1.73 m^2 for at least three months. In one embodiment, the individual or adult human patient has Stage 3A CKD, Stage 3B CKD, or Stage 4 CKD.

[00247] While the methods described above refer to daily dose, a further aspect of the disclosure include the methods disclosed herein in which the dose is administered less frequently than once per day (while still being administered on a regular basis). In any of the disclosure, the daily dose specified may, instead, be administrated on a less frequent basis. For example, the doses disclosed here may be administered once every two or three days. Or the doses disclosed here may be administered once, twice or three times a week.

[00248] In addition to (or as a surrogate for) serum bicarbonate, other biomarkers of acid-base imbalance may be used as a measure of acid-base status. For example, blood (serum or plasma) pH, total CO_2, anion gap, and/or the concentration of other electrolytes (*e.g.*, sodium, potassium, calcium, magnesium, chloride and/or sulfate) may be used as an indicator of acid-base imbalance.

Similarly, net acid excretion ("NAE"), urine pH, urine ammonium concentration, and/or the concentration of other electrolytes in the urine (*e.g.*, sodium, potassium, calcium, magnesium, chloride and/or sulfate) may be used as an indicator of acid-base imbalance.

Fluid	Biomarker of interest	Normal/Target Value	Analytical Technique
Blood (serum or plasma)	Total CO_2	23 – 29 mmol/L	Blood gas analyzer; enzymatic assay; ion selective electrode
	Anion gap	3 – 11 mEq/L	Obtained from standard chemistry electrolyte panel
	pH	7.36 to 7.44	Blood gas analyzer; enzymatic assay; ion selective electrode
	Electrolytes	Na = 135-145 mEq/L; K = 3.5–5 mEq/L; Total Ca = 8–10.5 mEq/L, depending on age and sex; Mg = 1.5 – 2.5 mEq/L, depending on age; Cl = 95-105 mEq/L; phosphate = 2.5-4.5 mEq/L; sulfate = 1 mEq/L	Obtained from standard chemistry electrolyte panel; ion selective electrodes can be used for Na, Cl and K
urine	pH	4.5 – 8.0	pH meter
	ammonium	3 – 65 mmol/L	Enzymatic
	citrate	150 – 1,191 mg/24-hour urine collection; ranges for 20 to 60 years of age	Enzymatic
	sodium	20 mEq/L in spot samples, 41 – 227 mEq/L per day (depending upon salt and fluid intake)	Ion-selective electrode
	potassium	17 – 77 mmol/24 hours; spot sample is ~45 mmol/L	Ion-selective electrode
	calcium	Urinary calcium is <250 mg/24 hours in males, <200 mg/24 hours in females	Enzymatic
	magnesium	Urinary magnesium is 51 – 269 mg/24 hours; spot values are usually reported as a ratio with creatinine and are >0.035 mg Mg/mg creatinine	Enzymatic
	chloride	Urinary chloride is 40 – 224 mmol/24 hours	Ion-selective electrode
	Urine Anion Gap ("UAG")	UAG = 0-10 mEq/L; Metabolic acidosis indicated when UAG > 20 mEq/L	UAG = $(Na^+ + K^+) - Cl^-$ in urine. It is a measure of ammonium excretion, the

			primary mechanism for acid excretion.
	Net Acid Excretion	Urinary net acid excretion is the total amount of acid excreted by the kidney per day; the NAE value depends on the age of the subject, gender, and protein intake; typical NAE values range from 9 mEq/day to 38 mEq/day	24-hour urine collection required; Direct NAE measurement (mEq/day) = $[NH_4^+]$ + [TA] – $[HCO_3^-]$, where TA is concentration of titratable acids Indirect NAE measurement (mEq/day) = (Cl + P + SO_4 + organic anions) – (Na + K + Ca+ Mg).

[00249] In one embodiment, treatment of an individual as described herein may improve an individuals' serum anion gap. For example, treating an acid base imbalance with a neutral composition having the capacity to bind both protons and anions (unaccompanied by the delivery of sodium or potassium ions) can increase serum bicarbonate without an accompanying increase in sodium or potassium (see Example 3 and Figs 13A, 13C and 13D). Consequently, the serum anion gap may be improved (decreased) by at least 1 mEq/l or more (e.g., at least 2 mEq/l) within a period as short as 2 weeks (see Example 3).

[00250] The various aspects and embodiments may have a range of advantages, such as improved or successful treatment of metabolic acidosis. Such improvements may also include reduced side effects, increased patient compliance, reduced drug loads, increased speed of treatment, increased magnitude of treatment, avoiding unwanted changes to other electrolytes and/or reduced drug-drug interactions. A further improvement may include reducing a patient's anion gap (as defined above) as part of the methods and other aspects disclosed herein. Further useful features of the disclosed aspects can be found in the examples.

Certain specific compositions for use in treatment

[00251] As previously noted, one aspect disclosed here is a composition for use in a method of treating metabolic acidosis in an adult human patient wherein in said treatment 0.1 – 12 g of said composition is administered to the patient per day, said composition being a nonabsorbable composition having the capacity to remove protons from the patient, wherein the nonabsorbable composition is characterized by

a chloride ion binding capacity of at least 2.5 mEq/g in a Simulated Small Intestine Inorganic ("SIB") assay. This aspect is based on the data in the examples showing the absorption and removal of HCl to successfully treat patients, allowing the amount of the composition to be set based on its capacity to bind chloride in the SIB assay. As shown in the examples, a composition with this specified level of chloride binding in the "SIB" assay can be used in the specified dose range to successfully treat metabolic acidosis in adult humans. In this aspect, the composition may be administered orally, and so would be an orally administered nonabsorbable composition as defined herein.

[00252] This aspect is based on the data in the examples showing the absorption and removal of HCl to successfully treat patients using a composition according to this aspect, allowing the amount of the composition to be set based on its capacity to bind chloride in the SIB assay. Surprisingly, the amounts required for successful treatment were relatively low.

[00253] Another aspect of the present disclosure is a composition for use in a method of treating metabolic acidosis in an adult human patient by increasing that patient's serum bicarbonate value by at least 1 mEq/L over 15 days of treatment, said composition being a nonabsorbable composition having the capacity to remove protons from the patient. In this aspect, the composition may be administered orally, and so would be an orally administered nonabsorbable composition as defined herein.

[00254] This aspect is based on the data in the examples showing the absorption and removal of HCl to successfully treat patients using a composition according to this aspect which provides new detail regarding the reductions possible using a composition of the disclosure. This aspect includes surprisingly rapid increases in the patient's serum bicarbonate level, for example in the first few days, as well as surprisingly large increases in serum bicarbonate level.

[00255] Another aspect of the present disclosure is a composition for use in a method of treating metabolic acidosis in an adult human patient, said patient having a serum bicarbonate level of less than 20 mEq/L prior to treatment, said composition being a nonabsorbable composition having the capacity to remove protons from the patient. In this aspect, the composition may be administered orally,

and so would be an orally administered nonabsorbable composition as defined herein.

[00256] This aspect is based on the data in the examples showing, for the first time, the successful treatment of patients with a low serum bicarbonate level, for example levels that have not been shown to be so readily treated previously. The patients with lower serum bicarbonate levels responded particularly well to the treatment and this improvement for this subgroup is one advantage of this aspect.

[00257] Another aspect of the present disclosure is a composition for use in a method of treating metabolic acidosis in an adult human patient by increasing that patient's serum bicarbonate value by at least 1 mEq/L over 15 days of treatment, wherein in said treatment >12 – 100g of said polymer is administered to the patient per day, said composition being a nonabsorbable composition having the capacity to remove protons from the patient, wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 2.5 mEq/g in a Simulated Small Intestine Inorganic Buffer ("SIB") assay. In this aspect, the composition may be administered orally, and so would be an orally administered nonabsorbable composition as defined herein.

[00258] Another aspect of the present disclosure is a composition for use in a method of treating metabolic acidosis in an adult human patient wherein in said treatment >12 – 100g of said composition is administered to the patient per day, said composition being a nonabsorbable composition having the capacity to remove protons from the patient, wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of less than 2.5 mEq/g in a Simulated Small Intestine Inorganic Buffer ("SIB") assay. In this aspect, the composition may be administered orally, and so would be an orally administered nonabsorbable composition as defined herein.

[00259] The chloride ion binding capacity in the SIB assay is affected by both the composition's selectivity for binding chloride and the total space available for chloride binding. The term "composition" refers to the active pharmaceutical ingredient, including any counter ions, but not to excipients. So, the "amount" of the composition is the amount of active pharmaceutical ingredient without including other parts of any unit dose form.

[00260] More specifically in these aspects, the amount of composition may be any amount disclosed herein in other sections within the range 0.1g – 12 g. For example, 1 – 11 g, 2 – 10 g, 3 – 9 g, 3 – 8 g, 3 – 7 g, 3 – 6 g, 3.5 – 5.5 g, 4 – 5 g, or 4.5 – 5 g of said polymer is administered to the patient per day, or 0.5 g, 1 g, 1.5 g, 2 g, 2.5 g, 3 g, 3.5 g, 4.0 g, 4.5 g or 5.0 g of the composition is administered to the patient per day.

[00261] More specifically in these aspects, the chloride ion binding capacity in a Simulated Small Intestine Inorganic Buffer ("SIB") assay may be greater than 3, 3.5, 4, or 4.5 mEq/g. One upper limit for the chloride ion binding capacity in a SIB assay is 10 mEq/g. Other the upper limits may be 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5 or 10 mEq/g, or there may be no upper limit specified.

[00262] All combinations of the amount of composition and the chloride ion binding capacity mentioned here are also disclosed. For example, in one embodiment, the composition has a chloride ion binding capacity in a SIB assay is of at least 4.5 mEq/g and only 0.1 – 6gs of composition is administered in the method of treating metabolic acidosis.

[00263] The composition in these aspects can additionally have any of the properties or features specified elsewhere herein. For example, the composition may be a nonabsorbable composition as described in the following section. In a similar fashion, the methods of treatment specified in these aspects may include any of the features disclosed in the preceding section regarding certain methods of treatment.

Nonabsorbable Compositions

[00264] As previously noted, the nonabsorbable compositions having the medical uses described herein possess the capacity to remove clinically significant quantities of one or more target species: (i) protons, (ii) the conjugate base(s) of one or more strong acids (*e.g.*, chloride, bisulfate (HSO_4^-) and/or sulfate (SO_4^-) ions) and/or (iii) one or more strong acids (*e.g.*, HCl and/or H_2SO_4). To bind such target species, the nonabsorbable compositions may be selected from the group consisting of cation exchange compositions, anion exchange compositions, amphoteric ion exchange compositions, neutral compositions having the capacity to bind both protons and anions, composites thereof and mixtures thereof.

[00265] In general, the nonabsorbable composition has a preferred particle size range that is (i) large enough to avoid passive or active absorption through the GI tract and (ii) small enough to not cause grittiness or unpleasant mouth feel when ingested as a powder, sachet and/or chewable tablet/dosage form with a mean particle size of at least 3 microns. For example, in one such embodiment the nonabsorbable composition comprises a population of particles having a mean particle size (volume distribution) in the range of 5 to 1,000 microns. By way of further example, in one such embodiment the nonabsorbable composition comprises a population of particles having a mean particle size (volume distribution) in the range of 5 to 500 microns. By way of further example, in one such embodiment the nonabsorbable composition comprises a population of particles having a mean particle size (volume distribution) in the range of 10 to 400 microns. By way of further example, in one such embodiment the nonabsorbable composition comprises a population of particles having a mean particle size (volume distribution) in the range of 10 to 300 microns. By way of further example, in one such embodiment the nonabsorbable composition comprises a population of particles having a mean particle size (volume distribution) in the range of 20 to 250 microns. By way of further example, in one such embodiment the nonabsorbable composition comprises a population of particles having a mean particle size (volume distribution) in the range of 30 to 250 microns. By way of further example, in one such embodiment the nonabsorbable composition comprises a population of particles having a mean particle size (volume distribution) in the range of 40 to 180 microns. In certain embodiments, less than 7% of the particles in the population (volume distribution) have a diameter less than 10 microns. For example, in such embodiments less than 5% of the particles in the particles in the population (volume distribution) have a diameter less than 10 microns. By way of further example, in such embodiments less than 2.5% of the particles in the particles in the population (volume distribution) have a diameter less than 10 microns. By way of further example, in such embodiments less than 1% of the particles in the particles in the population (volume distribution) have a diameter less than 10 microns. In all embodiments, the particle size may be measured using the protocol set out in the abbreviations and definitions section (above).

[00266] To minimize GI side effects in patients that are often related to a large volume polymer gel moving through the GI tract, a low Swelling Ratio of the nonabsorbable composition is preferred (0.5 to 10 times its own weight in water). For example, in one such embodiment the nonabsorbable composition has a Swelling Ratio of less than 9. By way of further example, in one such embodiment the nonabsorbable composition has a Swelling Ratio of less than 8. By way of further example, in one such embodiment the nonabsorbable composition has a Swelling Ratio of less than 7. By way of further example, in one such embodiment the nonabsorbable composition has a Swelling Ratio of less than 6. By way of further example, in one such embodiment the nonabsorbable composition has a Swelling Ratio of less than 5. By way of further example, in one such embodiment the nonabsorbable composition has a Swelling Ratio of less than 4. By way of further example, in one such embodiment the nonabsorbable composition has a Swelling Ratio of less than 3. By way of further example, in one such embodiment the nonabsorbable composition has a Swelling Ratio of less than 2.

[00267] The amount of the target species (proton, conjugate base of a strong acid and/or strong acid) that is bound as the nonabsorbable composition transits the GI tract is largely a function of the binding capacity of the composition for the target species (protons, the conjugate base of a strong acid, and/or a strong acid) and the quantity of the nonabsorbable composition administered per day as a daily dose. In general, the theoretical binding capacity for a target species may be determined using a SGF assay and determining the amount of a species that appeared in or disappeared from the SGF buffer during the SGF assay. For example, the theoretical proton binding capacity of a cation exchange resin may be determined by measuring the increase in the amount of cations (other than protons) in the buffer during a SGF assay. Similarly, the theoretical anion binding capacity of an anion exchange resin (in a form other than the chloride form) may be determined by measuring the increase in the amount of anions (other than chloride ions) in the buffer during a SGF assay. Additionally, the theoretical anion binding capacity of a neutral composition for protons and the conjugate base of a strong acid may be determined by measuring the decrease in chloride concentration in the buffer during a SGF assay.

[00268] In general, the nonabsorbable composition will have a theoretical binding capacity for the target species of at least about 0.5 mEq/g (as determined in an SGF assay). For example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for the target species of at least about 1 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for the target species of at least about 2 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for the target species of at least about 3 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for the target species of at least about 4 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for the target species of at least about 5 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for the target species of at least about 7.5 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for the target species of at least about 10 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for the target species of at least about 12.5 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for the target species of at least about 15 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for the target species of at least about 20 mEq/g. In general, the nonabsorbable composition will typically have a theoretical binding capacity for the target species that is not in excess of about 35 mEq/g. For example, in some embodiments, the theoretical binding capacity of the nonabsorbable compositions for the target species that is not be excess of 30 mEq/g. Thus, for example, the theoretical binding capacity of the nonabsorbable compositions for the target species may range from 2 to 25 mEq/g, 3 to 25 mEq/g, 5 to 25 mEq/g, 10 to 25 mEq/g, 5 to 20 mEq/g, 6 to 20 mEq/g, 7.5 to 20 mEq/g, or even 10 to 20 mEq/g. In those embodiments in which the target species comprises protons and at least one conjugate base, the binding capacities recited in this paragraph are the theoretical binding capacities for protons and the theoretical binding capacities for the conjugate base(s), independently and individually, and not the sum thereof.

[00269] In general, the nonabsorbable composition will have a theoretical binding capacity for protons of at least about 0.5 mEq/g (as determined in an SGF assay). For example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for protons of at least about 1 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for protons of at least about 2 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for protons of at least about 3 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for protons of at least about 4 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for protons of at least about 5 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for protons of at least about 7.5 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for protons of at least about 10 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for protons of at least about 12.5 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for protons of at least about 15 mEq/g. By way of further example, in some embodiments the nonabsorbable composition will have a theoretical binding capacity for protons of at least about 20 mEq/g. In general, the nonabsorbable composition will typically have a theoretical binding capacity for protons that is not in excess of about 35 mEq/g. For example, in some embodiments, the theoretical binding capacity of the nonabsorbable compositions for protons that is not be excess of 30 mEq/g. Thus, for example, the theoretical binding capacity of the nonabsorbable compositions for protons may range from 2 to 25 mEq/g, 3 to 25 mEq/g, 5 to 25 mEq/g, 10 to 25 mEq/g, 5 to 20 mEq/g, 6 to 20 mEq/g, 7.5 to 20 mEq/g, or even 10 to 20 mEq/g. In those embodiments in which the target species comprises protons and at least one conjugate base, the binding capacities recited in this paragraph are the theoretical binding capacities for protons and the theoretical binding capacities for the conjugate base(s), independently and individually, and not the sum thereof.

[00270] Phosphate, bicarbonate, bicarbonate equivalents, the conjugate bases of bile and fatty acids are potential interfering anions for chloride or other conjugate bases of strong acids (*e.g.*, HSO_4^- and SO_4^{2-}) in the stomach and small intestine. Therefore, rapid and preferential binding of chloride over phosphate, bicarbonate equivalents, and the conjugate bases of bile and fatty acids in the small intestine is desirable and the SIB assay may be used to determine kinetics and preferential binding. Since the transit time of the colon is slow (2-3 days) relative to the small intestine, and since conditions in the colon will not be encountered by an orally administered nonabsorbable composition until after stomach and small intestine conditions have been encountered, kinetics of chloride binding by a nonabsorbable composition do not need to be as rapid in the colon or under in vitro conditions designed to mimic the late small intestine/colon. It is, however, desirable that chloride binding and selectivity over other interfering anions is high, for example, at 24 and/or 48 hours or longer.

[00271] In one embodiment, the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 1 mEq/g in a Simulated Small Intestine Inorganic Buffer ("SIB") assay. For example, in one such embodiment the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 1.5 mEq/g in a SIB assay. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 2 mEq/g in a SIB assay. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 2.5 mEq/g in a SIB assay. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 3 mEq/g in a SIB assay. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 3.5 mEq/g in a SIB assay. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 4 mEq/g in a SIB assay. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 4.5 mEq/g in a SIB assay. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 5 mEq/g in

a SIB assay. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 5.5 mEq/g in a SIB assay. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 6 mEq/g in a SIB assay.

[00272] In one embodiment, the nonabsorbable composition binds a significant amount of chloride relative to phosphate as exhibited, for example, in a SIB assay. For example, in one embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.1:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.2:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.25:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.3:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.35:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.4:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.45:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.5:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 2:3, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.75:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.9:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 1:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 1.25:1, respectively. By way of further

example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 1.5:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 1.75:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 2:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 2.25:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 2.5:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 2.75:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 3:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 4:1, respectively. By way of further example, in one such embodiment the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 5:1, respectively.

[00273] In one embodiment, the orally administered nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity in Simulated Gastric Fluid of at least 1 mEq/g in a SGF assay. For example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity in a SGF assay of at least 2 mEq/g. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity in a SGF assay of at least 3 mEq/g. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity in a SGF assay of at least 4 mEq/g. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity in a SGF assay of at least 5 mEq/g. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity in a SGF assay of at

least 6 mEq/g. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity in a SGF assay of at least 7 mEq/g. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity in a SGF assay of at least 8 mEq/g. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity in a SGF assay of at least 9 mEq/g. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity in a SGF assay of at least 10 mEq/g. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity in a SGF assay of at least 11 mEq/g. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity in a SGF assay of at least 12 mEq/g. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity in a SGF assay of at least 13 mEq/g. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity in a SGF assay of at least 14 mEq/g. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity after 1 hour in SGF that is at least 50% of the proton-binding capacity and the chloride binding capacity, respectively, of the nonabsorbable composition at 24 hours in SGF. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity after 1 hour in SGF that is at least 60% of the proton-binding capacity and the chloride binding capacity, respectively, of the nonabsorbable composition at 24 hours in SGF. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity after 1 hour in SGF that is at least 70% of the proton-binding capacity and the chloride binding capacity, respectively, of the nonabsorbable composition at 24 hours in SGF. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-

binding capacity and a chloride binding capacity after 1 hour in SGF that is at least 80% of the proton-binding capacity and the chloride binding capacity, respectively, of the nonabsorbable composition at 24 hours in SGF. By way of further example, in one such embodiment the nonabsorbable composition is characterized by a proton-binding capacity and a chloride binding capacity after 1 hour in SGF that is at least 90% of the proton-binding capacity and the chloride binding capacity, respectively, of the nonabsorbable composition at 24 hours in SGF.

[00274] In one embodiment, the nonabsorbable composition is a cation exchange material comprising an insoluble (in the gastric environment) support structure and exchangeable cations. The cation exchange material may be organic (*e.g.*, polymeric), inorganic (*e.g.*, a zeolite) or a composite thereof. The exchangeable cations may be selected, for example, from the group consisting of lithium, sodium, potassium, calcium, magnesium, iron and combinations thereof, and more preferably from the group consisting of sodium, potassium, calcium, magnesium, and combinations thereof. In such embodiments it is generally preferred that the nonabsorbable composition contain a combination of exchangeable cations that establish or maintain electrolyte homeostasis. For example, in one such embodiment the nonabsorbable composition optionally contains exchangeable sodium ions, but when included, the amount of the sodium ions in a daily dose is insufficient to increase the patient's serum sodium ion concentration to a value outside the range of 135 to 145 mEq/l. By way of further example, in one such embodiment the nonabsorbable composition optionally contains exchangeable potassium ions, but when included, the amount of the potassium ions in a daily dose is insufficient to increase the patient's serum potassium ion concentration to a value outside the range of 3.7 to 5.2 mEq/L. By way of further example, in one such embodiment the nonabsorbable composition optionally contains exchangeable magnesium ions, but when included, the amount of the magnesium ions in a daily dose is insufficient to increase the patient's serum magnesium ion concentration to a value outside the range of 1.7 to 2.2 mg/dL. By way of further example, in one such embodiment the nonabsorbable composition optionally contains exchangeable calcium ions, but when included, the amount of the calcium ions in a daily dose is insufficient to increase the patient's serum calcium ion concentration to a value outside the range of 8.5 to 10.2 mg/dL. By way of further

example, in one such embodiment the nonabsorbable composition contains a combination of exchangeable cations selected from the group consisting of sodium, potassium, calcium, magnesium, and combinations thereof, designed to maintain serum Na^+ levels within the range of 135 to 145 mEq/l, serum K^+ levels within the range of 3.7 to 5.2 mEq/L, serum Mg^{2+} levels within the range of 1.7 to 2.2 mg/dL and serum Ca^{2+} levels within the range of 8.5 to 10.2 mg/dL.

[00275] In one embodiment, the nonabsorbable composition is a cation exchange material comprising an insoluble (in the gastric environment) support structure, optionally containing exchangeable sodium ions cations. The cation exchange material may be organic (*e.g.*, polymeric), inorganic (*e.g.*, a molecular sieve) or a composite thereof. In one such embodiment, the nonabsorbable composition contains less than 12% by weight sodium. For example, in one such embodiment the nonabsorbable composition contains less than 9% by weight sodium. By way of further example, in one such embodiment the nonabsorbable composition contains less than 6% by weight sodium. By way of further example, in one such embodiment the nonabsorbable composition contains less than 3% by weight sodium. By way of further example, in one such embodiment the nonabsorbable composition contains less than 1% by weight sodium. By way of further example, in one such embodiment the nonabsorbable composition contains less than 0.1% by weight sodium. By way of further example, in one such embodiment the nonabsorbable composition contains less than 0.01% by weight sodium. By way of further example, in one such embodiment the nonabsorbable composition contains between 0.05 and 3% by weight sodium.

[00276] In one exemplary embodiment, the nonabsorbable composition is a resin comprising any of a wide range of crosslinked polymeric materials that are able to bind protons in aqueous solutions. Exemplary crosslinked polymeric material comprises a polyanion crosslinked material selected from poly(carboxylic acids), poly(acrylic acids), poly(sulfonic acids), poly(maleic acids), poly(phenols), functionalized polyols and poly(alcohols), poly(hydroxamic acids), poly(imides) and copolymers thereof. In one embodiment, the polyanion is coordinated to exchangeable monovalent cations, divalent cations, or a combination thereof. Exemplary monovalent cations include lithium, sodium, and potassium, or any

combination thereof. Exemplary divalent cations include magnesium and calcium or combinations thereof.

[00277] In one exemplary embodiment, the nonabsorbable composition is a cation exchange resin comprising a polyanion backbone that exchanges cations for protons and has an average pKa of at least 4. For example, in one embodiment, the polyanion backbone has an average pKa of 4-5. By way of further example, in one such embodiment the polyanion backbone has an average pKa of 5-6. By way of further example, in one such embodiment the polyanion backbone has an average pKa of 6-7. By way of further example, in one such embodiment the polyanion backbone has an average pKa of greater than 7. Exemplary cation exchange resins include poly(carboxylic acids), poly(acrylic acids), poly(sulfonic acids), poly(maleic acids), poly(phenols), functionalized polyols and poly(alcohols), poly(hydroxamic acids), poly(imides) and copolymers thereof. In one embodiment, these polyanion backbones are further functionalized with functional groups to affect the pKa. These functional groups can increase pKa when electron donating, or decrease pKa when electron withdrawing. Exemplary electron donating groups include amino, hydroxyl, methyl ether, ether, phenyl, and amido. Exemplary electron withdrawing groups include flouro, chloro, halo, sulphonyl, nitroxyl, trifluoromethyl, and cyano. Further exemplary cation exchange resins include resins modified with protonable functional groups including carboxylic acids and functionalized alcohols.

[00278] Polymeric cation exchanger resins may be prepared using a range of chemistries, including for example, (i) substitution polymerization of polyfunctional reagents at least one of which comprises basic anionic or conjugate-acid moieties, (2) radical polymerization of a monomer comprising at least one acid or conjugate-acid containing moiety, and (3) crosslinking of a basic anionic or conjugate-acid containing intermediate with a polyfunctional crosslinker, optionally containing basic anionic or conjugate-acid moieties. The resulting crosslinked polymers may thus, for example, be crosslinked homopolymers or crosslinked copolymers. By way of further example, the resulting crosslinked polymers will typically possess repeat units comprising basic anionic or conjugate-acid, separated by the same or varying lengths of repeating linker (or intervening) units. In some embodiments, the polymers comprise repeat units comprising a basic anionic or conjugate-acid moiety and an intervening linker unit. In other embodiments, multiple basic anionic or

conjugate-acid containing repeat units are separated by one or more linker units. Additionally, the polyfunctional crosslinkers may comprise proton binding functional groups, e.g. basic anionic, ("active crosslinkers") or may lack proton binding functional groups such as acrylates ("passive crosslinkers").

[00279] In some embodiments, a basic anion or conjugate-acid monomer is polymerized and the polymer is concurrently crosslinked in a substitution polymerization reaction. The basic anion or conjugate-acid reactant (monomer) in the concurrent polymerization and crosslinking reaction can react more than one time for the substitution polymerization. In one such embodiment, the basic anion or conjugate-acid monomer is a branched basic anion or conjugate-acid possessing at least two reactive moieties to participate in the substitution polymerization reaction.

[00280] In one embodiment, the nonabsorbable composition comprises a cation exchange ceramic material. Porous inorganic binders exhibit a range of properties. Functionally, they are able to sequester materials on the basis of their size and polarity, as they exhibit a framework charge with porous structure. They are structurally diverse and can be crystalline or non-crystalline crystalline (amorphous). Classes of porous materials that fall under the class of inorganic binders include hydrous oxides (*e.g.*, aluminum oxide) and metal alumino-silicate compounds where the metal can be an alkali or alkali earth metal such sodium, potassium, lithium, magnesium or calcium. Many of these compounds have well-defined crystalline structures. This class of compounds has been used for various biopharmaceutical applications.

[00281] The pore diameters of inorganic microporous and mesoporous materials are measured in ångströms (Å) or nanometers (nm). According to IUPAC notation, microporous materials have pore diameters of less than 2 nm (20 Å) and macroporous materials have pore diameters of greater than 50 nm (500 Å); the mesoporous category thus lies in the middle with pore diameters between 2 and 50 nm (20-500 Å). The porosity of inorganic porous materials can be tuned or designed, by the appropriate use of poragen or "co-monomer metals" within the lattices of the porous material. By the appropriate choice of elements, the pore size has been seen to range in size from 3 Å to 8 Å. These compositions have a porous system allowing solute together with other dissolved species to enter the porous framework of the material, resulting in absorption of the dissolved species. Tuning

the cavities and pore size of the materials, can allow adsorption of molecules of particular dimensions, while rejecting those of larger dimensions. From a binding perspective using size as a selectivity mechanism the chloride ion has the advantage of its small size (the radius of chloride anion is 1.8 Å, and the molecular weight of chloride anion is 35.5) compared to the other species present in the digestive tract.

Molecules absorbed (small, polar organic or inorganic)	Molecules excluded (large, non polar and high molecular weight)
Water (Solubility in water; miscible, Mw 18)	Bile acids (Solubility in water; 0.24%, Mw 392.5)
HCl (Soluble in water (38%), Mw 36.5)	Phosphoric acid (Solubility in water; miscible, Mw 98.0)
Acetic acid (Solubility in water; miscible, Mw 60.0)	Fatty acids (Solubility in water, non miscible, Mw > 200

[00282] Exemplary cation exchange ceramic materials include any of a wide range of microporous or mesoporous ceramic materials. In one embodiment, the nonabsorbable composition comprises a molecular sieve, such as a molecular sieve selected from the group consisting of silica, titanosilicate, metalloaluminate, aluminophosphate and gallogerminate molecular sieves. In one embodiment, the nonabsorbable composition comprises a zeolite, a borosilicate, a gallosilicate, a ferrisilicate or a chromosilicate molecular sieve.

[00283] Inorganic porous materials exhibit the property of sequestering substances from an external environment. The mechanism to bind proton or chloride or HCl can be either an adsorptive or absorptive mechanism, where the ions are bound via the specific porosity of the matrix, or an ion exchange mechanism. The strong adsorptive force in zeolite molecular sieves are due to the polarity of the surface (hydroxyl metalloid) and cations that are exposed within the crystal lattice. The cations on the surface act as a site of strong localized positive charge that electrostatically attract the partial negative charges of polar molecules (for example, the chloride of HCl). A basic formula for zeolite can be represented by, $M_{2/n}O.Al_2O_3.xSiO_2.yH_2O$ where M is a cation of n valence. The fundamental building block of the molecular sieve structure is tetrahedral with 4 oxygen anions surrounding a silicon or alumina cation. Sodium ions or other cations (e.g. potassium, calcium) make up the positive charge deficit of the alumina tetrahedron to extend the crystal lattice. In many molecular sieve types the sodium can be exchanged or the sodium can function as a permanent positive charge within the

crystal lattice thus providing the electrostatic interaction. Given these mechanisms, hydrochloric acid can be sequestered from solution via a cation exchange mechanism (sodium for proton), anion exchange mechanism (hydroxide for chloride), or via electrostatic interaction of the hydrochloric acid ionic species.

[00284] The methods used to bind HCl are well known in the art and involve contacting the molecular sieve with a solution containing the desired HCl concentration in water. Exchange conditions include a temperature of about 25 °C to about 100 °C, and a time of about 20 minutes to about 2 hours. These conditions include conditions and exposure times encountered in the gastrointestinal tract.

[00285] In one embodiment, the nonabsorbable composition is an anion exchange material comprising an insoluble (in the gastric environment) support structure and exchangeable anions. The anion exchange material may be organic (*e.g.*, polymeric), inorganic (*e.g.*, an apatite, hydrotalcite or a hydrated gel of aluminum, iron(III) or zirconium hydroxide) or a composite thereof.

[00286] In one embodiment, the nonabsorbable composition comprises an anion exchange material. Exemplary anion exchange materials include strongly and weakly basic anion exchange materials. For example, the anion exchange material may include any of a wide range of polymers comprising quaternary amine moieties, phosphonium salts, N-heteroaromatic salts, or combinations thereof. Other exemplary anion exchange materials include poly(ionic liquids), wherein the side chain is selected from the group consisting of salts of tetraalkyl ammonium, imidazolium, pyridinium, pyrrolidonium, guanidinium, piperidinium, and tetraalkyl phosphonium cations and combinations thereof. By way of further example, in one such embodiment the anion exchange material is a halide responsive polymer such that a conformational change occurs when about 1 mEq/g to about 35 mEq/g of chloride is initially bound to the polymer and subsequently retained for the duration of the GI transit time. In certain embodiments, the halide response conformational change occurs when 2 mEq/g to about 25 mEq/g chloride is bound, and in certain more specific embodiments, the halide response conformational change occurs when 3 to 25 mEq/g, 5 to 25 mEq/g, 10 to 25 mEq/g, 5 to 20 mEq/g, 6 to 20 mEq/g, 7.5 to 20 mEq/g, or even 10 to 20 mEq/g chloride is bound. The polymeric backbone of any of the aforementioned polymers can derive from vinyl, allyl, styrenic, acrylamide, meth(acrylamide), or copolymers thereof. By way of further example,

the anion exchange functionality may be incorporated into the backbone of the polymer. Examples include poly(tetraalkyl ammonium), poly(imidazolium), poly(pyridinium), poly(pyrrolidonium), poly(piperidinium), and poly(tetraalkyl phosphonium) cations or combinations thereof. The exchangeable anion can consist of hydroxide, bicarbonate, acetate, nitrate or any pharmaceutically and biologically acceptable base or combination thereof.

[00287] In one embodiment, the nonabsorbable composition is an anion exchange material comprising at least 1 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion, or a combination thereof. In this embodiment, the nonabsorbable composition has the capacity to induce an increase in the individual's serum bicarbonate value, at least in part, by delivering a physiologically significant amount of hydroxide, carbonate, citrate or other bicarbonate equivalent, or a combination thereof. Exemplary bicarbonate equivalent anions include acetate, lactate and the conjugate bases of other short chain carboxylic acids. In one such embodiment, the nonabsorbable composition comprises at least 2 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion. By way of further example, in one such embodiment the nonabsorbable composition comprises at least 3 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion. By way of further example, in one such embodiment the nonabsorbable composition comprises at least 4 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion. By way of further example, in one such embodiment the nonabsorbable composition comprises at least 5 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion.

[00288] In one embodiment, the nonabsorbable composition is an anion exchange material comprising less than 10 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion, or a combination thereof. In one such embodiment, the nonabsorbable composition comprises less than 7.5 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion. By way of further example, in one such embodiment the nonabsorbable composition

comprises less than 5 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion. By way of further example, in one such embodiment the nonabsorbable composition comprises less than 2.5 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion. By way of further example, in one such embodiment the nonabsorbable composition comprises less than 1 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion. By way of further example, in one such embodiment the nonabsorbable composition comprises less than 0.1 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion.

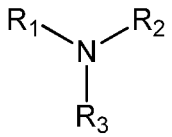
[00289] In one embodiment, the nonabsorbable composition comprises an amphoteric ion exchange resin. Exemplary amphoteric ion-exchange resins include crosslinked polystyrene, polyethylene or the like as a base material and quaternary ammonium group, carboxylic acid group and the like in (i) the same pendant groups (*e.g.*, betaine-containing pendant groups) such as the amphoteric resin sold under the trade designation DIAION AMP03 (Mitsubishi Chemical Corporation) or (ii) different pendant groups (*e.g.*, mixed charged copolymers containing the residues of at least two different monomers, one containing ammonium groups and one containing carboxylic acid groups), to provide a function of ion-exchanging the both of cations and negative ions. Exemplary amphoteric ion-exchange resins containing a mixture of cation and anion exchange sites also include resins in which a linear polymer is trapped inside a crosslinked ion exchange resin, such as the amphoteric resin sold under the trade designation DOWEX™ Retardion 11A8 (Dow Chemical Company).

[00290] In one embodiment, the nonabsorbable composition comprises a neutral composition having the capacity to bind both protons and anions. Exemplary neutral nonabsorbable compositions that bind both protons and anions include polymers functionalized with propylene oxide, polymers functionalized with Michael acceptors, expanded porphyrins, covalent organic frameworks, and polymers containing amine and/or phosphine functional groups.

[00291] In those embodiments in which the nonabsorbable composition binds chloride ions, it is generally preferred that the nonabsorbable composition

selectively bind chloride ions relative to other counter ions such as bicarbonate equivalent anions, phosphate anions, and the conjugate bases of bile and fatty acids. Stated differently, it is generally preferred in these embodiments that the nonabsorbable composition (i) remove more chloride ions than bicarbonate equivalent anions (ii) remove more chloride ions than phosphate anions, and (iii) remove more chloride ions than the conjugate bases of bile and fatty acids. Advantageously, therefore, treatment with the nonabsorbable composition does not induce or exacerbate hypophosphatemia (*i.e.*, a serum phosphorous concentration of less than about 2.4 mg/dL, does not significantly elevate low density lipoproteins ("LDL"), or otherwise negatively impact serum or colon levels of metabolically relevant anions.

[00292] In some embodiments, the pharmaceutical composition comprises a crosslinked polymer containing the residue of an amine corresponding to Formula 1:



Formula 1

wherein R_1, R_2 and R_3 are independently hydrogen, hydrocarbyl, substituted hydrocarbyl provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen. Stated differently, at least one of R_1, R_2 and R_3 is hydrocarbyl or substituted hydrocarbyl, and the others of R_1, R_2 and R_3 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl. In one embodiment, for example, R_1, R_2 and R_3 are independently hydrogen, aryl, aliphatic, heteroaryl, or heteroaliphatic provided, however, each of R_1, R_2 and R_3 are not hydrogen. By way of further example, in one such embodiment R_1, R_2 and R_3 are independently hydrogen, saturated hydrocarbons, unsaturated aliphatic, unsaturated heteroaliphatic, heteroalkyl, heterocyclic, aryl or heteroaryl, provided, however, each of R_1, R_2 and R_3 are not hydrogen. By way of further example, in one such embodiment R_1, R_2 and R_3 are independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic provided, however, each of R_1, R_2 and R_3 are not hydrogen. By way of further example, in one such embodiment R_1, R_2 and R_3 are independently hydrogen, alkyl, aminoalkyl,

alkanol, aryl, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic provided, however, each of R_1, R_2 and R_3 are not hydrogen. By way of further example, in one such embodiment R_1 and R_2 (in combination with the nitrogen atom to which they are attached) together constitute part of a ring structure, so that the monomer as described by Formula 1 is a nitrogen-containing heterocycle (*e.g.*, piperidine) and R_3 is hydrogen, or heteroaliphatic. By way of further example, in one embodiment R_1, R_2 and R_3 are independently hydrogen, aliphatic or heteroaliphatic provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen. By way of further example, in one embodiment R_1, R_2 and R_3 are independently hydrogen, allyl, or aminoalkyl.

[00293] In one embodiment, the crosslinked polymer comprises the residue of an amine corresponding to Formula 1 wherein R_1, R_2, and R_3 are independently hydrogen, heteroaryl, aryl, aliphatic or heteroaliphatic provided, however, at least one of R_1, R_2, and R_3 is aryl or heteroaryl. For example, in this embodiment R_1 and R_2, in combination with the nitrogen atom to which they are attached, may form a saturated or unsaturated nitrogen-containing heterocyclic ring. By way of further example, R_1 and R_2, in combination with the nitrogen atom to which they are attached may constitute part of a pyrrolidino, pyrrole, pyrazolidine, pyrazole, imidazolidine, imidazole, piperidine, pyridine, piperazine, diazine, or triazine ring structure. By way of further example, R_1 and R_2, in combination with the nitrogen atom to which they are attached may constitute part of a piperidine ring structure.

[00294] In one embodiment, the crosslinked polymer comprises the residue of an amine corresponding to Formula 1 wherein R_1, R_2, and R_3 are independently hydrogen, aliphatic, or heteroaliphatic provided, however, at least one of R_1, R_2, and R_3 is other than hydrogen. For example, in this embodiment R_1, R_2, and R_3 may independently be hydrogen, alkyl, alkenyl, allyl, vinyl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, or heterocyclic provided, however, at least one of R_1, R_2, and R_3 is other than hydrogen. By way of further example, in one such embodiment R_1 and R_2, in combination with the nitrogen atom to which they are attached, may form a saturated or unsaturated nitrogen-containing heterocyclic ring. By way of further example, in one such embodiment R_1 and R_2, in combination with the nitrogen atom to which they are attached may constitute part of a pyrrolidino, pyrrole, pyrazolidine, pyrazole, imidazolidine, imidazole, piperidine, piperazine, or diazine ring structure.

By way of further example, in one such embodiment R_1 and R_2, in combination with the nitrogen atom to which they are attached may constitute part of a piperidine ring structure. By way of further example, in one such embodiment the amine corresponding to Formula 1 is acyclic and at least one of R_1, R_2, and R_3 is aliphatic or heteroaliphatic. By way of further example, in one such embodiment R_1, R_2, and R_3 are independently hydrogen, alkyl, allyl, vinyl, alicyclic, aminoalkyl, alkanol, or heterocyclic, provided at least one of R_1, R_2, and R_3 is other than hydrogen.

[00295] In one embodiment, the crosslinked polymer comprises the residue of an amine corresponding to Formula 1 and the crosslinked polymer is prepared by substitution polymerization of the amine corresponding to Formula 1 with a polyfunctional crosslinker (optionally also comprising amine moieties) wherein R_1, R_2, and R_3 are independently hydrogen, alkyl, aminoalkyl, or alkanol, provided at least one of R_1, R_2, and R_3 is other than hydrogen.

[00296] In some embodiments, the molecular weight per nitrogen of the polymers of the present disclosure may range from about 40 to about 1000 Daltons. In one embodiment, the molecular weight per nitrogen of the polymer is from about 40 to about 500 Daltons. In another embodiment, the molecular weight per nitrogen of the polymer is from about 50 to about 170 Daltons. In another embodiment, the molecular weight per nitrogen of the polymer is from about 60 to about 110 Daltons.

[00297] In some embodiments, an amine-containing monomer is polymerized and the polymer is concurrently crosslinked in a substitution polymerization reaction in the first reaction step. The amine reactant (monomer) in the concurrent polymerization and crosslinking reaction can react more than one time for the substitution polymerization. In one such embodiment, the amine monomer is a linear amine possessing at least two reactive amine moieties to participate in the substitution polymerization reaction. In another embodiment, the amine monomer is a branched amine possessing at least two reactive amine moieties to participate in the substitution polymerization reaction. Crosslinkers for the concurrent substitution polymerization and crosslinking typically have at least two amine-reactive moieties such as alkyl-chlorides, and alkyl-epoxides. In order to be incorporated into the polymer, primary amines react at least once and potentially may react up to three times with the crosslinker, secondary amines can react up to twice with the crosslinkers, and tertiary amines can only react once with the

crosslinker. In general, however, the formation of a significant number of quaternary nitrogens/amines is generally not preferred because quaternary amines cannot bind protons.

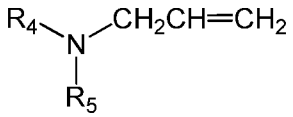
[00298] Exemplary amines that may be used in substitution polymerization reactions described herein include 1,3-Bis[bis(2-aminoethyl)amino]propane, 3-Amino-1-{[2-(bis{2-[bis(3-aminopropyl)amino]ethyl}amino)ethyl](3-aminopropyl)amino}propane, 2-[Bis(2-aminoethyl)amino]ethanamine, Tris(3-aminopropyl)amine, 1,4-Bis[bis(3-aminopropyl)amino]butane, 1,2-Ethanediamine, 2-Amino-1-(2-aminoethylamino)ethane, 1,2-Bis(2-aminoethylamino)ethane, 1,3-Propanediamine, 3,3'-Diaminodipropylamine, 2,2-dimethyl-1,3-propanediamine, 2-methyl-1,3-propanediamine, N,N'-dimethyl-1,3-propanediamine, N-methyl-1,3-diaminopropane, 3,3'-diamino-N-methyldipropylamine, 1,3-diaminopentane, 1,2-diamino-2-methylpropane, 2-methyl-1,5-diaminopentane, 1,2-diaminopropane, 1,10-diaminodecane, 1,8-diaminooctane, 1,9-diaminooctane, 1,7-diaminoheptane, 1,6-diaminohexane, 1,5-diaminopentane, 3-bromopropylamine hydrobromide, N,2-dimethyl-1,3-propanediamine, N-isopropyl-1,3-diaminopropane, N,N'-bis(2-aminoethyl)-1,3-propanediamine, N,N'-bis(3-aminopropyl)ethylenediamine, N,N'-bis(3-aminopropyl)-1,4-butanediamine tetrahydrochloride, 1,3-diamino-2-propanol, N-ethylethylenediamine, 2,2'-diamino-N-methyldiethylamine, N,N'-diethylethylenediamine, N-isopropylethylenediamine, N-methylethylenediamine, N,N'-di-tert-butylethylenediamine, N,N'-diisopropylethylenediamine, N,N'-dimethylethylenediamine, N-butylethylenediamine, 2-(2-aminoethylamino)ethanol, 1,4,7,10,13,16-hexaazacyclooctadecane, 1,4,7,10-tetraazacyclododecane, 1,4,7-triazacyclononane, N,N'-bis(2-hydroxyethyl)ethylenediamine, piperazine, bis(hexamethylene)triamine, N-(3-hydroxypropyl)ethylenediamine, N-(2-Aminoethyl)piperazine, 2-Methylpiperazine, Homopiperazine, 1,4,8,11-Tetraazacyclotetradecane, 1,4,8,12-Tetraazacyclopentadecane, 2-(Aminomethyl)piperidine, 3-(Methylamino)pyrrolidine

[00299] Exemplary crosslinking agents that may be used in substitution polymerization reactions and post-polymerization crosslinking reactions include, but are not limited to, one or more multifunctional crosslinking agents such as: dihaloalkanes, haloalkyloxiranes, alkyloxirane sulfonates, di(haloalkyl)amines, tri(haloalkyl) amines, diepoxides, triepoxides, tetraepoxides, bis

(halomethyl)benzenes, tri(halomethyl)benzenes, tetra(halomethyl)benzenes, epihalohydrins such as epichlorohydrin and epibromohydrin poly(epichlorohydrin), (iodomethyl)oxirane, glycidyl tosylate, glycidyl 3-nitrobenzenesulfonate, 4-tosyloxy-1,2-epoxybutane, bromo-1,2-epoxybutane, 1,2-dibromoethane, 1,3-dichloropropane, 1,2- dichloroethane, l-bromo-2-chloroethane, 1,3- dibromopropane, bis(2-chloroethyl)amine, tris(2- chloroethyl)amine, and bis(2-chloroethyl)methylamine, 1,3-butadiene diepoxide, 1,5-hexadiene diepoxide, diglycidyl ether, 1,2,7,8-diepoxyoctane, 1,2,9,10-diepoxydecane, ethylene glycol diglycidyl ether, propylene glycol diglycidyl ether, 1,4-butanediol diglycidyl ether, 1,2 ethanedioldiglycidyl ether, glycerol diglycidyl ether, 1,3-diglycidyl glyceryl ether, N,N-diglycidylaniline, neopentyl glycol diglycidyl ether, diethylene glycol diglycidyl ether, 1,4-bis(glycidyloxy)benzene, resorcinol digylcidyl ether, 1,6-hexanediol diglycidyl ether, trimethylolpropane diglycidyl ether, 1,4-cyclohexanedimethanol diglycidyl ether, 1,3-bis-(2,3-epoxypropyloxy)-2-(2,3-dihydroxypropyloxy)propane, 1,2-cyclohexanedicarboxylic acid diglycidyl ester, 2,2'-bis(glycidyloxy) diphenylmethane, bisphenol F diglycidyl ether, 1,4-bis(2',3'epoxypropyl)perfluoro-n-butane, 2,6-di(oxiran-2-ylmethy1)-1,2,3,5,6,7-hexahydropyrrolo[3,4-f]isoindol-1,3,5,7- tetraone, bisphenol A diglycidyl ether, ethyl 5-hydroxy-6,8- di(oxiran-2-ylmethyl)-4-oxo-4-h-chromene-2-carboxylate, bis[4-(2,3-epoxy-propylthio)phenyl]-sulfide, 1,3-bis(3-glycidoxypropyl) tetramethyldisiloxane, 9,9-bis[4-(glycidyloxy)phenyl]fluorine, triepoxyisocyanurate, glycerol triglycidyl ether, N,N-diglycidyl-4-glycidyloxyaniline, isocyanuric acid (S,S,S)-triglycidyl ester, isocyanuric acid (R,R,R)-triglycidyl ester, triglycidyl isocyanurate, trimethylolpropane triglycidyl ether, glycerol propoxylate triglycidyl ether, triphenylolmethane triglycidyl ether, 3,7,14-tris[[3-(epoxypropoxy)propyl]dimethylsilyloxy]-1,3,5,7,9,11,14- heptacyclopentyltricyclo [7,3,3,15, 11]heptasiloxane, 4,4 'methylenebis(N,N-diglycidylaniline), bis(halomethyl)benzene, bis(halomethyl)biphenyl and bis(halomethyl)naphthalene, toluene diisocyanate, acrylol chloride, methyl acrylate, ethylene bisacrylamide, pyrometallic dianhydride, succinyl dichloride, dimethylsuccinate, 3-chloro-1-(3-chloropropylamino-2-propanol, 1,2-bis(3-chloropropylamino)ethane, Bis(3-chloropropyl)amine, 1,3-Dichloro-2-propanol, 1,3-Dichloropropane, 1-chloro-2,3-epoxypropane, tris[(2-oxiranyl)methyl]amine.

[00300] In some embodiments, the carbon to nitrogen ratio of the polymers of the present disclosure may range from about 2:1 to about 6:1, respectively. For example, in one such embodiment, the carbon to nitrogen ratio of the polymers of the present disclosure may range from about 2.5:1 to about 5:1, respectively. By way of further example, in one such embodiment, the carbon to nitrogen ratio of the polymers of the present disclosure may range from about 3:1 to about 4.5:1, respectively. By way of further example, in one such embodiment, the carbon to nitrogen ratio of the polymers of the present disclosure may range from about 3.25:1 to about 4.25:1, respectively. By way of further example, in one such embodiment, the carbon to nitrogen ratio of the polymers of the present disclosure may range from about 3.4:1 to about 4:1, respectively. In another embodiment, the molecular weight per nitrogen of the polymer is from about 60 to about 110 Daltons.

[00301] In some embodiments, the crosslinked polymer comprises the residue of an amine corresponding to Formula 1a and the crosslinked polymer is prepared by radical polymerization of an amine corresponding to Formula 1a:

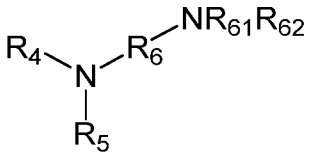


Formula 1a

wherein R_4 and R_5 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl. In one embodiment, for example, R_4 and R_5 are independently hydrogen, saturated hydrocarbon, unsaturated aliphatic, aryl, heteroaryl, unsaturated heteroaliphatic, heterocyclic, or heteroalkyl. By way of further example, in one such embodiment R_4 and R_5 are independently hydrogen, aliphatic, heteroaliphatic, aryl, or heteroaryl. By way of further example, in one such embodiment R_4 and R_5 are independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic. By way of further example, in one such embodiment R_4 and R_5 are independently hydrogen, alkyl, allyl, aminoalkyl, alkanol, aryl, haloalkyl, hydroxyalkyl, ethereal, or heterocyclic. By way of further example, in one such embodiment R_4 and R_5 (in combination with the nitrogen atom to which they are attached) together constitute part of a ring structure, so that the monomer as described by Formula 1a is a nitrogen-containing heterocycle (*e.g.*, piperidine). By way of further example, in one embodiment R_4 and

R_5 are independently hydrogen, aliphatic or heteroaliphatic. By way of further example, in one embodiment R_4 and R_5 are independently hydrogen, allyl, or aminoalkyl.

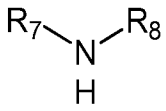
[00302] In some embodiments, the crosslinked polymer comprises the residue of an amine corresponding to Formula 1b and the crosslinked polymer is prepared by substitution polymerization of the amine corresponding to Formula 1b with a polyfunctional crosslinker (optionally also comprising amine moieties):



Formula 1b

wherein R_4 and R_5 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl, R_6 is aliphatic and R_{61} and R_{62} are independently hydrogen, aliphatic, or heteroaliphatic. In one embodiment, for example, R_4 and R_5 are independently hydrogen, saturated hydrocarbon, unsaturated aliphatic, aryl, heteroaryl, heteroalkyl, or unsaturated heteroaliphatic. By way of further example, in one such embodiment R_4 and R_5 are independently hydrogen, aliphatic, heteroaliphatic, aryl, or heteroaryl. By way of further example, in one such embodiment R_4 and R_5 are independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic. By way of further example, in one such embodiment R_4 and R_5 are independently hydrogen, alkyl, alkenyl, aminoalkyl, alkanol, aryl, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic. By way of further example, in one such embodiment R_4 and R_5 (in combination with the nitrogen atom to which they are attached) together constitute part of a ring structure, so that the monomer as described by Formula 1a is a nitrogen-containing heterocycle (*e.g.*, piperidine). By way of further example, in one embodiment R_4 and R_5 are independently hydrogen, aliphatic or heteroaliphatic. By way of further example, in one embodiment R_4 and R_5 are independently hydrogen, allyl, or aminoalkyl. By way of further example, in each of the embodiments recited in this paragraph, R_6 may be methylene, ethylene or propylene, and R_{61} and R_{62} may independently be hydrogen, allyl or aminoalkyl.

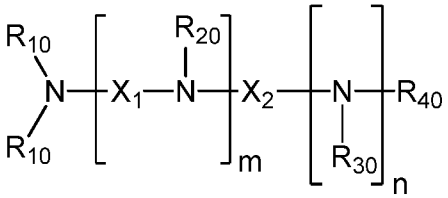
[00303] In some embodiments, the crosslinked polymer comprises the residue of an amine corresponding to Formula 1c:



Formula 1c

wherein R_7 is hydrogen, aliphatic or heteroaliphatic and R_8 is aliphatic or heteroaliphatic. For example, in one such embodiment, for example, R_7 is hydrogen and R_8 is aliphatic or heteroaliphatic. By way of further example, in one such embodiment R_7 and R_8 are independently aliphatic or heteroaliphatic. By way of further example, in one such embodiment at least one of R_7 and R_8 comprises an allyl moiety. By way of further example, in one such embodiment at least one of R_7 and R_8 comprises an aminoalkyl moiety. By way of further example, in one such embodiment R_7 and R_8 each comprise an allyl moiety. By way of further example, in one such embodiment R_7 and R_8 each comprise an aminoalkyl moiety. By way of further example, in one such embodiment R_7 comprises an allyl moiety and R_8 comprises an aminoalkyl moiety.

[00304] In some embodiments, the crosslinked polymer comprises the residue of an amine corresponding to Formula 2:

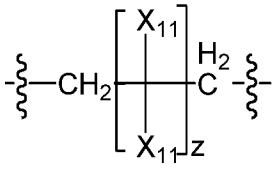


Formula 2

wherein

m and n are independently non-negative integers;

R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl;

X_1 is  ;

X_2 is hydrocarbyl or substituted hydrocarbyl;

each X_{11} is independently hydrogen, hydrocarbyl, substituted hydrocarbyl, hydroxyl, amino, boronic acid, or halo; and

z is a non-negative number.

[00305] In one embodiment, the crosslinked polymer comprises the residue of an amine corresponding to Formula 2, the crosslinked polymer is prepared by (i) substitution polymerization of the amine corresponding to Formula 2 with a polyfunctional crosslinker (optionally also comprising amine moieties) or (2) radical polymerization of an amine corresponding to Formula 2, and m and n are independently 0, 1, 2 or 3 and n is 0 or 1.

[00306] In one embodiment, the crosslinked polymer comprises the residue of an amine corresponding to Formula 2, the crosslinked polymer is prepared by (i) substitution polymerization of the amine corresponding to Formula 2 with a polyfunctional crosslinker (optionally also comprising amine moieties) or (2) radical polymerization of an amine corresponding to Formula 2, and R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, aliphatic, aryl, heteroaliphatic, or heteroaryl. By way of further example, in one such embodiment R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, aliphatic, or heteroaliphatic. By way of further example, in one such embodiment R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, alkyl, allyl, vinyl, or aminoalkyl. By way of further example, in one such embodiment R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, alkyl, allyl, vinyl, $-(CH_2)_dNH_2$, $-(CH_2)_dN[(CH_2)_eNH_2)]_2$ where d and e are independently 2-4. In each of the foregoing exemplary embodiments of this paragraph, m and z may independently be 0, 1, 2 or 3 and n is 0 or 1.

[00307] In one embodiment, the crosslinked polymer comprises the residue of an amine corresponding to Formula 2, the crosslinked polymer is prepared by (i) substitution polymerization of the amine corresponding to Formula 2 with a polyfunctional crosslinker (optionally also comprising amine moieties) or (2) radical polymerization of an amine corresponding to Formula 2, and X_2 is aliphatic or heteroaliphatic. For example, in one such embodiment X_2 is aliphatic or heteroaliphatic and R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, aliphatic, heteroaliphatic. By way of further example, in one such embodiment X_2 is alkyl or

aminoalkyl and R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, aliphatic, or heteroaliphatic. By way of further example, in one such embodiment X_2 is alkyl or aminoalkyl and R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, alkyl, allyl, vinyl, or aminoalkyl. In each of the foregoing exemplary embodiments of this paragraph, m and z may independently be 0, 1, 2 or 3 and n is 0 or 1.

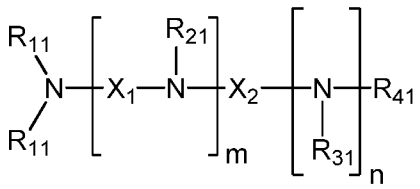
[00308] In one embodiment, the crosslinked polymer comprises the residue of an amine corresponding to Formula 2, the crosslinked polymer is prepared by (i) substitution polymerization of the amine corresponding to Formula 2 with a polyfunctional crosslinker (optionally also comprising amine moieties) or (2) radical polymerization of an amine corresponding to Formula 2, and m is a positive integer. For example, in one such embodiment m is a positive integer, z is zero and R_{20} is hydrogen, aliphatic or heteroaliphatic. By way of further example, in one such embodiment m is a positive integer (*e.g.*, 1 to 3), z is a positive integer (*e.g.*, 1 to 2), X_{11} is hydrogen, aliphatic or heteroaliphatic, and R_{20} is hydrogen, aliphatic or heteroaliphatic. By way of further example, in one such embodiment m is a positive integer, z is zero, one or two, X_{11} is hydrogen alkyl, alkenyl, or aminoalkyl, and R_{20} is hydrogen, alkyl, alkenyl, or aminoalkyl.

[00309] In one embodiment, the crosslinked polymer comprises the residue of an amine corresponding to Formula 2, the crosslinked polymer is prepared by (i) substitution polymerization of the amine corresponding to Formula 2 with a polyfunctional crosslinker (optionally also comprising amine moieties) or (2) radical polymerization of an amine corresponding to Formula 2, and n is a positive integer and R_{30} is hydrogen, aliphatic or heteroaliphatic. By way of further example, in one such embodiment n is 0 or 1, and R_{30} is hydrogen, alkyl, alkenyl, or aminoalkyl.

[00310] In one embodiment, the crosslinked polymer comprises the residue of an amine corresponding to Formula 2, the crosslinked polymer is prepared by (i) substitution polymerization of the amine corresponding to Formula 2 with a polyfunctional crosslinker (optionally also comprising amine moieties) or (2) radical polymerization of an amine corresponding to Formula 2, and m and n are independently non-negative integers and X_2 is aliphatic or heteroaliphatic. For example, in one such embodiment m is 0 to 2, n is 0 or 1, X_2 is aliphatic or heteroaliphatic, and R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, aliphatic, or heteroaliphatic. By way of further example, in one such embodiment m is 0 to 2, n is

0 or 1, X_2 is alkyl or aminoalkyl, and R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, aliphatic, or heteroaliphatic. By way of further example, in one such embodiment m is 0 to 2, n is 0 or 1, X_2 is alkyl or aminoalkyl, and R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, alkyl, alkenyl, or aminoalkyl.

[00311] In some embodiments, the crosslinked polymer comprises the residue of an amine corresponding to Formula 2a and the crosslinked polymer is prepared by substitution polymerization of the amine corresponding to Formula 2a with a polyfunctional crosslinker (optionally also comprising amine moieties):



Formula 2a

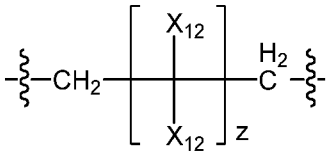
wherein

m and n are independently non-negative integers;

each R_{11} is independently hydrogen, hydrocarbyl, heteroaliphatic, or heteroaryl;

R_{21} and R_{31}, are independently hydrogen or heteroaliphatic;

R_{41} is hydrogen, substituted hydrocarbyl, or hydrocarbyl;

X_1 is  ;

X_2 is alkyl or substituted hydrocarbyl;

each X_{12} is independently hydrogen, hydroxy, amino, aminoalkyl, boronic acid or halo; and

z is a non-negative number.

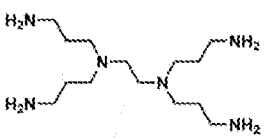
[00312] In one embodiment, the crosslinked polymer comprises the residue of an amine corresponding to Formula 2a, the crosslinked polymer is prepared by substitution polymerization of the amine corresponding to Formula 1 with a

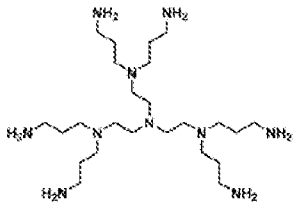
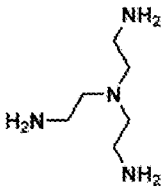
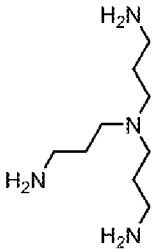
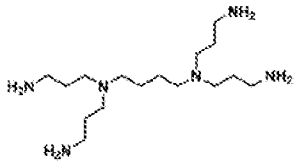
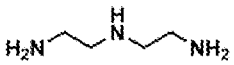
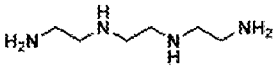
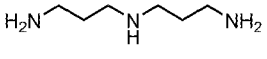
polyfunctional crosslinker (optionally also comprising amine moieties). For example, in one such embodiment, m and z are independently 0, 1, 2 or 3, and n is 0 or 1.

[00313] In one embodiment, the crosslinked polymer comprises the residue of an amine corresponding to Formula 2a, the crosslinked polymer is prepared by substitution polymerization of the amine corresponding to Formula 2a with a polyfunctional crosslinker (optionally also comprising amine moieties), and each R_{11} is independently hydrogen, aliphatic, aminoalkyl, haloalkyl, or heteroaryl, R_{21} and R_{31} are independently hydrogen or heteroaliphatic and R_{41} is hydrogen, aliphatic, aryl, heteroaliphatic, or heteroaryl. For example, in one such embodiment each R_{11} is hydrogen, aliphatic, aminoalkyl, or haloalkyl, R_{21} and R_{31} are independently hydrogen or heteroaliphatic and R_{41} is hydrogen, alkylamino, aminoalkyl, aliphatic, or heteroaliphatic. By way of further example, in one such embodiment each R_{11} is hydrogen, aliphatic, aminoalkyl, or haloalkyl, R_{21} and R_{31} are hydrogen or aminoalkyl, and R_{41} is hydrogen, aliphatic, or heteroaliphatic. By way of further example, in one such embodiment each R_{11} and R_{41} is independently hydrogen, alkyl, or aminoalkyl, and R_{21} and R_{31} are independently hydrogen or heteroaliphatic. By way of further example, in one such embodiment each R_{11} and R_{41} is independently hydrogen, alkyl, $–(CH_2)_dNH_2$, $–(CH_2)_dN[(CH_2)_eNH_2)]_2$ where d and e are independently 2-4, and R_{21} and R_{31} are independently hydrogen or heteroaliphatic. In each of the foregoing exemplary embodiments of this paragraph, m and z may independently be 0, 1, 2 or 3, and n is 0 or 1.

[00314] Exemplary amines for the synthesis of polymers comprising repeat units corresponding to Formula 2a include, but are not limited to, amines appearing in Table A.

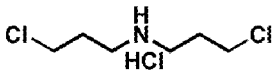
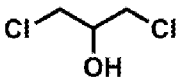
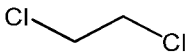
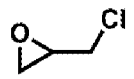
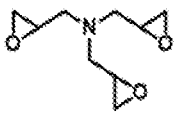
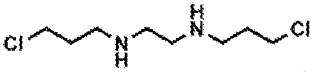
Table A

Abbreviation	IUPAC name	Other names		MW (g/mol)
C2A3BTA	1,3-Bis[bis(2-aminoethyl)amino]propane			288.48

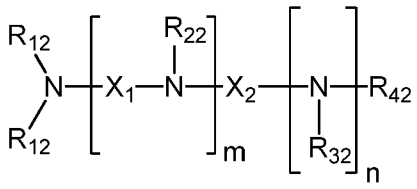
C2A3G2	3-Amino-1-{[2-(bis{2-[bis(3-aminopropyl)amino]ethyl}amino)ethyl](3-aminopropyl)amino}propane			488.81
C2PW	2-[Bis(2-aminoethyl)amino]ethanamine	2,2′,2″-Triaminotriethylamine or 2,2′,2″-Nitrilotriethylamine		146.24
C3PW	Tris(3-aminopropyl)amine			188.32
C4A3BTA	1,4-Bis[bis(3-aminopropyl)amino]butane			316.54
EDA1	1,2-Ethanediamine			60.1
EDA2	2-Amino-1-(2-aminoethylamino)ethane	Bis(2-aminoethyl)amine or 2,2′-Diaminodiethylamine		103.17
EDA3	1,2-Bis(2-aminoethylamino)ethane	*N,N′-Bis*(2-aminoethyl)ethane-1,2-diamine		146.24
PDA1	1,3-Propanediamine			74.3
PDA2	3,3'-Diaminodipropylamine			131.22

[00315] Exemplary crosslinkers for the synthesis of polymers comprising the residue of amines corresponding to Formula 2a include but are not limited to crosslinkers appearing in Table B.

Table B

Abbreviation	Common name	IUPAC name		MW (g/mol)
BCPA	Bis(3-chloropropyl)amine	Bis(3-chloropropyl)amine		206.54
DC2OH	1,3-dichloroisopropanol	1,3-Dichloro-2-propanol		128.98
DCE	dichloroethane	1,2- dichloroethane		98.96
DCP	Dichloropropane	1,3-Dichloropropane		112.98
ECH	Epichlorohydrin	1-chloro-2,3-epoxypropane		92.52
TGA	Triglycidyl amine	Tris[(2-oxiranyl)methyl]amine		185.22
BCPOH	Bis(3-chloropropyl) amine-OH	3-Chloro-1-(3-chloropropylamino)-2-propanol		186.08
BCPEDA	Bis(chloropropyl) ethylenediamine	1,2-Bis(3-chloropropylamino)ethane		213.15

[00316] In some embodiments, the crosslinked polymer comprises the residue of an amine corresponding to Formula 2b and the crosslinked polymer is prepared by radical polymerization of an amine corresponding to Formula 2b:



Formula 2b

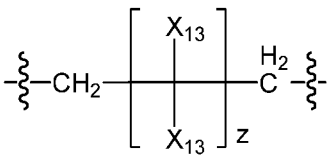
wherein

m and n are independently non-negative integers;

each R_{12} is independently hydrogen, substituted hydrocarbyl, or hydrocarbyl;

R_{22} and R_{32} are independently hydrogen substituted hydrocarbyl, or hydrocarbyl;

R_{42} is hydrogen, hydrocarbyl or substituted hydrocarbyl;

X_1 is  ;

X_2 is alkyl, aminoalkyl, or alkanol;

each X_{13} is independently hydrogen, hydroxy, alicyclic, amino, aminoalkyl, halogen, alkyl, heteroaryl, boronic acid or aryl;

z is a non-negative number, and

the amine corresponding to Formula 2b comprises at least one allyl group.

[00317] In one embodiment, the crosslinked polymer comprises the residue of an amine corresponding to Formula 2b, the crosslinked polymer is prepared by radical polymerization of an amine corresponding to Formula 2b, and m and z are independently 0, 1, 2 or 3, and n is 0 or 1.

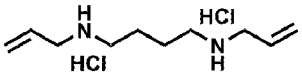
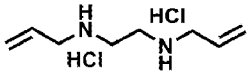
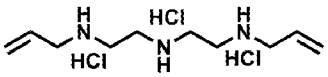
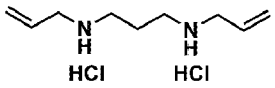
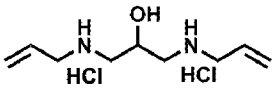
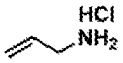
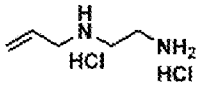
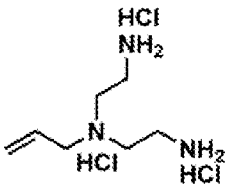
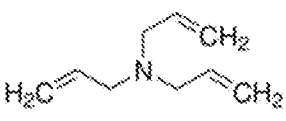
[00318] In one embodiment, the crosslinked polymer comprises the residue of an amine corresponding to Formula 2b, the crosslinked polymer is prepared by radical polymerization of an amine corresponding to Formula 1, and (i) R_{12} or R_{42} independently comprise at least one allyl or vinyl moiety, (ii) m is a positive integer

and R_{22} comprises at least one allyl or vinyl moiety, and/or (iii) n is a positive integer and R_{32} comprises at least one allyl moiety. For example, in one such embodiment, m and z are independently 0, 1, 2 or 3 and n is 0 or 1. For example, in one such embodiment R_{12} or R_{42}, in combination comprise at least two allyl or vinyl moieties. By way of further example, in in one such embodiment, m is a positive integer and R_{12}, R_{22} and R_{42}, in combination comprise at least two allyl or vinyl moieties. By way of further example, in in one such embodiment, n is a positive integer and R_{12}, R_{32} and R_{42}, in combination comprise at least two allyl or vinyl moieties. By way of further example, in in one such embodiment, m is a positive integer, n is a positive integer and R_{12}, R_{22}, R_{32} and R_{42}, in combination, comprise at least two allyl or vinyl moieties.

[00319] In one embodiment, the crosslinked polymer comprises the residue of an amine corresponding to Formula 2b, the crosslinked polymer is prepared by radical polymerization of an amine corresponding to Formula 2b, and each R_{12} is independently hydrogen, aminoalkyl, allyl, or vinyl, R_{22} and R_{32} are independently hydrogen, alkyl, aminoalkyl, haloalkyl, alkenyl, alkanol, heteroaryl, alicyclic heterocyclic, or aryl, and R_{42} is hydrogen or substituted hydrocarbyl. For example, in one such embodiment each R_{12} is aminoalkyl, allyl or vinyl, R_{22} and R_{32} are independently hydrogen, alkyl, aminoalkyl, haloalkyl, alkenyl, or alkanol, and R_{42} is hydrogen or substituted hydrocarbyl. By way of further example, in one such embodiment each R_{12} and R_{42} is independently hydrogen, alkyl, allyl, vinyl, $-(CH_2)_dNH_2$ or $-(CH_2)_dN[(CH_2)_eNH_2]_2$ where d and e are independently 2-4, and R_{22} and R_{32} are independently hydrogen or heteroaliphatic.

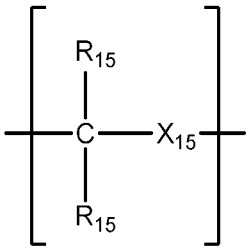
[00320] Exemplary amines and crosslinkers (or the salts thereof, for example the hydrochloric acid, phosphoric acid, sulfuric acid, or hydrobromic acid salts thereof) for the synthesis of polymers described by Formula 2b include but are not limited to the ones in Table C.

Table C

Abbreviation	Common name	IUPAC name		MW (g/mol)
DABDA1	Diallylbutyldiamine	1,4-Bis(allylamino) butane		241.2
DAEDA1	Diallylethyldiamine	1,2-Bis(allylamino) ethane		213.15
DAEDA2	Diallyldiethylenetriamine	2-(Allylamino)-1-[2-(allylamino)ethylamino]ethane		292.67
DAPDA	Diallylpropyldiamine	1,3-Bis(allylamino) propane		227.17
POHDA	Diallylamineisopropanol	1,3-Bis(allylamino)-2-propanol		243.17
AAH	Allylamine	2-Propen-1-ylamine		93.5
AEAAH	Aminoethylallylamine	1-(Allylamino)-2-aminoethane		173.08
BAEAAH	Bis(2-aminoethyl)allylamine	1-[*N*-Allyl(2-aminoethyl)amino]-2-aminoethane		252.61
TAA	Triallylamine	*N,N,N*-triallylamine		137.22

[00321] In some embodiments, the crosslinked polymer is derived from a reaction of the resulting polymers that utilize monomers described in any of

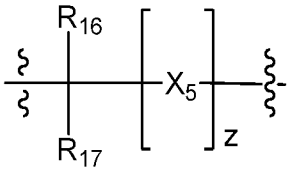
Formulae 1, 1a, 1b, 1c, 2, 2a and 2b or a linear polymer comprised of a repeat unit described by Formula 3 with external crosslinkers or pre-existing polymer functionality that can serve as crosslinking sites. Formula 3 can be a repeat unit of a copolymer or terpolymer where X_{15} is either a random, alternating, or block copolymer. The repeating unit in Formula 3 can also represent the repeating unit of a polymer that is branched, or hyperbranched, wherein the primary branch point can be from any atom in the main chain of the polymer:



Formula 3

wherein

R_{15}, R_{16} and R_{17} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, hydroxyl, amino, boronic acid or halo;

X_{15} is 

,

X_5 is hydrocarbyl, substituted hydrocarbyl, oxo (-O-), or amino and

z is a non-negative number.

[00322] In one embodiment, R_{15}, R_{16} and R_{17} are independently hydrogen, aryl, or heteroaryl, X_5 is hydrocarbyl, substituted hydrocarbyl, oxo or amino, and m and z are non-negative integers. In another embodiment, R_{15}, R_{16} and R_{17} are independently aliphatic or heteroaliphatic, X_5 is hydrocarbyl, substituted hydrocarbyl, oxo (-O-) or amino, and m and z are non-negative integers. In another embodiment, R_{15}, R_{16} and R_{17} are independently unsaturated aliphatic or unsaturated heteroaliphatic, X_5 is hydrocarbyl, substituted hydrocarbyl, oxo, or amino, and z is a non-negative integer. In another embodiment, R_{15}, R_{16} and R_{17} are independently alkyl or heteroalkyl, X_5 is hydrocarbyl, substituted hydrocarbyl, oxo, or amino, and z is a non-negative integer. In another embodiment, R_{15}, R_{16} and R_{17} are

independently alkylamino, aminoalkyl, hydroxyl, amino, boronic acid, halo, haloalkyl, alkanol, or ethereal, X_5 is hydrocarbyl, substituted hydrocarbyl, oxo, or amino, and z is a non-negative integer. In another embodiment, R_{15}, R_{16} and R_{17} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, hydroxyl, amino, boronic acid or halo, X_5 is oxo, amino, alkylamino, ethereal, alkanol, or haloalkyl, and z is a non-negative integer.

[00323] Exemplary crosslinking agents that may be used in radical polymerization reactions include, but are not limited to, one or more multifunctional crosslinking agents such as: 1,4-bis(allylamino)butane, 1,2-bis(allylamino)ethane, 2-(allylamino)-1-[2-(allylamino)ethylamino]ethane, 1,3-bis(allylamino)propane, 1,3-bis(allylamino)-2-propanol, triallylamine, diallylamine, divinylbenzene, 1,7-octadiene, 1,6-heptadiene, 1,8-nonadiene, 1,9-decadiene, 1,4-divinyloxybutane, 1,6-hexamethylenebisacrylamide, ethylene bisacrylamide, N,N′-bis(vinylsulfonylacetyl)ethylene diamine, 1,3-bis(vinylsulfonyl) 2-propanol, vinylsulfone, N,N′-methylenebisacrylamide polyvinyl ether, polyallylether, divinylbenzene, 1,4-divinyloxybutane, and combinations thereof.

[00324] Crosslinked polymers derived from the monomers and polymers in formulas 1 through 3 may be synthesized either in solution or bulk or in dispersed media. Examples of solvents that are suitable for the synthesis of polymers of the present disclosure include, but are not limited to water, low boiling alcohols (methanol, ethanol, propanol, butanol), dimethylformamide, dimethylsulfoxide, heptane, chlorobenzene, toluene.

[00325] Alternative polymer processes may include, a lone polymerization reaction, stepwise addition of individual starting material monomers via a series of reactions, the stepwise addition of blocks of monomers, combinations or any other method of polymerization such as living polymerization, direct polymerization, indirect polymerization, condensation, radical, emulsion, precipitation approaches, spray dry polymerization or using some bulk crosslinking reaction methods and size reduction processes such as grinding, compressing, extrusion. Processes can be carried out as a batch, semi-continuous and continuous processes. For processes in dispersed media, the continuous phase can be non-polar solvents, such as toluene, benzene, hydrocarbon, halogenated solvents, super critical carbon dioxide. With a

direct suspension reaction, water can be used and salt can be used to tune the properties of the suspension.

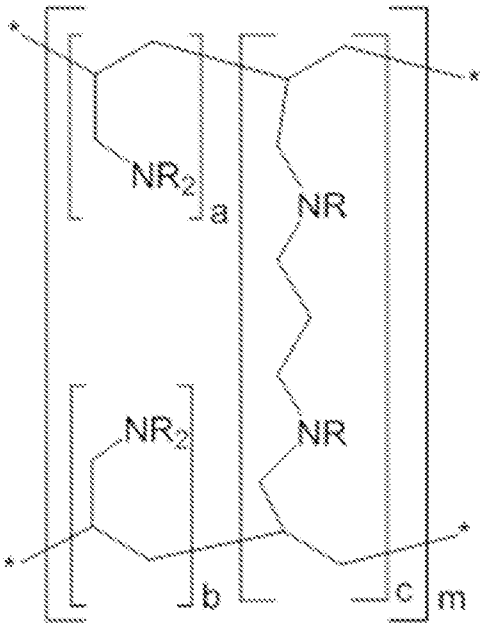
[00326] The starting molecules described in formulas 1 through 3 may be copolymerized with one or more other monomers of the invention, oligomers or other polymerizable groups. Such copolymer architectures can include, but are not limited to, block or block-like polymers, graft copolymers, and random copolymers. Incorporation of monomers described by formulas 1 through 3 can range from 1% to 99%. In some embodiments, the incorporation of comonomer is between 20% and 80%.

[00327] Non-limiting examples of comonomers which may be used alone or in combination include: styrene, allylamine hydrochloride, substituted allylamine hydrochloride, substituted styrene, alkyl acrylate, substituted alkyl acrylate, alkyl methacrylate, substituted alkyl methacrylate, acrylonitrile, methacrylonitrile, acrylamide, methacrylamide, N-alkylacrylamide, N-alkylmethacrylamide, N,N-dialkylacrylamide, N,N-dialkylmethacrylamide, isoprene, butadiene, ethylene, vinyl acetate, N-vinyl amide, maleic acid derivatives, vinyl ether, allyl, methallyl monomers and combinations thereof. Functionalized versions of these monomers may also be used. Additional specific monomers or comonomers that may be used in this invention include, but are not limited to, 2-propen-1-ylamine, 1-(allylamino)-2-aminoethane, 1-[N-allyl(2-aminoethyl)amino]-2-aminoethane, methyl methacrylate, ethyl methacrylate, propyl methacrylate (all isomers), butyl methacrylate (all isomers), 2-ethylhexyl methacrylate, isobornyl methacrylate, methacrylic acid, benzyl methacrylate, phenyl methacrylate, methacrylonitrile, amethylstyrene, methyl acrylate, ethyl acrylate, propyl acrylate (all isomers), butyl acrylate (all isomers), 2-ethylhexyl acrylate, isobornyl acrylate, acrylic acid, benzyl acrylate, phenyl acrylate, acrylonitrile, styrene, glycidyl methacrylate, 2-hydroxyethyl methacrylate, hydroxypropyl methacrylate (all isomers), hydroxybutyl methacrylate (all isomers), N,N-dimethylaminoethyl methacrylate, N,N-diethylaminoethyl methacrylate, triethyleneglycol methacrylate, itaconic anhydride, itaconic acid, glycidyl acrylate, 2-hydroxyethyl acrylate, hydroxypropyl acrylate (all isomers), hydroxybutyl acrylate (all isomers), N,N-dimethylaminoethyl acrylate, N,N-diethylaminoethyl acrylate, triethyleneglycol acrylate, methacrylamide, N-methylacrylamide, N,N-dimethylacrylamide, N-tert-butylmethacrylamide, N,N-butylmethacrylamide, N-

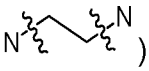
methylolmethacrylamide, N-ethylolmethacrylamide, N-tert-butylacryl amide, N,N-butylacrylamide, N-methylolacrylamide, N-ethylolacrylamide, 4-acryloylmorpholine, vinyl benzoic acid (all isomers), diethylaminostyrene (all isomers), a-methylvinyl benzoic acid (all isomers), diethylamino a-methylstyrene (all isomers), p-vinylbenzene sulfonic acid, p-vinylbenzene sulfonic sodium salt, trimethoxysilylpropyl methacrylate, triethoxysilylpropyl methacrylate, tributoxysilylpropyl methacrylate, dimethoxymethylsilylpropyl methacrylate, diethoxymethylsilylpropyl methacrylate, dibutoxymethylsilylpropyl methacrylate, diisopropoxymethylsilylpropyl methacrylate, dimethoxysilylpropyl methacrylate, diethoxysilylpropyl methacrylate, dibutoxysilylpropyl methacrylate, diisopropoxysilylpropyl methacrylate, trimethoxysilylpropyl acrylate, triethoxysilylpropyl acrylate, tributoxysilylpropyl acrylate, dimethoxymethylsilylpropyl acrylate, diethoxymethylsilylpropyl acrylate, dibutoxymethylsilylpropyl acrylate, diisopropoxymethylsilylpropyl acrylate, dimethoxysilylpropyl acrylate, diethoxysilylpropyl acrylate, dibutoxysilylpropyl acrylate, diisopropoxysilylpropyl acrylate, maleic anhydride, N-phenylmaleimide, N-butylmaleimide, N-vinylformamide, N-vinyl acetamide, allylamine, methallylamine, allylalcohol, methyl-vinylether, ethylvinylether, butylvinyltether, butadiene, isoprene, chloroprene, ethylene, vinyl acetate, and combinations thereof.

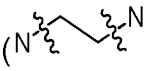
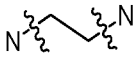
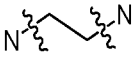
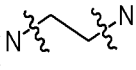
[00328] Additional modification to the preformed crosslinked polymer can be achieved through the addition of modifiers, including but not limited to amine monomers, additional crosslinkers, and polymers. Modification can be accomplished through covalent or non-covalent methods. These modifications can be evenly or unevenly dispersed throughout the preformed polymer material, including modifications biased to the surface of the preformed crosslinked polymer. Furthermore, modifications can be made to change the physical properties of the preformed crosslinked polymer, including but not limited to reactions that occur with remaining reactive groups such as haloalkyl groups and allyl groups in the preformed polymer. Reactions and modifications to the preformed crosslinked polymer can include but are not limited to acid-base reactions, nucleophilic substitution reactions, Michael reactions, non-covalent electrostatic interactions, hydrophobic interactions, physical interactions (crosslinking) and radical reactions.

[00329] In one embodiment, the post-polymerization crosslinked amine polymer is a crosslinked amine polymer comprising a structure corresponding to Formula 4:



Formula 4

wherein each R is independently hydrogen or an ethylene crosslink between two nitrogen atoms of the crosslinked amine polymer () and a, b, c, and m are integers. Typically, m is a large integer indicating an extended polymer network. In one such embodiment, a ratio of the sum of a and b to c (*i.e.*, a+b:c) is in the range of about 1:1 to 5:1. For example, in one such embodiment a ratio of the sum of a and b to c (*i.e.*, a+b:c) is in the range of about 1.5:1 to 4:1. By way of further example, in one such embodiment a ratio of the sum of a and b to c (*i.e.*, a+b:c) is in the range of about 1.75:1 to 3:1. For example, in one such embodiment a ratio of the sum of a and b is 57, c is 24 and m is large integer indicating an extended polymer network. In each of the foregoing embodiments a ratio of the sum of a and b to c (*i.e.*, a+b:c) may be in the range of about 2:1 to 2.5:1. For example, in such embodiments the ratio of the sum of a and b to c (*i.e.*, a+b:c) may be in the range of about 2.1:1 to 2.2:1. By way of further example, in such embodiments the ratio of the sum of a and b to c (*i.e.*, a+b:c) may be in the range of about 2.2:1 to 2.3:1. By way of further example, in such embodiments the ratio of the sum of a and b to c (*i.e.*, a+b:c) may be in the range of about 2.3:1 to 2.4:1. By way of further example, in such embodiments the ratio of the sum of a and b to c (*i.e.*, a+b:c) may be in the

range of about 2.4:1 to 2.5:1. In each of the foregoing embodiments, each R may independently be hydrogen or an ethylene crosslink between two nitrogen atoms. Typically, however, 35-95% of the R substituents will be hydrogen and 5-65% will be an ethylene crosslink (). For example, in one such embodiment, 50-95% of the R substituents will be hydrogen and 5-50% will be an ethylene crosslink (). For example, in one such embodiment, 55-90% of the R substituents are hydrogen and 10-45% are an ethylene crosslink (). By way of further example, in one such embodiment, 60-90% of the R substituents are hydrogen and 10-40% are an ethylene crosslink. By way of further example, in one such embodiment, 65-90% of the R substituents are hydrogen and 10-35% are an ethylene crosslink. (). By way of further example, in one such embodiment, 70-90% of the R substituents are hydrogen and 10-30% are an ethylene crosslink. By way of further example, in one such embodiment, 75-85% of the R substituents are hydrogen and 15-25% are an ethylene crosslink. By way of further example, in one such embodiment, 65-75% of the R substituents are hydrogen and 25-35% are an ethylene crosslink. By way of further example, in one such embodiment, 55-65% of the R substituents are hydrogen and 35-45% are an ethylene crosslink. In some embodiments, a, b, c and R are such that the carbon to nitrogen ratio of the polymer of Formula 4 may range from about 2:1 to about 6:1, respectively. For example, in one such embodiment, the carbon to nitrogen ratio of the polymer of Formula 4 may range from about 2.5:1 to about 5:1, respectively. By way of further example, in one such embodiment, the carbon to nitrogen ratio of the polymer of Formula 4 may range from about 3:1 to about 4.5:1, respectively. By way of further example, in one such embodiment, the carbon to nitrogen ratio of the polymer of Formula 4 may range from about 3.25:1 to about 4.25:1, respectively. By way of further example, in one such embodiment, the carbon to nitrogen ratio of the polymer of Formula 4 may range from about 3.4:1 to about 4:1, respectively. By way of further example, in one such embodiment, the carbon to nitrogen ratio of the polymer of Formula 4 may range from about 3.5:1 to about 3.9:1, respectively. By way of further example, in one such embodiment, the carbon to nitrogen ratio of the polymer of Formula 4 may range from about 3.55:1 to about 3.85:1, respectively. In each of the foregoing

embodiments recited in this paragraph, the polymer of Formula 4 is derived from monomers and crosslinkers, each of which comprise less than 5 wt% oxygen.

[00330] In certain embodiments, polymers in which crosslinking and/or entanglement were increased were found to have lower swelling than those with lower crosslinking and/or entanglement, yet also had a binding capacity for target ion (e.g., chloride) that was as great as or greater than the lower crosslinking and/or entanglement polymers while binding of interfering ions such as phosphate were significantly reduced. The selectivity effect may be introduced in two different manners: 1) Overall capacity was sacrificed for chloride specificity. Crosslinkers that don't include chloride binding sites (*e.g.*, epichlorohydrin) allow for increased crosslinking while overall capacity is decreased proportional to the amount of crosslinker incorporated into the polymer. 2) Overall capacity is preserved for chloride specificity: Crosslinkers that include chloride binding sites (*e.g.*, diallylamines) allow for increased crosslinking while overall capacity is staying the same or is reduced by only a small amount.

[00331] As previously noted, crosslinked polymers having a high capacity for chloride binding and high selectivity for chloride over other competing anions such as phosphate may be prepared in a two-step process in accordance with one embodiment of the present disclosure. In general, the selectivity of the polymer is a function of its crosslinking density and the capacity of the polymer is a function of the free amine density of the crosslinked polymer. Advantageously, the two-step process disclosed herein provides both, high capacity for chloride binding, and high selectivity for chloride over other competing ions by relying primarily upon carbon-carbon crosslinking in the first step, and nitrogen-nitrogen crosslinking in the second step.

[00332] In the first step, the crosslinking is preferably capacity-sparing, *i.e.*, free amine sparing, crosslinking from carbon to carbon. In the second step, the crosslinking is amine-consuming and is directed towards tuning for selectivity. Based on the desired high capacity, the C-N ratio is preferably optimized to maximize amine functionalities for HCl binding, while still maintaining a spherical polymer particle of controlled particle size to ensure nonabsorption and acceptable mouth feel that is stable under GI conditions. The preferred extent of carbon-carbon

crosslinking achieved after the first step is sufficient to permit the resulting bead to swell between 4X and 6X in water (i.e., a Swelling Ratio of 4 to 6).

[00333] In one embodiment, crosslinked polymers having a high capacity for chloride binding and high selectivity for chloride over other competing anions such as phosphate may be prepared in a two-step process, and the product of the first polymerization step is preferably in the form of beads whose diameter is controlled in the 5 to 1000 micrometer range, preferably 10 to 500 micrometers and most preferred 40 – 180 micrometers.

[00334] The product of the first polymerization step is preferably in the form of beads whose Swelling Ratio in water is between 2 and 10, more preferably about 3 to about 8, and most preferably about 4 to about 6.

[00335] Additionally, if the crosslinked polymer beads resulting from the first polymerization step are protonated, this may reduce the amount of nitrogen-nitrogen crosslinking in the second crosslinking step. Accordingly, in certain embodiments the preformed amine polymer is at least partially deprotonated by treatment with a base, preferably a strong base such as a hydroxide base. For example, in one embodiment the base may be NaOH, KOH, NH_4OH, $NaHCO_3$, Na_2CO_3, K_2CO_3, LiOH, Li_2CO_3, CsOH or other metal hydroxides. If the charges are removed from the preformed crosslinked amine polymer bead by deprotonation, the bead will tend to collapse and the crosslinking agent used in the second step may not be able to access binding sites on the polymer unless the bead is prevented from collapsing. One means of preventing the crosslinked polymer bead from collapsing is the use of a swelling agent such as water to swell the bead, thereby allowing the second-step crosslinker to access binding sites.

[00336] The preformed polymer may be crosslinked to form the post-polymerization crosslinked polymer using any of a range of crosslinking compounds containing at least two amine-reactive functional groups. In one such embodiment, the crosslinker is a compound containing at least two amine-reactive groups selected from the group consisting of halides, epoxides, phosgene, anhydrides, carbamates, carbonates, isocyanates, thioisocyanates, esters, activated esters, carboxylic acids and derivatives thereof, sulfonates and derivatives thereof, acyl halides, aziridines, α,β-unsaturated carbonyls, ketones, aldehydes, and pentafluoroaryl groups. The

crosslinker may be, for example, any of the crosslinkers disclosed herein, including a crosslinker selected from Table B. By way of further example, in one such embodiment the crosslinker is a dihalide such as a dichloroalkane.

[00337] As noted above, in certain embodiments a swelling agent for the preformed amine polymer may be included in the reaction mixture for the second polymerization step along with the crosslinking agent. In general, the swelling agent and the crosslinking agent may be miscible or immiscible and the swelling agent may be any composition or combination of compositions that have the capacity to swell the preformed amine polymer. Exemplary swelling agents include polar solvents such as water, methanol, ethanol, *n*-propanol, isopropanol, *n*-butanol, formic acid, acetic acid, acetonitrile, dimethylformamide, dimethylsulfoxide, nitromethane, propylene carbonate, or a combination thereof. Additionally, the amount of swelling agent included in the reaction mixture will typically be less than absorption capacity of the preformed amine polymer for the swelling agent. For example, it is generally preferred that the weight ratio of swelling agent to preformed polymer in the reaction mixture be less than 4:1. By way of further example, in some embodiments the weight ratio of swelling agent to preformed polymer in the reaction mixture will be less than 3:1. By way of further example, in some embodiments the weight ratio of swelling agent to preformed polymer in the reaction mixture will be less than 2:1. By way of further example, in some embodiments the weight ratio of swelling agent to preformed polymer in the reaction mixture will be less than 1:1. By way of further example, in some embodiments the weight ratio of swelling agent to preformed polymer in the reaction mixture will be less than 0.5:1. By way of further example, in some embodiments the weight ratio of swelling agent to preformed polymer in the reaction mixture will be less than 0.4:1. By way of further example, in some embodiments the weight ratio of swelling agent to preformed polymer in the reaction mixture will be less than 0.3:1. In general, however, the weight ratio of swelling agent to preformed polymer in the reaction mixture will typically be at least 0.05:1, respectively.

[00338] In general, the crosslinked polymers may be crosslinked homopolymers or crosslinked copolymers comprising free amine moieties. The free amine moieties may be separated, for example, by the same or varying lengths of repeating linker (or intervening) units. In some embodiments, the polymers comprise

repeat units containing an amine moiety and an intervening linker unit. In other embodiments, multiple amine-containing repeat units are separated by one or more linker units. Additionally, the polyfunctional crosslinkers may comprise HCl binding functional groups, *e.g.*, amines, ("active crosslinkers") or may lack HCl binding functional groups such as amines ("passive crosslinkers").

[00339] In a preferred embodiment, the first polymerization (crosslinking) step yields preformed amine polymer beads having a target size and chloride binding capacity. For example, in one such embodiment the beads have a chloride binding capacity of at least 10 mmol/g in Simulated Gastric Fluid ("SGF") and a Swelling Ratio in the range of 1 to 6. The resulting preformed amine polymer is then preferably (at least partially) deprotonated with a base and combined with a non-protonating swelling agent to swell the free amine polymer without protonating the amine functions. Furthermore, the amount of the non-protonating swelling agent is selected to tune the subsequent degree of crosslinking effectively forming a template that is then locked into place via the amine consuming crosslinking step. In the second crosslinking step, the swollen, deprotonated preformed amine polymer is crosslinked with a crosslinker containing amine reactive moieties to form a post-polymerization crosslinked polymer.

[00340] In general, selectivity for chloride over other competing ions is achieved with highly crosslinked polymers. For example, relatively high chloride binding capacity maybe be attained by reacting a preformed amine polymer bead with neat crosslinker in the presence of a swelling agent (water). While this "non-dispersed" reaction provides access to high selectivity for chloride over competing ions in the SIB assay, it also results in macroscopically (and microscopically) aggregated polymer beads. Accordingly, it is advantageous to include a solvent (*e.g.*, heptane) in the second crosslinking step to disperse the preformed crosslinked polymer beads so as to avoid inter-bead reactions and resulting aggregation. The use of too much solvent (dispersant), however, can dilute the reaction solution to the point where the resulting bead is not sufficiently crosslinked to have the desired selectivity for chloride over other competing anions. By using a crosslinking agent that also functions as a solvent (dispersant), however, sufficient solvent (dispersant) may be included in the reaction mixture to avoid inter-bead reactions and aggregation without diluting the mixture to the point where the degree of amine-

consuming crosslinking is insufficient. For example, in an effort to utilize the dispersing properties of a solvent (to avoid aggregation during the reaction) while maintaining reactivity, DCE and DCP were used neat, thus performing a dual purpose role, as both solvent (dispersant) and crosslinker. Interestingly, DCE was discovered to have excellent dispersal properties as a solvent, when compared to similar reactions with DCP and/or heptane. Additionally, less aggregation was observed when the beads were first dispersed in DCE and then in a second operation, the water is added to swell the beads. If water is added to the preformed amine polymer before the bead is dispersed in the DCE, aggregation may occur.

[00341] The use of 1,2-dichloroethane ("DCE") as the crosslinking solvent also generates HCl molecules during the second step. These HCl molecules protonate some of the free amine sites which block the reaction sites for the crosslinking reaction and thereby limit the number of binding sites available for crosslinking. Consequently, the use of DCE creates a self-limiting effect on the secondary crosslinking.

[00342] In each of the foregoing embodiments, the reaction mixture may contain a wide range of amounts of crosslinking agents. For example, in one embodiment the crosslinker may be used in large excess relative to the amount of preformed amine polymer in the reaction mixtures. Stated differently, in such embodiments the crosslinking agent is a crosslinking solvent, *i.e.*, it is both a solvent for the reaction mixture and a crosslinking agent for the preformed amine polymer. In such embodiments, other solvents may optionally be included in the reaction mixture but are not required. Alternatively, the preformed amine polymer, swelling agent and crosslinker may be dispersed in a solvent that is miscible with the crosslinker and immiscible with the swelling agent. For example, in some embodiments the swelling agent may be a polar solvent; in some such embodiments, for example, the swelling agent may comprise water, methanol, ethanol, n-propanol, isopropanol, formic acid, acetic acid, acetonitrile, *N,N*-dimethylformamide, dimethylsulfoxide, nitromethane, or a combination thereof. By way of further example, when the swelling agent comprises a polar solvent, the solvent system for the reaction mixture will typically comprise a non-polar solvent such as pentane, cyclopentane, hexane, cyclohexane, benzene, toluene, 1,4-dioxane, chloroform, diethyl ether, dichloromethane, dichloroethane,

dichloropropane, dichlorobutane, or a combination thereof. In certain embodiments, the crosslinker and the solvent may be the same; i.e., the solvent is a crosslinking solvent such as 1,2-dichloroethane, 1,3-dichloropropane, 1,4-dichlorobutane or a combination thereof.

[00343] It is notable that in a crosslinking solvent (*e.g.*, a DCE-dispersed reaction), there is a large excess of crosslinker regardless of the amount of crosslinking solvent (*e.g.*, DCE) used to disperse the bead (*e.g.*, both 1 g:3 mL::bead:DCE and 1 g:10 mL::bead:DCE are a large excess of crosslinker, most of which is not consumed during the reaction). Despite this, the relative degree of crosslinking, and the performance in SIB assay, are unaffected by changes in the ratio of reactive crosslinker to polymer bead. This is possible because the reaction is limited by the acid-neutralizing capacity of the polymer bead, rather than the amount of crosslinker (*e.g.*, DCE).

[00344] To more efficiently react with DCE or other crosslinker, the amines of the preformed polymer bead preferably have a free electron pair (neutral, deprotonated). As the free amines of the preformed polymer bead react with the crosslinker (e.g., DCE), HCl is produced and the amines become protonated, thus limiting the reaction. For this reason, the preformed amine polymer beads preferably start as the free amine in the second crosslinking step. If the preformed amine polymer bead is protonated after the first step of carbon-carbon crosslinking, amine-consuming crosslinking in the second step will be limited, thus reducing the desired selectivity for chloride over other competing ions. This has been demonstrated by adding known quantities of HCl to preformed amine polymer beads immediately before second step crosslinking with DCE. When less than 3 mol % HCl (to amine in preformed polymer amine bead) is added prior to second step crosslinking, total chloride capacity (SGF) and chloride selectivity in SIB are similar to beads not treated with HCl in the second step. When greater than 5 mol % HCl (to amine in preformed polymer amine bead) is added prior to second step crosslinking, total chloride capacity (SGF) increases and chloride selectivity in SIB decreases, indicating lower incorporation of crosslinker.

[00345] The benefits of deprotonated preformed polymer beads in the second step crosslinking highlights the advantages of using two steps to achieve the final product. In the first step, to form the amine polymer bead, all monomers (*e.g.*,

allylamine and DAPDA) are protonated to remain in the aqueous phase and to avoid the radical transfer reactions that severely limit the polymerization of non-protonated allylamine (and derivatives). Once the bead is formed through carbon-carbon crosslinks, the bead can then be deprotonated and further crosslinked with an amine reactive crosslinker in a second step.

[00346] Given the large excess of dual crosslinker/solvent, mono-incorporation of this reagent can occur leading to alkyl chloride functional groups on the crosslinked polymer bead that are hydrophobic in nature and can increase non-specific interactions with undesirable solutes other than HCl that are more hydrophobic in nature. Washing with ammonium hydroxide solution converts the alkyl-chloride to alkyl-amine functions that are hydrophilic and minimize non-specific interactions with undesirable solutes. Other modifications that yield more hydrophilic groups than alkyl chloride such as -OH are suitable to quench mono-incorporated crosslinker/solvent.

[00347] Any of a range of polymerization chemistries may be employed in the first reaction step, provided that the crosslinking mechanism is primarily carbon-carbon crosslinking. Thus, in one exemplary embodiment, the first reaction step comprises radical polymerization. In such reactions, the amine monomer will typically be a mono-functional vinyl, allyl, or acrylamide (*e.g.*, allylamine) and crosslinkers will have two or more vinyl, allyl or acrylamide functionalities (*e.g.*, diallylamine). Concurrent polymerization and crosslinking occurs through radically initiated polymerization of a mixture of the mono- and multifunctional allylamines. The resulting polymer network is thusly crosslinked through the carbon backbone. Each crosslinking reaction forms a carbon-carbon bond (as opposed to substitution reactions in which a carbon-heteroatom bond is formed during crosslinking). During the concurrent polymerization and crosslinking, the amine functionalities of the monomers do not undergo crosslinking reactions and are preserved in the final polymer (*i.e.*, primary amines remain primary, secondary amines remain secondary, and tertiary amines remain tertiary).

[00348] In those embodiments in which the first reaction step comprises radical polymerization, a wide range of initiators may be used including cationic and radical initiators. Some examples of suitable initiators that may be used include: the free radical peroxy and azo type compounds, such as azodiisobutyronitrile,

azodiisovaleronitrile, dimethylazodiisobutyrate, 2,2'azo bis(isobutyronitrile), 2,2'-azobis(N,N'-dimethy1-eneisobutyramidine)dihydrochloride, 2,2'-azobis(2-amidinopropane)dihydrochloride, 2,2'-azobis(N,N'-dimethyleneisobutyramidine), 1,1'-azo bis(l-cyclohexanecarbo-nitrile), 4,4'-azobis(4-cyanopentanoic acid), 2,2'-azobis(isobutyramide)dihydrate, 2,2'-azobis(2-methylpropane), 2,2'-azobis(2-methylbutyronitrile), VAZO 67, cyanopentanoic acid, the peroxypivalates, dodecylbenzene peroxide, benzoyl peroxide, di-t-butyl hydroperoxide, t-butyl peracetate, acetyl peroxide, dicumyl peroxide, cumylhydroperoxide, dimethyl bis(butylperoxy)hexane.

[00349] Exemplary amine-containing polymers as described above are more fully disclosed and exemplified in WO2016/094685 A1 and WO2014/197725 A1, the entire contents of which are incorporated herein by reference.

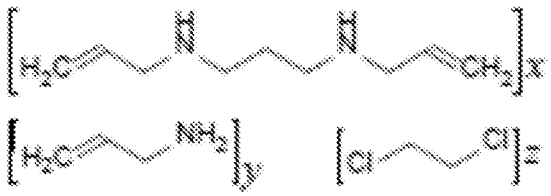
[00350] The composition, nonabsorbable composition, pharmaceutical composition or proton-binding, crosslinked amine polymer of the present invention can comprise or consist essentially of, or be a polymer as defined anywhere herein. For example, the composition, nonabsorbable composition, pharmaceutical composition or crosslinked amine polymer can comprise, consists essentially of, or be the drug substance TRC101, which has the USAN veverimer. veverimer (TRC101) is a non-absorbed free-flowing powder composed of low-swelling, spherical beads, approximately 100 micrometers in diameter; each bead is a single crosslinked, high molecular weight molecule.

[00351] The veverimer polymer (TRC101) can be defined chemically as follows:

1) 1,3-Propanediamine, N^1,N^3-di-2-propen-1-yl-, polymer with 1,2-dichloroethane and 2-propen-1-amine;

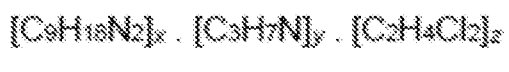
2) N^1,N^3-bis(prop-2-en-1-yl)propan-1,3-diamine copolymer with 1,2-dichloroethane and prop-2-en-1-amine.

Veverimer (TRC101) has the following structural formula:



, wherein x, y and z are positive integers.

Veverimer (TRC101) has the following molecular formula:



, wherein x, y and z are positive integers.

[00352] Veverimer (TRC101) is obtainable by first copolymerizing allylamine hydrochloride and N,N'-diallyl-1,3-diaminopropane dihydrochloride, or the salts thereof to form a preformed amine polymer, followed by crosslinking the preformed amine polymer with 1,2-dichloroethane. The synthesis of veverimer (TRC101) is described in Exemplary Synthesis A and in WO2016/094685 A1. Veverimer (TRC101) is the polymer with unique ID 019070-A3 FA in Table S-1 of Exemplary Synthesis A. In the present application, veverimer and TRC101 are used interchangeably.

[00353] In one embodiment, the pharmaceutical composition comprises a mixture of any of the previously-identified nonabsorbable materials. For example, in one embodiment the pharmaceutical composition comprises a mixture of a cation exchange composition with at least one anion exchange composition, amphoteric ion exchange composition, or neutral composition having the capacity to bind both protons and anions. In another embodiment, the pharmaceutical composition comprises a mixture of an anion exchange composition with at least one cation exchange composition, amphoteric ion exchange composition, or neutral composition having the capacity to bind both protons and anions. In yet another embodiment, the pharmaceutical composition comprises a mixture of a neutral composition having the capacity to bind both protons and anions with at least one cation exchange composition, amphoteric ion exchange composition, or anion exchange composition.

[00354] As schematically depicted in Figs. 1A-1C and in accordance with one embodiment, a nonabsorbable free-amine polymer of the present disclosure is

orally ingested and used to treat metabolic acidosis (including by increasing serum bicarbonate and normalizing blood pH) in a mammal by binding HCl in the gastrointestinal ("GI") tract and removing HCl through the feces. Free-amine polymer is taken orally (Fig. 1A) at compliance enhancing dose targeted to chronically bind sufficient amounts of HCl to enable clinically meaningful increase in serum bicarbonate of 3 mEq/L. In the stomach (Fig. 1B), free amine becomes protonated by binding H^+. Positive charge on polymer is then available to bind Cl^-; by controlling access of binding sites through crosslinking and hydrophilicity/ hydrophobicity properties, other larger organic anions (e.g., acetate, propionate, butyrate, etc., depicted as X^- and Y^-) are bound to a lesser degree, if at all. The net effect is therefore binding of HCl. In the lower GI tract/colon (Fig. 1C), Cl^- is not fully released and HCl is removed from the body through regular bowel movement and fecal excretion, resulting in net alkalinization in the serum. Cl^- bound in this fashion is not available for exchange via the Cl^-/HCO_3^- antiporter system.

[00355] In one embodiment, the polymer is designed to simultaneously maximize efficacy (net HCl binding and excretion) and minimize GI side effects (through low swelling particle design and particle size distribution). Optimized HCl binding may be accomplished through a careful balance of capacity (number of amine binding sites), selectivity (preferred binding of chloride versus other anions, in particular organic anions in the colon) and retention (not releasing significant amounts of chloride in the lower GI tract to avoid the activity of the Cl^-/HCO_3^- exchanger [antiporter] in the colon and intestine; if chloride is not tightly bound to the polymer the Cl^-/HCO_3^- exchanger can mediate uptake of chloride ion from the intestinal lumen and reciprocal exchange for bicarbonate from the serum, thus effectively decreasing serum bicarbonate.

[00356] Competing anions that displace chloride lead to a decrease in net bicarbonate through the following mechanisms. First, displacement of chloride from the polymer in the GI lumen, particularly the colon lumen, provides for a facile exchange with bicarbonate in the serum. The colon has an anion exchanger (chloride/bicarbonate antiporter) that moves chloride from the luminal side in exchange for secreted bicarbonate. When free chloride is released from the polymer in the GI tract it will exchange for bicarbonate, which will then be lost in the stool and cause a reduction in total extracellular bicarbonate (Davis, 1983; D'Agostino, 1953).

The binding of short chain fatty acids (SCFA) in exchange for bound chloride on the polymer, will result in the depletion of extracellular HCO_3^- stores. Short chain fatty acids are the product of bacterial metabolism of complex carbohydrates that are not catabolized by normal digestive processes (Chemlarova, 2007). Short chain fatty acids that reach the colon are absorbed and distributed to various tissues, with the common metabolic fate being the generation of H_2O and CO_2, which is converted to bicarbonate equivalents. Thus, binding of SCFA to the polymer to neutralize the proton charge would be detrimental to overall bicarbonate stores and buffering capacity, necessitating the design of chemical and physical features in the polymer that limit SCFA exchange. Finally, phosphate binding to the polymer should be limited as well, since phosphate represents an additional source of buffering capacity in the situation where ammoniagenesis and/or hydrogen ion secretion is compromised in chronic renal disease.

[00357] For each binding of proton, an anion is preferably bound as the positive charge seeks to leave the human body as a neutral polymer. "Binding" of an ion, is more than minimal binding, *i.e.*, at least about 0.2 mmol of ion/g of polymer, at least about 1 mmol of ion/g of polymer in some embodiments, at least about 1.5 mmol of ion/g of polymer in some embodiments, at least about 3 mmol of ion/g of polymer in some embodiments, at least about 5 mmol of ion/g of polymer in some embodiments, at least about 10 mmol of ion/g of polymer in some embodiments, at least about 12 mmol of ion/g of polymer in some embodiments, at least about 13 mmol of ion/g of polymer in some embodiments, or even at least about 14 mmol of ion/g of polymer in some embodiments. In one embodiment, the polymers are characterized by their high capacity of proton binding while at the same time providing selectivity for anions; selectivity for chloride is accomplished by reducing the binding of interfering anions that include but are not limited to phosphate, citrate, acetate, bile acids and fatty acids. For example, in some embodiments, polymers of the present disclosure bind phosphate with a binding capacity of less than about 5 mmol/g, less than about 4 mmol/g, less than about 3 mmol/g, less than about 2 mmol/g or even less than about 1 mmol/g. In some embodiments, polymers of the invention bind bile and fatty acids with a binding capacity of less than about less than about 5 mmol/g, less than about 4 mmol/g, less than about 3 mmol/g, less than about 2 mmol/g, less than about 1 mmol/g in some embodiments, less than about

0.5 mmol/g in some embodiments, less than about 0.3 mmol/g in some embodiments, and less than about 0.1 mmol/g in some embodiments.

Pharmaceutical Compositions & Administration

[00358] In general, the dosage levels of the nonabsorbable compositions for therapeutic and/or prophylactic uses may range from about 0.5 g/day to about 100 g/day. To facilitate patient compliance, it is generally preferred that the dose be in the range of about 1 g/day to about 50 g/day. For example, in one such embodiment, the dose will be about 2 g/day to about 25 g/day. By way of further example, in one such embodiment, the dose will be about 3 g/day to about 25 g/day. By way of further example, in one such embodiment, the dose will be about 4 g/day to about 25 g/day. By way of further example, in one such embodiment, the dose will be about 5 g/day to about 25 g/day. By way of further example, in one such embodiment, the dose will be about 2.5 g/day to about 20 g/day. By way of further example, in one such embodiment, the dose will be about 2.5 g/day to about 15 g/day. By way of further example, in one such embodiment, the dose will be about 1 g/day to about 10 g/day. Optionally, the daily dose may be administered as a single dose (*i.e.*, one time a day), or divided into multiple doses (*e.g.*, two, three or more doses) over the course of a day. In general, the nonabsorbable compositions may be administered as a fixed daily dose or titrated based on the serum bicarbonate values of the patient in need of treatment or other indicators of acidosis. The titration may occur at the onset of treatment or throughout, as required, and starting and maintenance dosage levels may differ from patient to patient based on severity of the underlying disease.

[00359] The effectiveness of the nonabsorbable composition may be established in animal models, or in human volunteers and patients. In addition, *in vitro*, *ex vivo* and *in vivo* approaches are useful to establish HCl binding. *In vitro* binding solutions can be used to measure the binding capacity for proton, chloride and other ions at different pHs. *Ex vivo* extracts, such as the gastrointestinal lumen contents from human volunteers or from model animals can be used for similar purposes. The selectivity of binding and/or retaining certain ions preferentially over others can also be demonstrated in such *in vitro* and *ex vivo* solutions. *In vivo* models of metabolic acidosis can be used to test the effectiveness of the nonabsorbable composition in normalizing acid/base balance - for example 5/6

nephrectomized rats fed casein-containing chow (as described in Phisitkul S, Hacker C, Simoni J, Tran RM, Wesson DE. Dietary protein causes a decline in the glomerular filtration rate of the remnant kidney mediated by metabolic acidosis and endothelin receptors. Kidney international. 2008;73(2):192-9), or adenine-fed rats (Terai K, K Mizukami and M Okada. 2008. Comparison of chronic renal failure rats and modification of the preparation protocol as a hyperphosphatemia model. Nephrol. 13: 139-146).

[00360] In one embodiment, the nonabsorbable compositions are provided (by oral administration) to an animal, including a human, in a dosing regimen of one, two or even multiple (*i.e.*, at least three) doses per day to treat an acid-base disorder (*e.g.*, metabolic acidosis) and achieve a clinically significant and sustained increase of serum bicarbonate as previously described. For example, in one embodiment a daily dose of the nonabsorbable composition (whether orally administered in a single dose or multiple doses over the course of the day) has sufficient capacity to remove at least 5 mmol of protons, chloride ions or each per day. By way of further example, in one such embodiment a daily dose of the nonabsorbable composition has sufficient capacity to remove at least 10 mmol of protons, chloride ions or each per day. By way of further example, in one such embodiment a daily dose of the nonabsorbable composition has sufficient capacity to remove at least 20 mmol of protons, the conjugate base of a strong acid (e.g., Cl^-, HSO_4^- and SO_4^{2-}) and/or a strong acid (e.g., HCl or H_2SO_4) each per day. By way of further example, in one such embodiment a daily dose of the nonabsorbable composition has sufficient capacity to remove at least 30 mmol of protons, the conjugate base of a strong acid, and/or a strong acid each per day. By way of further example, in one such embodiment a daily dose of the nonabsorbable composition has sufficient capacity to remove at least 40 mmol of protons, the conjugate base of a strong acid, and/or a strong acid each per day. By way of further example, in one such embodiment a daily dose of the nonabsorbable composition has sufficient capacity to remove at least 50 mmol of protons, the conjugate base of a strong acid, and/or a strong acid each per day.

[00361] The dosage unit form of the pharmaceutical comprising the nonabsorbable composition may be any form appropriate for oral administration. Such dosage unit forms include powders, tablets, pills, lozenges, sachets, cachets,

elixirs, suspensions, syrups, soft or hard gelatin capsules, and the like. In one embodiment, the pharmaceutical composition comprises only the nonabsorbable composition. Alternatively, the pharmaceutical composition may comprise a carrier, a diluent, or excipient in addition to the nonabsorbable composition. Examples of carriers, excipients, and diluents that may be used in these formulations as well as others, include foods, drinks, lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, methyl cellulose, methylhydroxybenzoates, propylhydroxybenzoates, propylhydroxybenzoates, and talc. Pharmaceutical excipients useful in the pharmaceutical compositions further include a binder, such as microcrystalline cellulose, colloidal silica and combinations thereof (Prosolv 90), carbopol, providone and xanthan gum; a flavoring agent, such as sucrose, mannitol, xylitol, maltodextrin, fructose, or sorbitol; a lubricant, such as magnesium stearate, stearic acid, sodium stearyl fumurate and vegetable based fatty acids; and, optionally, a disintegrant, such as croscarmellose sodium, gellan gum, low-substituted hydroxypropyl ether of cellulose, sodium starch glycolate. Other additives may include plasticizers, pigments, talc, and the like. Such additives and other suitable ingredients are well-known in the art; see, e.g., Gennaro A R (ed), Remington's Pharmaceutical Sciences, 20th Edition.

[00362] In one embodiment, the nonabsorbable composition may be co-administered with other active pharmaceutical agents depending on the condition being treated. This co-administration may include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. For example, for the treatment of metabolic acidosis, the nonabsorbable composition may be co-administered with common treatments that are required to treat underlying co-morbidities including but not limited to edema, hypertension, diabetes, obesity, heart failure and complications of Chronic Kidney Disease. These medications and the nonabsorbable composition can be formulated together in the same dosage form and administered simultaneously as long as they do not display any clinically significant drug-drug-interactions. Alternatively, these treatments and the nonabsorbable composition may be separately and sequentially administered with the administration of one being followed by the administration of the other.

[00363] In one embodiment, the daily dose of the chronic metabolic acidosis treatment is compliance enhancing (approximately 15 g or less per day) and achieves a clinically significant and sustained increase of serum bicarbonate of approximately 3 mEq/L at these daily doses. The non-absorbed nature of the polymer and the lack of sodium load and/or introduction of other deleterious ions for such an oral drug enable for the first time a safe, chronic treatment of metabolic acidosis without worsening blood pressure / hypertension and/or without causing increased fluid retention and fluid overload. Another benefit is further slowing of the progression of kidney disease and time to onset of lifelong renal replacement therapy (End Stage Renal Disease "ESRD" including 3 times a week dialysis) or need for kidney transplants. Both are associated with significant mortality, low quality of life and significant burden to healthcare systems around the world. In the United States alone, approximately 20 % of the 400,000 ESRD patients die and 100,000 new patients start dialysis every year.

[00364] A further aspect of the present disclosure is a method of slowing the progression to dialysis of a patient afflicted with chronic kidney disease and an acid-base disorder characterized by a baseline serum bicarbonate value of ≤22 mEq/L, the method comprising oral administration of a pharmaceutical composition capable of increasing and maintaining the patient's serum bicarbonate above 20 mEq/L for a period of at least twelve weeks, the pharmaceutical composition having the capacity to bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids.

[00365] A further aspect of the present disclosure is a method of slowing the progression to dialysis of a patient afflicted with chronic kidney disease and an acid-base disorder, wherein the patient has a baseline serum bicarbonate value of ≤22 mEq/L, comprising orally administering to the patient an effective amount of TRC101 once daily for a period of time sufficient to increase the patient's serum bicarbonate by at least 1 mEq/L.

[00366] A further aspect of the present disclosure is a method of slowing the progression to dialysis of a patient afflicted with chronic kidney disease and metabolic acidosis disease, the method comprising administering to the patient a daily dose of a nonabsorbed crosslinked amine polymer, which

daily dose: (a) is sufficient to increase the patient's serum bicarbonate concentration by at least 1 mEq/L; (b) results in a sustained serum bicarbonate increase of at least 1 mEq/L over a period of at least twelve weeks; and (c) is sufficient to slow the progression to dialysis.

[00367] A further aspect of the present disclosure is a pharmaceutical composition for slowing the progression to dialysis of a human patient afflicted with chronic kidney disease and an acid-base disorder, the patient having a baseline serum bicarbonate level of ≤22 mEq/L prior to treatment, the composition being a nonabsorbable composition having the capacity to: (a) remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) slow the progression to dialysis of the human patient over at least a twelve-week period.

[00368] A further aspect of the present disclosure is a pharmaceutical composition for slowing the progression to dialysis of a human patient afflicted with chronic kidney disease and an acid-base disorder by increasing that patient's serum bicarbonate value by at least 1 mEq/L over at least twelve weeks of treatment, the composition: (a) being a nonabsorbable composition having the capacity to remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (b) characterized by a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (c) having the capacity to slow the progression to dialysis over at least the twelve-week period.

[00369] A further aspect of the present disclosure is a pharmaceutical composition for slowing the progression to dialysis of a human patient also suffering from metabolic acidosis disease, wherein: (a) an effective amount of the pharmaceutical composition is administered to the patient per day over at least a twelve-week period; (b) the pharmaceutical composition is nonabsorbable with the capacity to remove from the patient a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (c) the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 3 mEq/g in a Simulated Small Intestine

Inorganic Buffer (SIB) assay; and (d) the progression to dialysis of the patient is slowed over the twelve-week period compared to a placebo control group not receiving the pharmaceutical composition.

[00370] In one embodiment, the rate of progression to dialysis of the individual is decreased. In one embodiment, the rate of progression to dialysis decreases for at least about 1 month. In one embodiment, the rate of progression to dialysis decreases for at least about 4 months. In one embodiment, the rate of progression to dialysis decreases for at least about 6 months. In one embodiment, the rate of progression to dialysis decreases for at least about 12 months.

[00371] A further aspect of the present disclosure is a method of decreasing the rate of progression to dialysis of an individual, the method comprising administering a composition, or part thereof, described anywhere herein. In one embodiment, the method includes the method of treatment, or part thereof, described anywhere herein.

[00372] In one embodiment, the rate of decrease in the progression to dialysis is measurable by a decreased rate of change in eGFR. In one embodiment, the individual or adult human patient has a baseline eGFR value of at least about 15 mL/min/1.73 m^2. In one embodiment, the individual or adult human patient has a baseline eGFR value of at least about 30 mL/min/1.73 m^2. In one embodiment, the individual or adult human patient has a baseline eGFR value of less than about 45 mL/min/1.73 m^2 for at least three months. In one embodiment, the individual or adult human patient has a baseline eGFR value of less than about 60 mL/min/1.73 m^2 for at least three months. In one embodiment, the decreased rate of change in eGFR value is less than about 1 mL/min/1.73 m^2 over a period of about 1 month. In one embodiment, the decreased rate of change in eGFR value is less than about 5 mL/min/1.73 m^2 over a period of about 1 month. In one embodiment, the decreased rate of change in eGFR value is less than about 10 mL/min/1.73 m^2 over a period of about 1 month. In one embodiment, the decreased rate of change in eGFR value is less than about 15 mL/min/1.73 m^2 over a period of about 1 month. In one embodiment, the decreased rate of change in eGFR value is less than about 20 mL/min/1.73 m^2 over a period of about 1 month. In

one embodiment, the decreased rate of change in eGFR value is less than about 25 mL/min/1.73 m^2 over a period of about 1 month. In one embodiment, the decreased rate of change in eGFR occurs to the extent that eGFR stops decreasing. In one embodiment, the decreased rate of change in eGFR occurs to the extent that there is an improvement in eGFR.

[00373] In one embodiment, the delay in the progression to dialysis is measurable by reduced change in mGFR, or a halt in change to mGFR, or improvement in mGFR. In one embodiment, the delay in the progression to dialysis is measurable by reduced change in mGFR, or a halt in change to mGFR, or improvement in mGFR. In one embodiment, the individual or adult human patient has a baseline mGFR value of at least about 15 mL/min/1.73 m^2. In one embodiment, the individual or adult human patient has a baseline mGFR value of at least about 30 mL/min/1.73 m^2. In one embodiment, the individual or adult human patient has a baseline mGFR value of less than about 45 mL/min/1.73 m^2 for at least three months. In one embodiment, the individual or adult human patient has a baseline mGFR value of less than about 60 mL/min/1.73 m^2 for at least three months. In one embodiment, the decreased rate of change in mGFR value is less than about 1 mL/min/1.73 m^2 over a period of about 1 month. In one embodiment, the decreased rate of change in mGFR value is less than about 5 mL/min/1.73 m^2 over a period of about 1 month. In one embodiment, the delay in the progression to dialysis includes the individual's stage of chronic kidney disease remaining constant. In one embodiment, the decrease in the rate of progression to dialysis may be determined relative to the baseline rate of progression prior to treatment.

[00374] In methods of slowing the progression to dialysis, the decision to dialyse may be as follows. In one embodiment, the method comprises a decision to initiate dialysis. In one embodiment, the method comprises administering a composition, or part thereof, described anywhere herein. In one embodiment, the method includes the method of treatment, or part thereof, described anywhere herein.

[00375] In one embodiment, the decision to initiate dialysis is based on an overall clinical assessment of uremic signs and/or symptoms of the patient. For

example, in one embodiment, the decision to initiate dialysis is based on physical functioning of the patient, which may act as one indicator of protein-energy wasting. In one embodiment, the physical functioning of the patient is determined using any of the methods for assessing physical function described herein. In one embodiment, the decision to initiate dialysis is based on evidence of protein wasting. In one embodiment, the decision to initiate dialysis is based on the ability to manage complications from the disorder, such as acidosis and volume overload.

[00376] The examples of the present application show that veverimer (TRC101) corrects acidosis and improves physical function, possibly by reducing protein catabolism and/or by allowing a higher protein intake to be tolerated. It is therefore plausible that use of veverimer could forestall initiation of dialysis, independent of any effects on kidney function.

[00377] A further aspect of the present disclosure is a pharmaceutical product comprising a sealed package and the nonabsorbable composition of the present disclosure within the sealed package. The sealed package is preferably substantially impermeable to moisture and oxygen to increase the stability of the pharmaceutical composition. For example, the dosage unit form may comprise a sealed container (*e.g.*, a sealed sachet) that prevents or reduces ingress of moisture and oxygen upon packaging the nonabsorbable composition in the container. The container size can be optimized to reduce head space in the container after packaging and any head space may be filled with an inert gas such as nitrogen. Furthermore, container material of construction can be chosen to minimize the moisture and oxygen ingress inside the container after packaging. For example, the nonabsorbable composition may be packaged in a multilayer sachet containing at least one or more layer that serves as a barrier layer to moisture and oxygen ingress. In another example, the nonabsorbable composition may be packaged in a single layer or multilayer plastic, metal or glass container that has at least one or more barrier layers incorporated in the structure that limits oxygen and/or moisture ingress after packaging. For example, in one such embodiment the sachet (or other container or package) may comprise a multi-layer laminate of an inner contact layer, an outer layer; and a barrier layer disposed between the contact layer and outer layer. In one exemplary embodiment, the container includes one or more oxygen-scavenging layers.

[00378] In further embodiments, enumerated as embodiments 1-1682 below, the present disclosure includes:

[00379] Embodiment 1. A method of treating an individual afflicted with an acid-base disorder characterized by a baseline serum bicarbonate value of less than 22 mEq/l, the method comprising oral administration of a daily dose of a pharmaceutical composition having the capacity to bind at least 5 mEq of a target species as it transits the digestive system to increase the serum bicarbonate value to a value within the range of 24 to 29 mEq/l within a treatment period not greater than 1 month, the target species being selected from the group consisting of protons, strong acids, and conjugate bases of strong acids.

[00380] Embodiment 2. A method of treating an individual afflicted with an acid-base disorder characterized by a baseline serum bicarbonate value of less than 22 mEq/l, the method comprising oral administration of a pharmaceutical composition, wherein the pharmaceutical composition given orally binds at least 5 mEq per day on average of a target species in the digestive system to maintain the serum bicarbonate value at a value within the range of 24 to 29 mEq/l, the target species being selected from the group consisting of protons, strong acids, and conjugate bases of strong acids.

[00381] Embodiment 3. The method of embodiment 2 wherein the oral administration is as frequent as at least weekly within the treatment period.

[00382] Embodiment 4. The method of embodiment 2 pharmaceutical composition wherein the oral administration is as frequent as at least semi-weekly within the treatment period.

[00383] Embodiment 5. The method of embodiment 2 pharmaceutical composition wherein the oral administration is as frequent as at least daily within the treatment period.

[00384] Embodiment 6. The method of embodiment 1, 2, 3 or 5 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of less than 21 mEq/l.

[00385] Embodiment 7. The method of embodiment 1, 2, 3 or 5 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of less than 20 mEq/l.

[00386] Embodiment 8. The method of embodiment 1, 2, 3 or 5 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of less than 19 mEq/l.

[00387] Embodiment 9. The method of embodiment 1, 2, 3 or 5 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of less than 18 mEq/l.

[00388] Embodiment 10. The method of embodiment 1, 2, 3 or 5 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of less than 17 mEq/l.

[00389] Embodiment 11. The method of embodiment 1, 2, 3 or 5 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of less than 16 mEq/l.

[00390] Embodiment 12. The method of embodiment 1, 2, 3 or 5 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of less than 15 mEq/l.

[00391] Embodiment 13. The method of embodiment 1, 2, 3 or 5 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of less than 14 mEq/l.

[00392] Embodiment 14. The method of embodiment 1, 2, 3 or 5 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of less than 13 mEq/l.

[00393] Embodiment 15. The method of embodiment 1, 2, 3 or 5 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of less than 12 mEq/l.

[00394] Embodiment 16. The method of embodiment 1, 2, 3 or 5 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of less than 11 mEq/l.

[00395] Embodiment 17. The method of embodiment 1, 2, 3 or 5 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of less than 10 mEq/l.

[00396] Embodiment 18. The method of any preceding enumerated embodiment wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 9 mEq/l.

[00397] Embodiment 19. The method of any of embodiments 1 – 16 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 10 mEq/l.

[00398] Embodiment 20. The method of any of embodiments 1 – 15 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 11 mEq/l.

[00399] Embodiment 21. The method of any of embodiments 1 – 14 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 12 mEq/l.

[00400] Embodiment 22. The method of any of embodiments 1 – 13 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 13 mEq/l.

[00401] Embodiment 23. The method of any of embodiments 1 – 12 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 14 mEq/l.

[00402] Embodiment 24. The method of any of embodiments 1 – 11 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 15 mEq/l.

[00403] Embodiment 25. The method of any of embodiments 1 – 10 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 16 mEq/l.

[00404] Embodiment 26. The method of any of embodiments 1 – 9 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 17 mEq/l.

[00405] Embodiment 27. The method of any of embodiments 1 – 8 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 18 mEq/l.

[00406] Embodiment 28. The method of any of embodiments 1 – 7 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 19 mEq/l.

[00407] Embodiment 29. The method of any of embodiments 1 – 6 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 20 mEq/l.

[00408] Embodiment 30. The method of embodiment 1, 2, 3 or 5 wherein the acid-base disorder is characterized by a baseline serum bicarbonate value of at least 21 mEq/l.

[00409] Embodiment 34. The method of any preceding enumerated embodiment wherein the method increases the serum bicarbonate value from the baseline serum bicarbonate value to an increased serum bicarbonate value of at least 25 mEq/l.

[00410] Embodiment 35. The method of any preceding enumerated embodiment wherein the method increases the serum bicarbonate value from the baseline serum bicarbonate value to an increased serum bicarbonate value of at least 26 mEq/l.

[00411] Embodiment 36. The method of any preceding enumerated embodiment wherein the method increases the serum bicarbonate value from the baseline serum bicarbonate value to an increased serum bicarbonate value of at least 27 mEq/l.

[00412] Embodiment 37. The method of any preceding enumerated embodiment wherein the method increases the serum bicarbonate value from the baseline serum bicarbonate value to an increased serum bicarbonate value of at least 28 mEq/l.

[00413] Embodiment 38. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to an increased serum bicarbonate value not in excess of 29 mEq/l.

[00414] Embodiment 39. The method of any of embodiments 1 to 36 wherein the method increases the baseline serum bicarbonate value to an increased serum bicarbonate value not in excess of 28 mEq/l.

[00415] Embodiment 40. The method of any of embodiments 1 to 35 wherein the method increases the baseline serum bicarbonate value to an increased serum bicarbonate value not in excess of 27 mEq/l.

[00416] Embodiment 41. The method of any of embodiments 1 to 34 wherein the method increases the baseline serum bicarbonate value to an increased serum bicarbonate value not in excess of 26 mEq/l.

[00417] Embodiment 42. The method of any of embodiments 1 to 33 wherein the method increases the baseline serum bicarbonate value to an increased serum bicarbonate value not in excess of 25 mEq/l.

[00418] Embodiment 45. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 1 mEq/l.

[00419] Embodiment 46. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 1.5 mEq/l.

[00420] Embodiment 47. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 2 mEq/l.

[00421] Embodiment 48. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 2.5 mEq/l.

[00422] Embodiment 49. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 3 mEq/l.

[00423] Embodiment 50. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 3.5 mEq/l.

[00424] Embodiment 51. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 4 mEq/l.

[00425] Embodiment 52. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 4.5 mEq/l.

[00426] Embodiment 53. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 5 mEq/l.

[00427] Embodiment 54. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 5.5 mEq/l.

[00428] Embodiment 55. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 6 mEq/l.

[00429] Embodiment 56. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 6.5 mEq/l.

[00430] Embodiment 57. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 7 mEq/l.

[00431] Embodiment 58. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 7.5 mEq/l.

[00432] Embodiment 59. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 8 mEq/l.

[00433] Embodiment 60. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 8.5 mEq/l.

[00434] Embodiment 61. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value at least 9 mEq/l.

[00435] Embodiment 62. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l within a treatment period of less than one month.

[00436] Embodiment 63. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l within a treatment period of 25 days.

[00437] Embodiment 64. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l within a treatment period of 3 weeks.

[00438] Embodiment 65. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l within a treatment period of 15 days.

[00439] Embodiment 66. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l within a treatment period of 2 weeks.

[00440] Embodiment 67. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l within a treatment period of 10 days.

[00441] Embodiment 68. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l within a treatment period of 1 week.

[00442] Embodiment 69. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l within 6 days of the initiation of the treatment.

[00443] Embodiment 70. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l within a treatment period of 5 days.

[00444] Embodiment 71. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l within a treatment period of 4 days.

[00445] Embodiment 72. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l within a treatment period of 3 days.

[00446] Embodiment 73. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l within a treatment period of 2 days.

[00447] Embodiment 74. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l within a treatment period of 1 day.

[00448] Embodiment 75. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l within a treatment period of 12 hours.

[00449] Embodiment 76. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l without any change in the individual's diet or dietary habits relative to the period immediately preceding the initiation of treatment.

[00450] Embodiment 77. The method of any preceding enumerated embodiment wherein the method increases the baseline serum bicarbonate value to a value within the range of 24 to 29 mEq/l independent of the individual's diet or dietary habits.

[00451] Embodiment 78. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 1 month of the cessation of treatment.

[00452] Embodiment 79. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 3 weeks of the cessation of treatment.

[00453] Embodiment 80. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 2 weeks of the cessation of treatment.

[00454] Embodiment 81. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 10 days of the cessation of treatment.

[00455] Embodiment 82. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 9 days of the cessation of treatment.

[00456] Embodiment 83. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 8 days of the cessation of treatment.

[00457] Embodiment 84. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 7 days of the cessation of treatment.

[00458] Embodiment 85. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 6 days of the cessation of treatment.

[00459] Embodiment 86. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 5 days of the cessation of treatment.

[00460] Embodiment 87. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 4 days of the cessation of treatment.

[00461] Embodiment 88. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 3 days of the cessation of treatment.

[00462] Embodiment 89. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 2 days of the cessation of treatment.

[00463] Embodiment 90. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2.5 mEq/l within 1 day of the cessation of treatment.

[00464] Embodiment 91. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 1 month of the cessation of treatment.

[00465] Embodiment 92. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 3 weeks of the cessation of treatment.

[00466] Embodiment 93. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 2 weeks of the cessation of treatment.

[00467] Embodiment 94. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 10 days of the cessation of treatment.

[00468] Embodiment 95. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 9 days of the cessation of treatment.

[00469] Embodiment 96. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 8 days of the cessation of treatment.

[00470] Embodiment 97. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 7 days of the cessation of treatment.

[00471] Embodiment 98. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 6 days of the cessation of treatment.

[00472] Embodiment 99. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 5 days of the cessation of treatment.

[00473] Embodiment 100. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 4 days of the cessation of treatment.

[00474] Embodiment 101. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 3 days of the cessation of treatment.

[00475] Embodiment 102. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 2 days of the cessation of treatment.

[00476] Embodiment 103. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 2 mEq/l within 1 day of the cessation of treatment.

[00477] Embodiment 104. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 1 month of the cessation of treatment.

[00478] Embodiment 105. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 3 weeks of the cessation of treatment.

[00479] Embodiment 106. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 2 weeks of the cessation of treatment.

[00480] Embodiment 107. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 10 days of the cessation of treatment.

[00481] Embodiment 108. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 9 days of the cessation of treatment.

[00482] Embodiment 109. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 8 days of the cessation of treatment.

[00483] Embodiment 110. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 7 days of the cessation of treatment.

[00484] Embodiment 111. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 6 days of the cessation of treatment.

[00485] Embodiment 112. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 5 days of the cessation of treatment.

[00486] Embodiment 113. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 4 days of the cessation of treatment.

[00487] Embodiment 114. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 3 days of the cessation of treatment.

[00488] Embodiment 115. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 2 days of the cessation of treatment.

[00489] Embodiment 116. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1.5 mEq/l within 1 day of the cessation of treatment.

[00490] Embodiment 117. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 1 month of the cessation of treatment.

[00491] Embodiment 118. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 3 weeks of the cessation of treatment.

[00492] Embodiment 119. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 2 weeks of the cessation of treatment.

[00493] Embodiment 120. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 10 days of the cessation of treatment.

[00494] Embodiment 121. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 9 days of the cessation of treatment.

[00495] Embodiment 122. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 8 days of the cessation of treatment.

[00496] Embodiment 123. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 7 days of the cessation of treatment.

[00497] Embodiment 124. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 6 days of the cessation of treatment.

[00498] Embodiment 125. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 5 days of the cessation of treatment.

[00499] Embodiment 126. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 4 days of the cessation of treatment.

[00500] Embodiment 127. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 3 days of the cessation of treatment.

[00501] Embodiment 128. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 2 days of the cessation of treatment.

[00502] Embodiment 129. The method of any preceding enumerated embodiment wherein the individual's serum bicarbonate value returns to the baseline value ± 1 mEq/l within 1 day of the cessation of treatment.

[00503] Embodiment 130. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1 mEq/l within 1 month of the cessation of treatment.

[00504] Embodiment 131. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1 mEq/l within 3 weeks of the cessation of treatment.

[00505] Embodiment 132. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1 mEq/l within 2 weeks of the cessation of treatment.

[00506] Embodiment 133. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1 mEq/l within 10 days of the cessation of treatment.

[00507] Embodiment 134. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1 mEq/l within 9 days of the cessation of treatment.

[00508] Embodiment 135. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1 mEq/l within 8 days of the cessation of treatment.

[00509] Embodiment 136. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1 mEq/l within 7 days of the cessation of treatment.

[00510] Embodiment 137. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1 mEq/l within 6 days of the cessation of treatment.

[00511] Embodiment 138. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1 mEq/l within 5 days of the cessation of treatment.

[00512] Embodiment 139. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1 mEq/l within 4 days of the cessation of treatment.

[00513] Embodiment 140. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1 mEq/l within 3 days of the cessation of treatment.

[00514] Embodiment 141. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1 mEq/l within 2 days of the cessation of treatment.

[00515] Embodiment 142. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1 mEq/l within 1 day of the cessation of treatment.

[00516] Embodiment 143. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 1 month of the cessation of treatment.

[00517] Embodiment 144. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 3 weeks of the cessation of treatment.

[00518] Embodiment 145. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 2 weeks of the cessation of treatment.

[00519] Embodiment 146. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 10 days of the cessation of treatment.

[00520] Embodiment 147. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 9 days of the cessation of treatment.

[00521] Embodiment 148. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 8 days of the cessation of treatment.

[00522] Embodiment 149. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 7 days of the cessation of treatment.

[00523] Embodiment 150. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 6 days of the cessation of treatment.

[00524] Embodiment 151. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 5 days of the cessation of treatment.

[00525] Embodiment 152. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 4 days of the cessation of treatment.

[00526] Embodiment 153. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 3 days of the cessation of treatment.

[00527] Embodiment 154. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 2 days of the cessation of treatment.

[00528] Embodiment 155. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 1.5 mEq/l within 1 day of the cessation of treatment.

[00529] Embodiment 156. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2 mEq/l within 1 month of the cessation of treatment.

[00530] Embodiment 157. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2 mEq/l within 3 weeks of the cessation of treatment.

[00531] Embodiment 158. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2 mEq/l within 2 weeks of the cessation of treatment.

[00532] Embodiment 159. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2 mEq/l within 10 days of the cessation of treatment.

[00533] Embodiment 160. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2 mEq/l within 9 days of the cessation of treatment.

[00534] Embodiment 161. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2 mEq/l within 8 days of the cessation of treatment.

[00535] Embodiment 162. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2 mEq/l within 7 days of the cessation of treatment.

[00536] Embodiment 163. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2 mEq/l within 6 days of the cessation of treatment.

[00537] Embodiment 164. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2 mEq/l within 5 days of the cessation of treatment.

[00538] Embodiment 165. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2 mEq/l within 4 days of the cessation of treatment.

[00539] Embodiment 166. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2 mEq/l within 3 days of the cessation of treatment.

[00540] Embodiment 167. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2 mEq/l within 2 days of the cessation of treatment.

[00541] Embodiment 168. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2 mEq/l within 1 day of the cessation of treatment.

[00542] Embodiment 169. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 1 month of the cessation of treatment.

[00543] Embodiment 170. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 3 weeks of the cessation of treatment.

[00544] Embodiment 171. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 2 weeks of the cessation of treatment.

[00545] Embodiment 172. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 10 days of the cessation of treatment.

[00546] Embodiment 173. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 9 days of the cessation of treatment.

[00547] Embodiment 174. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 8 days of the cessation of treatment.

[00548] Embodiment 175. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 7 days of the cessation of treatment.

[00549] Embodiment 176. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 6 days of the cessation of treatment.

[00550] Embodiment 177. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 5 days of the cessation of treatment.

[00551] Embodiment 178. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 4 days of the cessation of treatment.

[00552] Embodiment 179. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 3 days of the cessation of treatment.

[00553] Embodiment 180. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 2 days of the cessation of treatment.

[00554] Embodiment 181. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 2.5 mEq/l within 1 day of the cessation of treatment.

[00555] Embodiment 182. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3 mEq/l within 1 month of the cessation of treatment.

[00556] Embodiment 183. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3 mEq/l within 3 weeks of the cessation of treatment.

[00557] Embodiment 184. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3 mEq/l within 2 weeks of the cessation of treatment.

[00558] Embodiment 185. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3 mEq/l within 10 days of the cessation of treatment.

[00559] Embodiment 186. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3 mEq/l within 9 days of the cessation of treatment.

[00560] Embodiment 187. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3 mEq/l within 8 days of the cessation of treatment.

[00561] Embodiment 188. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3 mEq/l within 7 days of the cessation of treatment.

[00562] Embodiment 189. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3 mEq/l within 6 days of the cessation of treatment.

[00563] Embodiment 190. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3 mEq/l within 5 days of the cessation of treatment.

[00564] Embodiment 191. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3 mEq/l within 4 days of the cessation of treatment.

[00565] Embodiment 192. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3 mEq/l within 3 days of the cessation of treatment.

[00566] Embodiment 193. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3 mEq/l within 2 days of the cessation of treatment.

[00567] Embodiment 194. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3 mEq/l within 1 day of the cessation of treatment.

[00568] Embodiment 195. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 1 month of the cessation of treatment.

[00569] Embodiment 196. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 3 weeks of the cessation of treatment.

[00570] Embodiment 197. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 2 weeks of the cessation of treatment.

[00571] Embodiment 198. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 10 days of the cessation of treatment.

[00572] Embodiment 199. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 9 days of the cessation of treatment.

[00573] Embodiment 200. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 8 days of the cessation of treatment.

[00574] Embodiment 201. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 7 days of the cessation of treatment.

[00575] Embodiment 202. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 6 days of the cessation of treatment.

[00576] Embodiment 203. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 5 days of the cessation of treatment.

[00577] Embodiment 204. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 4 days of the cessation of treatment.

[00578] Embodiment 205. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 3 days of the cessation of treatment.

[00579] Embodiment 206. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 2 days of the cessation of treatment.

[00580] Embodiment 207. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 3.5 mEq/l within 1 day of the cessation of treatment.

[00581] Embodiment 208. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4 mEq/l within 1 month of the cessation of treatment.

[00582] Embodiment 209. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4 mEq/l within 3 weeks of the cessation of treatment.

[00583] Embodiment 210. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4 mEq/l within 2 weeks of the cessation of treatment.

[00584] Embodiment 211. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4 mEq/l within 10 days of the cessation of treatment.

[00585] Embodiment 212. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4 mEq/l within 9 days of the cessation of treatment.

[00586] Embodiment 213. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4 mEq/l within 8 days of the cessation of treatment.

[00587] Embodiment 214. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4 mEq/l within 7 days of the cessation of treatment.

[00588] Embodiment 215. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4 mEq/l within 6 days of the cessation of treatment.

[00589] Embodiment 216. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4 mEq/l within 5 days of the cessation of treatment.

[00590] Embodiment 217. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4 mEq/l within 4 days of the cessation of treatment.

[00591] Embodiment 218. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4 mEq/l within 3 days of the cessation of treatment.

[00592] Embodiment 219. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4 mEq/l within 2 days of the cessation of treatment.

[00593] Embodiment 220. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4 mEq/l within 1 day of the cessation of treatment.

[00594] Embodiment 221. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 1 month of the cessation of treatment.

[00595] Embodiment 222. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 3 weeks of the cessation of treatment.

[00596] Embodiment 223. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 2 weeks of the cessation of treatment.

[00597] Embodiment 224. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 10 days of the cessation of treatment.

[00598] Embodiment 225. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 9 days of the cessation of treatment.

[00599] Embodiment 226. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 8 days of the cessation of treatment.

[00600] Embodiment 227. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 7 days of the cessation of treatment.

[00601] Embodiment 228. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 6 days of the cessation of treatment.

[00602] Embodiment 229. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 5 days of the cessation of treatment.

[00603] Embodiment 230. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 4 days of the cessation of treatment.

[00604] Embodiment 231. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 3 days of the cessation of treatment.

[00605] Embodiment 232. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 2 days of the cessation of treatment.

[00606] Embodiment 233. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 4.5 mEq/l within 1 day of the cessation of treatment.

[00607] Embodiment 234. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 5 mEq/l within 1 month of the cessation of treatment.

[00608] Embodiment 235. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 5 mEq/l within 3 weeks of the cessation of treatment.

[00609] Embodiment 236. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 5 mEq/l within 2 weeks of the cessation of treatment.

[00610] Embodiment 237. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 5 mEq/l within 10 days of the cessation of treatment.

[00611] Embodiment 238. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 5 mEq/l within 9 days of the cessation of treatment.

[00612] Embodiment 239. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 5 mEq/l within 8 days of the cessation of treatment.

[00613] Embodiment 240. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 5 mEq/l within 7 days of the cessation of treatment.

[00614] Embodiment 241. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 5 mEq/l within 6 days of the cessation of treatment.

[00615] Embodiment 242. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 5 mEq/l within 5 days of the cessation of treatment.

[00616] Embodiment 243. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 5 mEq/l within 4 days of the cessation of treatment.

[00617] Embodiment 244. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 5 mEq/l within 3 days of the cessation of treatment.

[00618] Embodiment 245. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 5 mEq/l within 2 days of the cessation of treatment.

[00619] Embodiment 246. The method of any preceding enumerated embodiment wherein, upon cessation of the treatment, the individual's serum bicarbonate value decreases by at least 5 mEq/l within 1 day of the cessation of treatment.

[00620] Embodiment 247. The method of any preceding enumerated embodiment wherein the baseline serum bicarbonate value is the value of the serum bicarbonate concentration determined at a single time point.

[00621] Embodiment 248. The method of any of embodiments 1 to 246 wherein the baseline serum bicarbonate value is the mean value of at least two serum bicarbonate concentrations determined at different time-points.

[00622] Embodiment 249. The method of any of embodiments 1 to 246 wherein the baseline serum bicarbonate value is the mean value of at least two serum bicarbonate concentrations for serum samples drawn on different days.

[00623] Embodiment 250. The method of embodiment 249 wherein the baseline serum bicarbonate value is the mean value of at least two serum bicarbonate concentrations for serum samples drawn on consecutive days.

[00624] Embodiment 251. The method of embodiment 249 wherein the baseline serum bicarbonate value is the mean value of at least two serum bicarbonate concentrations for serum samples drawn on two consecutive days and prior to the initiation of the treatment.

[00625] Embodiment 252. The method of embodiment 249 wherein the baseline serum bicarbonate value is the mean or median value of at least two serum bicarbonate concentrations for serum samples drawn on non-consecutive days.

[00626] Embodiment 253. The method of embodiment 252 wherein the non-consecutive days are separated by at least two days.

[00627] Embodiment 254. The method of embodiment 252 wherein the non-consecutive days are separated by at least one week.

[00628] Embodiment 255. The method of embodiment 252 wherein the non-consecutive days are separated by at least two weeks.

[00629] Embodiment 256. The method of embodiment 252 wherein the non-consecutive days are separated by at least three weeks.

[00630] Embodiment 257. The method of any preceding enumerated embodiment wherein the individual is being treated for acute metabolic acidosis.

[00631] Embodiment 258. The method of any preceding enumerated embodiment wherein the individual is being treated for chronic metabolic acidosis.

[00632] Embodiment 259. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 7.5 mEq of a target species as it transits the digestive system.

[00633] Embodiment 260. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 10 mEq of a target species as it transits the digestive system.

[00634] Embodiment 261. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 15 mEq of a target species as it transits the digestive system.

[00635] Embodiment 262. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 20 mEq of a target species as it transits the digestive system.

[00636] Embodiment 263. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 25 mEq of a target species as it transits the digestive system.

[00637] Embodiment 264. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 30 mEq of a target species as it transits the digestive system.

[00638] Embodiment 265. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 35 mEq of a target species as it transits the digestive system.

[00639] Embodiment 266. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 40 mEq of a target species as it transits the digestive system.

[00640] Embodiment 267. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 45 mEq of a target species as it transits the digestive system.

[00641] Embodiment 268. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 50 mEq of a target species as it transits the digestive system.

[00642] Embodiment 269. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 55 mEq of a target species as it transits the digestive system.

[00643] Embodiment 270. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 60 mEq of a target species as it transits the digestive system.

[00644] Embodiment 271. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 65 mEq of a target species as it transits the digestive system.

[00645] Embodiment 272. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 70 mEq of a target species as it transits the digestive system.

[00646] Embodiment 273. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 75 mEq of a target species as it transits the digestive system.

[00647] Embodiment 274. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 80 mEq of a target species as it transits the digestive system.

[00648] Embodiment 275. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 85 mEq of a target species as it transits the digestive system.

[00649] Embodiment 276. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 90 mEq of a target species as it transits the digestive system.

[00650] Embodiment 277. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 95 mEq of a target species as it transits the digestive system.

[00651] Embodiment 278. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 100 mEq of a target species as it transits the digestive system.

[00652] Embodiment 279. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 105 mEq of a target species as it transits the digestive system.

[00653] Embodiment 280. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least 110 mEq of a target species as it transits the digestive system.

[00654] Embodiment 281. The method of any preceding enumerated embodiment wherein the daily dose is no more than 100 g/day.

[00655] Embodiment 282. The method of any preceding enumerated embodiment wherein the daily dose is no more than 90 g/day.

[00656] Embodiment 283. The method of any preceding enumerated embodiment wherein the daily dose is less than 75 g/day.

[00657] Embodiment 284. The method of any preceding enumerated embodiment wherein the daily dose is less than 65 g/day.

[00658] Embodiment 285. The method of any preceding enumerated embodiment wherein the daily dose is less than 50 g/day.

[00659] Embodiment 286. The method of any preceding enumerated embodiment wherein the daily dose is less than 40 g/day.

[00660] Embodiment 287. The method of any preceding enumerated embodiment wherein the daily dose is less than 30 g/day.

[00661] Embodiment 288. The method of any preceding enumerated embodiment wherein the daily dose is less than 25 g/day.

[00662] Embodiment 289. The method of any preceding enumerated embodiment wherein the daily dose is less than 20 g/day.

[00663] Embodiment 290. The method of any preceding enumerated embodiment wherein the daily dose is less than 15 g/day.

[00664] Embodiment 291. The method of any preceding enumerated embodiment wherein the daily dose is less than 10 g/day.

[00665] Embodiment 292. The method of any preceding enumerated embodiment wherein the daily dose is less than 5 g/day.

[00666] Embodiment 293. The method of any preceding enumerated embodiment wherein the individual is treated for at least one day.

[00667] Embodiment 294. The method of any preceding enumerated embodiment wherein the individual is treated for at least one week.

[00668] Embodiment 295. The method of any preceding enumerated embodiment wherein the individual is treated for at least one month.

[00669] Embodiment 296. The method of any preceding enumerated embodiment wherein the individual is treated for at least several months.

[00670] Embodiment 297. The method of any preceding enumerated embodiment wherein the individual is treated for at least six months.

[00671] Embodiment 298. The method of any preceding enumerated embodiment wherein the individual is treated for at least one year.

[00672] Embodiment 299. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles having a median particle diameter size (volume distribution) of at least 3 microns.

[00673] Embodiment 300. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles having a median particle diameter size (volume distribution) in the range of 5 to 1,000 microns.

[00674] Embodiment 301. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles having a median particle diameter size (volume distribution) in the range of 5 to 500 microns.

[00675] Embodiment 302. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles having a median particle diameter size (volume distribution) in the range of 10 to 400 microns.

[00676] Embodiment 303. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles having a median particle diameter size (volume distribution) in the range of 10 to 300 microns.

[00677] Embodiment 304. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable

composition comprising a population of particles having a median particle diameter size (volume distribution) in the range of 20 to 250 microns.

[00678] Embodiment 305. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles having a median particle diameter size (volume distribution) in the range of 30 to 250 microns.

[00679] Embodiment 306. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles having a median particle diameter size (volume distribution) in the range of 40 to 180 microns.

[00680] Embodiment 307. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles in which less than 7% of the particles in the population (volume distribution) have a diameter less than 10 microns.

[00681] Embodiment 308. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles in which less than 5% of the particles in the particles in the population (volume distribution) have a diameter less than 10 microns.

[00682] Embodiment 309. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles in which less than 2.5% of the particles in the particles in the population (volume distribution) have a diameter less than 10 microns.

[00683] Embodiment 310. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles in which less than 1% of the particles in the particles in the population (volume distribution) have a diameter less than 10 microns.

[00684] Embodiment 311. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable

composition comprising a population of particles having a particle size range that is (i) large enough to avoid passive or active absorption through the GI tract and (ii) small enough to not cause grittiness or unpleasant mouth feel when ingested as a powder, suspension, gel, and/or tablet.

[00685] Embodiment 312. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles have a Swelling Ratio of less than 9.

[00686] Embodiment 313. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles have a Swelling Ratio of less than 8.

[00687] Embodiment 314. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles have a Swelling Ratio of less than 7.

[00688] Embodiment 315. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles have a Swelling Ratio of less than 6.

[00689] Embodiment 316. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles have a Swelling Ratio of less than 5.

[00690] Embodiment 317. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles have a Swelling Ratio of less than 4.

[00691] Embodiment 318. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles have a Swelling Ratio of less than 3.

[00692] Embodiment 319. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a population of particles have a Swelling Ratio of less than 2.

[00693] Embodiment 320. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species of at least about 0.5 mEq/g.

[00694] Embodiment 321. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species of at least about 1 mEq/g.

[00695] Embodiment 322. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species of at least about 2 mEq/g.

[00696] Embodiment 323. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species of at least about 3 mEq/g.

[00697] Embodiment 324. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species of at least about 4 mEq/g.

[00698] Embodiment 325. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species of at least about 5 mEq/g.

[00699] Embodiment 326. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species of at least about 7.5 mEq/g.

[00700] Embodiment 327. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species of at least about 10 mEq/g.

[00701] Embodiment 328. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species of at least about 12.5 mEq/g.

[00702] Embodiment 329. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species of at least about 15 mEq/g.

[00703] Embodiment 330. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species of at least about 20 mEq/g.

[00704] Embodiment 331. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species of at least about 25 mEq/g.

[00705] Embodiment 332. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species of at least about 30 mEq/g.

[00706] Embodiment 333. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species of at least about 35 mEq/g.

[00707] Embodiment 334. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species in the range of 2 to 25 mEq/g.

[00708] Embodiment 335. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species in the range of 3 to 25 mEq/g.

[00709] Embodiment 336. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species in the range of 5 to 25 mEq/g.

[00710] Embodiment 337. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species in the range of 10 to 25 mEq/g.

[00711] Embodiment 338. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species in the range of 5 to 20 mEq/g.

[00712] Embodiment 339. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species in the range of 6 to 20 mEq/g.

[00713] Embodiment 340. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species in the range of 7.5 to 20 mEq/g.

[00714] Embodiment 341. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has a theoretical binding capacity for the target species in the range of 10 to 20 mEq/g.

[00715] Embodiment 342. The method of any preceding enumerated embodiment wherein the theoretical binding capacity for the target species is the theoretical binding capacity as determined in a SGF assay.

[00716] Embodiment 343. The method of any preceding enumerated embodiment wherein the target species comprises protons.

[00717] Embodiment 344. The method of any preceding enumerated embodiment wherein the target species comprises the conjugate base of a strong acid.

[00718] Embodiment 345. The method of any preceding enumerated embodiment wherein the target species comprises the conjugate base of a strong acid selected from the group consisting of chloride, bisulfate and sulfate ions.

[00719] Embodiment 346. The method of any preceding enumerated embodiment wherein the target species comprises chloride ions.

[00720] Embodiment 347. The method of any preceding enumerated embodiment wherein the target species comprises a strong acid.

[00721] Embodiment 348. The method of any preceding enumerated embodiment wherein the target species comprises hydrochloric acid.

[00722] Embodiment 349. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 1 mEq/g in a SIB assay.

[00723] Embodiment 350. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 1.5 mEq/g in a SIB assay.

[00724] Embodiment 351. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 2 mEq/g in a SIB assay.

[00725] Embodiment 352. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 2.5 mEq/g in a SIB assay.

[00726] Embodiment 353. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 3 mEq/g in a SIB assay.

[00727] Embodiment 354. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 3.5 mEq/g in a SIB assay.

[00728] Embodiment 355. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 4 mEq/g in a SIB assay.

[00729] Embodiment 356. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 4.5 mEq/g in a SIB assay.

[00730] Embodiment 357. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 5 mEq/g in a SIB assay.

[00731] Embodiment 358. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 5.5 mEq/g in a SIB assay.

[00732] Embodiment 359. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 6 mEq/g in a SIB assay.

[00733] Embodiment 360. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.1:1, respectively.

[00734] Embodiment 361. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.2:1, respectively.

[00735] Embodiment 362. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.25:1, respectively.

[00736] Embodiment 363. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.3:1, respectively.

[00737] Embodiment 364. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.35:1, respectively.

[00738] Embodiment 365. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.4:1, respectively.

[00739] Embodiment 366. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.45:1, respectively.

[00740] Embodiment 367. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.5:1, respectively.

[00741] Embodiment 368. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 2:3, respectively.

[00742] Embodiment 369. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.75:1, respectively.

[00743] Embodiment 370. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 0.9:1, respectively.

[00744] Embodiment 371. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 1:1, respectively.

[00745] Embodiment 372. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 1.25:1, respectively.

[00746] Embodiment 373. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 1.5:1, respectively.

[00747] Embodiment 374. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 1.75:1, respectively.

[00748] Embodiment 375. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 2:1, respectively.

[00749] Embodiment 376. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 2.25:1, respectively.

[00750] Embodiment 377. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 2.5:1, respectively.

[00751] Embodiment 378. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 2.75:1, respectively.

[00752] Embodiment 379. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 3:1, respectively.

[00753] Embodiment 380. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 4:1, respectively.

[00754] Embodiment 381. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 5:1, respectively.

[00755] Embodiment 382. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 6:1, respectively.

[00756] Embodiment 383. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride toc bound phosphate in a SIB assay is at least 7:1, respectively.

[00757] Embodiment 384. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 8:1, respectively.

[00758] Embodiment 385. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 9:1, respectively.

[00759] Embodiment 386. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 10:1, respectively.

[00760] Embodiment 387. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 12.5:1, respectively.

[00761] Embodiment 388. The method of any preceding enumerated embodiment wherein the ratio of the amount of bound chloride to bound phosphate in a SIB assay is at least 15:1, respectively.

[00762] Embodiment 389. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 5 mEq/day of the target species.

[00763] Embodiment 390. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 6 mEq/day of the target species.

[00764] Embodiment 391. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 7 mEq/day of the target species.

[00765] Embodiment 392. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 8 mEq/day of the target species.

[00766] Embodiment 393. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 9 mEq/day of the target species.

[00767] Embodiment 394. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 10 mEq/day of the target species.

[00768] Embodiment 395. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 11 mEq/day of the target species.

[00769] Embodiment 396. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 12 mEq/day of the target species.

[00770] Embodiment 397. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 13 mEq/day of the target species.

[00771] Embodiment 398. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 14 mEq/day of the target species.

[00772] Embodiment 399. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 15 mEq/day of the target species.

[00773] Embodiment 400. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 16 mEq/day of the target species.

[00774] Embodiment 401. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 17 mEq/day of the target species.

[00775] Embodiment 402. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 18 mEq/day of the target species.

[00776] Embodiment 403. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 19 mEq/day of the target species.

[00777] Embodiment 404. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 20 mEq/day of the target species.

[00778] Embodiment 405. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 21 mEq/day of the target species.

[00779] Embodiment 406. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 22 mEq/day of the target species.

[00780] Embodiment 407. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 23 mEq/day of the target species.

[00781] Embodiment 408. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 24 mEq/day of the target species.

[00782] Embodiment 409. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 25 mEq/day of the target species.

[00783] Embodiment 410. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 26 mEq/day of the target species.

[00784] Embodiment 411. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 27 mEq/day of the target species.

[00785] Embodiment 412. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 28 mEq/day of the target species.

[00786] Embodiment 413. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 29 mEq/day of the target species.

[00787] Embodiment 414. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 30 mEq/day of the target species.

[00788] Embodiment 415. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 31 mEq/day of the target species.

[00789] Embodiment 416. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 32 mEq/day of the target species.

[00790] Embodiment 417. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 33 mEq/day of the target species.

[00791] Embodiment 418. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 34 mEq/day of the target species.

[00792] Embodiment 419. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 35 mEq/day of the target species.

[00793] Embodiment 420. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 36 mEq/day of the target species.

[00794] Embodiment 421. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 37 mEq/day of the target species.

[00795] Embodiment 422. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 38 mEq/day of the target species.

[00796] Embodiment 423. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 39 mEq/day of the target species.

[00797] Embodiment 424. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 40 mEq/day of the target species.

[00798] Embodiment 425. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 41 mEq/day of the target species.

[00799] Embodiment 426. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 42 mEq/day of the target species.

[00800] Embodiment 427. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 43 mEq/day of the target species.

[00801] Embodiment 428. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 44 mEq/day of the target species.

[00802] Embodiment 429. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 45 mEq/day of the target species.

[00803] Embodiment 430. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 46 mEq/day of the target species.

[00804] Embodiment 431. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 47 mEq/day of the target species.

[00805] Embodiment 432. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 48 mEq/day of the target species.

[00806] Embodiment 433. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 49 mEq/day of the target species.

[00807] Embodiment 434. The method of any preceding enumerated embodiment wherein the daily dose has the capacity to remove at least about 50 mEq/day of the target species.

[00808] Embodiment 435. The method of any preceding enumerated embodiment wherein the daily dose removes less than 60 mEq/day of the target species.

[00809] Embodiment 436. The method of any preceding enumerated embodiment wherein the daily dose removes less than 55 mEq/day of the target species.

[00810] Embodiment 437. The method of any of embodiments 1 to 433 wherein the daily dose removes less than 50 mEq/day of the target species.

[00811] Embodiment 438. The method of any of embodiments 1 to 428 wherein the daily dose removes less than 45 mEq/day of the target species.

[00812] Embodiment 439. The method of any of embodiments 1 to 423 wherein the daily dose removes less than 40 mEq/day of the target species.

[00813] Embodiment 440. The method of any of embodiments 1 to 418 wherein the daily dose removes less than 35 mEq/day of the target species.

[00814] Embodiment 441. The method of any of embodiments 1 to 417 wherein the daily dose removes less than 34 mEq/day of the target species.

[00815] Embodiment 442. The method of any of embodiments 1 to 416 wherein the daily dose removes less than 33 mEq/day of the target species.

[00816] Embodiment 443. The method of any of embodiments 1 to 415 wherein the daily dose removes less than 32 mEq/day of the target species.

[00817] Embodiment 444. The method of any of embodiments 1 to 414 wherein the daily dose removes less than 31 mEq/day of the target species.

[00818] Embodiment 445. The method of any of embodiments 1 to 413 wherein the daily dose removes less than 30 mEq/day of the target species.

[00819] Embodiment 446. The method of any of embodiments 1 to 412 wherein the daily dose removes less than 29 mEq/day of the target species.

[00820] Embodiment 447. The method of any of embodiments 1 to 411 wherein the daily dose removes less than 28 mEq/day of the target species.

[00821] Embodiment 448. The method of any of embodiments 1 to 410 wherein the daily dose removes less than 27 mEq/day of the target species.

[00822] Embodiment 449. The method of any of embodiments 1 to 409 wherein the daily dose removes less than 26 mEq/day of the target species.

[00823] Embodiment 450. The method of any of embodiments 1 to 408 wherein the daily dose removes less than 25 mEq/day of the target species.

[00824] Embodiment 451. The method of any of embodiments 1 to 407 wherein the daily dose removes less than 24 mEq/day of the target species.

[00825] Embodiment 452. The method of any of embodiments 1 to 406 wherein the daily dose removes less than 23 mEq/day of the target species.

[00826] Embodiment 453. The method of any of embodiments 1 to 405 wherein the daily dose removes less than 22 mEq/day of the target species.

[00827] Embodiment 454. The method of any of embodiments 1 to 404 wherein the daily dose removes less than 21 mEq/day of the target species.

[00828] Embodiment 455. The method of any of embodiments 1 to 403 wherein the daily dose removes less than 20 mEq/day of the target species.

[00829] Embodiment 456. The method of any of embodiments 1 to 402 wherein the daily dose removes less than 19 mEq/day of the target species.

[00830] Embodiment 457. The method of any of embodiments 1 to 401 wherein the daily dose removes less than 18 mEq/day of the target species.

[00831] Embodiment 458. The method of any of embodiments 1 to 400 wherein the daily dose removes less than 17 mEq/day of the target species.

[00832] Embodiment 459. The method of any of embodiments 1 to 399 wherein the daily dose removes less than 16 mEq/day of the target species.

[00833] Embodiment 460. The method of any of embodiments 1 to 398 wherein the daily dose removes less than 15 mEq/day of the target species.

[00834] Embodiment 461. The method of any of embodiments 1 to 397 wherein the daily dose removes less than 14 mEq/day of the target species.

[00835] Embodiment 462. The method of any of embodiments 1 to 396 wherein the daily dose removes less than 13 mEq/day of the target species.

[00836] Embodiment 463. The method of any of embodiments 1 to 395 wherein the daily dose removes less than 12 mEq/day of the target species.

[00837] Embodiment 464. The method of any of embodiments 1 to 394 wherein the daily dose removes less than 11 mEq/day of the target species.

[00838] Embodiment 465. The method of any of embodiments 1 to 393 wherein the daily dose removes less than 10 mEq/day of the target species.

[00839] Embodiment 466. The method of any of embodiments 1 to 392 wherein the daily dose removes less than 9 mEq/day of the target species.

[00840] Embodiment 467. The method of any of embodiments 1 to 391 wherein the daily dose removes less than 8 mEq/day of the target species.

[00841] Embodiment 468. The method of any of embodiments 1 to 390 wherein the daily dose removes less than 7 mEq/day of the target species.

[00842] Embodiment 469. The method of any of embodiments 1 to 389 wherein the daily dose removes less than 6 mEq/day of the target species.

[00843] Embodiment 470. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material comprising an insoluble (in the gastric environment) support structure and exchangeable cations.

[00844] Embodiment 471. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material comprising an insoluble (in the gastric environment) support structure and exchangeable cations wherein the cation exchange material is organic, inorganic or a composite thereof.

[00845] Embodiment 472. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material comprising exchangeable cations selected from the group consisting of lithium, sodium, potassium, calcium, magnesium, iron and combinations thereof.

[00846] Embodiment 473. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material comprising exchangeable cations selected from the group consisting of sodium, potassium, calcium, magnesium, and combinations thereof.

[00847] Embodiment 474. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material comprising exchangeable cations selected from the group consisting of sodium, potassium, and combinations thereof.

[00848] Embodiment 475. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material comprising a combination of exchangeable cations that establish or maintain electrolyte homeostasis.

[00849] Embodiment 476. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material optionally containing exchangeable sodium ions provided, however, that the amount of the sodium ions in a daily dose is insufficient to increase the patient's serum sodium ion concentration to a value outside the range of 135 to 145 mEq/l.

[00850] Embodiment 477. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material optionally containing exchangeable potassium ions provided, however, that the amount of the sodium ions in a daily dose is insufficient to increase the patient's serum potassium ion concentration to a value outside the range of 3.7 to 5.2 mEq/L.

[00851] Embodiment 478. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material optionally containing exchangeable magnesium ions provided, however, that the amount of the magnesium ions in a daily dose is insufficient to increase the patient's serum magnesium ion concentration to a value outside the range of 1.7 to 2.2 mg/dL.

[00852] Embodiment 479. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material optionally containing exchangeable calcium ions provided, however, that the amount of the calcium ions in a daily dose is insufficient to increase the patient's serum calcium ion concentration to a value outside the range of 8.5 to 10.2 mg/dL.

[00853] Embodiment 480. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material optionally containing a combination of exchangeable cations selected from the group consisting of sodium, potassium, calcium, magnesium, and combinations thereof, designed to maintain serum Na^+ levels within the range of 135 to 145 mEq/l, serum K^+ levels within the range of 3.7 to 5.2 mEq/L, serum Mg^{2+} levels within the range of 1.7 to 2.2 mg/dL and serum Ca^{2+} levels within the range of 8.5 to 10.2 mg/dL.

[00854] Embodiment 481. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material containing exchangeable sodium ions and the composition contains less than 12% by weight sodium.

[00855] Embodiment 482. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material containing exchangeable sodium ions and the composition contains less than 9% by weight sodium.

[00856] Embodiment 483. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material containing exchangeable sodium ions and the composition contains less than 6% by weight sodium.

[00857] Embodiment 484. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material containing exchangeable sodium ions and the composition contains less than 3% by weight sodium.

[00858] Embodiment 485. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material containing exchangeable sodium ions and the composition contains less than 1% by weight sodium.

[00859] Embodiment 486. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material containing exchangeable sodium ions and the composition contains less than 0.1% by weight sodium.

[00860] Embodiment 487. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material containing exchangeable sodium ions and the composition contains less than 0.01% by weight sodium.

[00861] Embodiment 488. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange material containing exchangeable sodium ions and the composition contains between 0.05 and 3% by weight sodium.

[00862] Embodiment 489. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a polymeric material having the capacity to bind protons in aqueous solutions.

[00863] Embodiment 490. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a polymeric material having the capacity to bind protons in aqueous solutions and the nonabsorbable composition is selected from the group consisting of crosslinked polymeric materials containing a polyanion backbone.

[00864] Embodiment 491. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a polymeric material having the capacity to bind protons in aqueous solutions and the nonabsorbable composition is selected from the group consisting of crosslinked polymeric materials containing a polyanion backbone wherein the polyanion backbone is selected from the group consisting of poly(carboxylic acids), poly(acrylic acids), poly(sulfonic acids), poly(maleic acids), poly(phenols), functionalized polyols and poly(alcohols), poly(hydroxamic acids), poly(imides) and copolymers thereof.

[00865] Embodiment 492. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a polymeric material having the capacity to bind protons in aqueous solutions, the nonabsorbable composition is selected from the group consisting of crosslinked polymeric materials containing a polyanion backbone, and the polyanion backbone is coordinated to exchangeable monovalent cations, divalent cations, or a combination thereof.

[00866] Embodiment 493. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange resin comprising a polyanion backbone that exchanges cations for protons and has an average pKa of at least 4.

[00867] Embodiment 494. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange resin comprising a polyanion backbone that exchanges cations for protons and has an average pKa of 4-5.

[00868] Embodiment 495. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange resin comprising a polyanion backbone that exchanges cations for protons and has an average pKa of 5-6.

[00869] Embodiment 496. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange resin comprising a polyanion backbone that exchanges cations for protons and has an average pKa of 6-7.

[00870] Embodiment 497. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange resin

comprising a polyanion backbone that exchanges cations for protons and has an average pKa of at least 7.

[00871] Embodiment 498. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange resin selected from the group consisting of poly(carboxylic acids), poly(acrylic acids), poly(sulfonic acids), poly(maleic acids), poly(phenols), functionalized polyols and poly(alcohols), poly(hydroxamic acids), poly(imides) and copolymers thereof.

[00872] Embodiment 499. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange resin selected from the group consisting of poly(carboxylic acids), poly(acrylic acids), poly(sulfonic acids), poly(maleic acids), poly(phenols), functionalized polyols and poly(alcohols), poly(hydroxamic acids), poly(imides) and copolymers thereof wherein the polyanion backbone is further functionalized with functional groups to affect the pKa.

[00873] Embodiment 500. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange resin selected from the group consisting of poly(carboxylic acids), poly(acrylic acids), poly(sulfonic acids), poly(maleic acids), poly(phenols), functionalized polyols and poly(alcohols), poly(hydroxamic acids), poly(imides) and copolymers thereof wherein the polyanion backbone is further functionalized with functional groups to affect the pKa, the functional groups being electron withdrawing or electron donating functional groups.

[00874] Embodiment 501. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a cation exchange resin selected from the group consisting of poly(carboxylic acids), poly(acrylic acids), poly(sulfonic acids), poly(maleic acids), poly(phenols), functionalized polyols and poly(alcohols), poly(hydroxamic acids), poly(imides) and copolymers thereof wherein the polyanion backbone is further functionalized with functional groups to affect the pKa, the functional groups being electron withdrawing or electron donating functional groups selected from the group consisting of flouro, chloro, amino, hydroxyl, alkoxy, phenyl, subphyla, nitroxyl, and cyano.

[00875] Embodiment 502. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a ceramic material.

[00876] Embodiment 503. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a ceramic material and the ceramic material is microporous or mesoporous.

[00877] Embodiment 504. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a ceramic material and the ceramic material is microporous.

[00878] Embodiment 505. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a ceramic material and the ceramic material is mesoporous.

[00879] Embodiment 506. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a ceramic material and the ceramic material is a cation exchange ceramic composition.

[00880] Embodiment 507. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a ceramic material and the ceramic material comprises a molecular sieve.

[00881] Embodiment 508. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a ceramic material and the ceramic material comprises a molecular sieve selected from the group consisting of silicas, metalloaluminates, aluminophosphates and gallogerminates.

[00882] Embodiment 509. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a ceramic material and the ceramic material comprises a silica molecular sieve.

[00883] Embodiment 510. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a ceramic material and the ceramic material comprises a titanoslicate molecular sieve.

[00884] Embodiment 511. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a ceramic material and the ceramic material comprises a metallosilicate molecular sieve.

[00885] Embodiment 512. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a ceramic material and the ceramic material comprises a zeolite, a borosilicate, a gallosilicate, a ferrisilicate or a chromosilicate molecular sieve.

[00886] Embodiment 513. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a ceramic material and the ceramic material comprises a molecular sieve.

[00887] Embodiment 514. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is an anion exchange material comprising an insoluble (in the gastric environment) support structure and exchangeable anions.

[00888] Embodiment 515. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is an anion exchange material comprising an insoluble (in the gastric environment) support structure and exchangeable anions and the anion exchange material is organic, inorganic, or a composite thereof.

[00889] Embodiment 516. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a strongly basic anion exchange material.

[00890] Embodiment 517. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a weakly basic anion exchange material.

[00891] Embodiment 518. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is an anion exchange material comprising quaternary amine moieties, phosphonium salts, N-heteroaromatic salts, or combinations thereof.

[00892] Embodiment 519. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is an anion exchange material comprising a poly(ionic liquid), wherein the side chain is selected from the group consisting of salts of tetraalkyl ammonium, imidazolium, pyridinium, pyrrolidonium, guanidinium, piperidinium, and tetraalkyl phosphonium cations and combinations thereof.

[00893] Embodiment 520. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is an anion exchange material having the capacity to induce an increase in the individual's serum bicarbonate value, at least in part, by delivering a physiologically significant amount of hydroxide, carbonate, citrate or other bicarbonate equivalent, or a combination thereof.

[00894] Embodiment 521. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is an anion exchange material comprising at least 1 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion, or a combination thereof.

[00895] Embodiment 522. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is an anion exchange material comprising at least 2 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion.

[00896] Embodiment 523. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is an anion exchange material comprising at least 5 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion.

[00897] Embodiment 524. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is an anion exchange material comprising at least 10 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion.

[00898] Embodiment 525. The method of any of embodiments 1 to 523 wherein the nonabsorbable composition is an anion exchange material comprising less than 10 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion, or a combination thereof.

[00899] Embodiment 526. The method of any of embodiments 1 to 522 wherein the nonabsorbable composition is an anion exchange material comprising less than 5 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion.

[00900] Embodiment 527. The method of any of embodiments 1 to 522 wherein the nonabsorbable composition is an anion exchange material comprising less than 2.5 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion.

[00901] Embodiment 528. The method of any of embodiments 1 to 520 wherein the nonabsorbable composition is an anion exchange material comprising less than 1 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion.

[00902] Embodiment 529. The method of any of embodiments 1 to 519 wherein the nonabsorbable composition is an anion exchange material comprising less than 0.1 mEq/g of an anion selected from the group consisting of hydroxide, carbonate, citrate or other bicarbonate equivalent anion.

[00903] Embodiment 530. The method of any of embodiments 521 to 529 wherein the bicarbonate equivalent anion is selected from the group consisting of acetate, lactate and the conjugate bases of other short chain carboxylic acids.

[00904] Embodiment 531. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is an amphoteric ion exchange resin.

[00905] Embodiment 532. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a neutral composition having the capacity to bind both protons and anions.

[00906] Embodiment 533. The method of any preceding enumerated embodiment wherein the nonabsorbable composition is a neutral composition having

the capacity to bind both protons and anions selected from the group consisting of polymers functionalized with propylene oxide, polymers functionalized with Michael acceptors, expanded porphyrins, covalent organic frameworks, and polymers containing amine and/or phosphine functional groups.

[00907] Embodiment 534. The method of any preceding enumerated embodiment wherein the nonabsorbable composition (i) removes more chloride ions than bicarbonate equivalent anions (ii) removes more chloride ions than phosphate anions, and (iii) removes more chloride ions than the conjugate bases of bile and fatty acids.

[00908] Embodiment 535. The method of any preceding enumerated embodiment wherein the treatment with the nonabsorbable composition does not have a clinically significant impact upon the serum or colon levels of a metabolically relevant species.

[00909] Embodiment 536. The method of any preceding enumerated embodiment wherein the treatment with the nonabsorbable composition does not have a clinically significant impact upon the serum or colon levels of a metabolically relevant cationic species.

[00910] Embodiment 537. The method of any preceding enumerated embodiment wherein the treatment with the nonabsorbable composition does not have a clinically significant impact upon the serum or colon levels of a metabolically relevant anionic species.

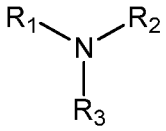
[00911] Embodiment 538. The method of any preceding enumerated embodiment wherein the treatment with the nonabsorbable composition does not have a clinically significant impact upon the serum potassium levels of a statistically significant number of individuals.

[00912] Embodiment 539. The method of any preceding enumerated embodiment wherein the treatment with the nonabsorbable composition does not have a clinically significant impact upon the serum phosphate levels of a statistically significant number of individuals.

[00913] Embodiment 540. The method of any preceding enumerated embodiment wherein the treatment with the nonabsorbable composition does not

have a clinically significant impact upon the serum low density lipoprotein (LDL) levels of a statistically significant number of individuals.

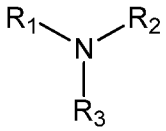
[00914] Embodiment 541. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a proton-binding, crosslinked amine polymer comprising the residue of an amine corresponding to Formula 1:



Formula 1

wherein R_1, R_2 and R_3 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen.

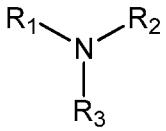
[00915] Embodiment 542. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a proton-binding, crosslinked amine polymer comprising the residue of an amine corresponding to Formula 1:



Formula 1

wherein R_1, R_2 and R_3 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen, and the crosslinked amine polymer has (i) an equilibrium proton binding capacity of at least 5 mmol/g and a chloride ion binding capacity of at least 5 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C, and (ii) an equilibrium swelling ratio in deionized water of about 2 or less.

[00916] Embodiment 543. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising the residue of an amine corresponding to Formula 1:



Formula 1

wherein R_1, R_2 and R_3 are independently hydrogen, hydrocarbyl, substituted hydrocarbyl provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen, the crosslinked amine polymer has an equilibrium swelling ratio in deionized water of about 5 or less, and the crosslinked amine polymer binds a molar ratio of chloride ions to interfering ions of at least 0.35:1, respectively, in an interfering ion buffer at 37 °C wherein the interfering ions are phosphate ions and the interfering ion buffer is a buffered solution at pH 5.5 of 36mM chloride and 20mM phosphate.

[00917] Embodiment 544. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has an equilibrium chloride binding capacity of at least 7.5 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C.

[00918] Embodiment 545. The method of any preceding enumerated embodiment wherein the nonabsorbable composition has an equilibrium chloride binding capacity of at least 10 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C.

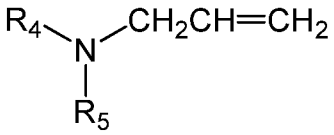
[00919] Embodiment 546. The method of any of embodiments 541 to 545 wherein R_1, R_2 and R_3 are independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic provided, however, each of R_1, R_2 and R_3 is not hydrogen.

[00920] Embodiment 547. The method of any of embodiments 541 to 545 wherein R_1, R_2 and R_3 are independently hydrogen, aliphatic or heteroaliphatic provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen.

[00921] Embodiment 548. The method of any of embodiments 541 to 547 wherein the crosslinked amine polymer is prepared by substitution polymerization of the amine with a polyfunctional crosslinker, optionally also comprising amine moieties.

[00922] Embodiment 549. The method of any of embodiments 541 to 548 wherein the crosslinked amine polymer comprises the residue of an amine

corresponding to Formula 1a and the crosslinked amine polymer is prepared by radical polymerization of an amine corresponding to Formula 1a:



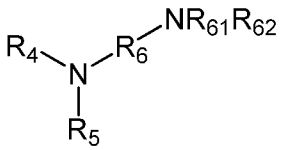
Formula 1a

wherein R_4 and R_5 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl.

[00923] Embodiment 550. The method of embodiment 549 wherein R_4 and R_5 are independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic.

[00924] Embodiment 551. The method of embodiment 549 wherein R_4 and R_5 are independently hydrogen, aliphatic or heteroaliphatic.

[00925] Embodiment 552. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a crosslinked amine polymer containing the residue of an amine corresponding to Formula 1b and the crosslinked amine polymer is prepared by substitution polymerization of the amine corresponding to Formula 1b with a polyfunctional crosslinker:



Fromula 1b

wherein R_4 and R_5 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl, R_6 is aliphatic and R_{61} and R_{62} are independently hydrogen, aliphatic, or heteroaliphatic.

[00926] Embodiment 553. The method of embodiment 552 wherein R_4 and R_5 are independently hydrogen, saturated hydrocarbon, unsaturated aliphatic, aryl, heteroaryl, heteroalkyl, or unsaturated heteroaliphatic.

[00927] Embodiment 554. The method of embodiment 552 wherein R_4 and R_5 are independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic.

[00928] Embodiment 555. The method of embodiment 552 wherein R_4 and R_5 are independently hydrogen, allyl, or aminoalkyl.

[00929] Embodiment 556. The method of any preceding enumerated embodiment wherein the pharmaceutical composition is in a dosage unit form.

[00930] Embodiment 557. The method of embodiment 556 wherein the dosage unit form is a capsule, tablet or sachet dosage form.

[00931] Embodiment 558. The method of any preceding enumerated embodiment wherein the pharmaceutical composition comprises a pharmaceutically acceptable carrier, excipient, or diluent.

[00932] Embodiment 559. The method of any preceding enumerated embodiment wherein the daily dose is administered once-a-day (QD).

[00933] Embodiment 560. The method of any preceding enumerated embodiment wherein the daily dose is administered twice-a-day (BID).

[00934] Embodiment 561. The method of any preceding enumerated embodiment wherein the daily dose is administered three times a day.

[00935] Embodiment 562. The method of any preceding enumerated embodiments wherein the daily dose is obtained from a pharmaceutical product comprising a sealed container and the nonabsorbable composition within the sealed container.

[00936] Embodiment 563. The method of embodiment 562 wherein the sealed container comprises a moisture barrier.

[00937] Embodiment 564. The method of embodiment 562 or 563 wherein the sealed container comprises an oxygen barrier.

[00938] Embodiment 565. The method of any of embodiments 562 to 564 wherein the sealed container is a sealed sachet.

[00939] Embodiment 566. The method of any of embodiments 562 to 564 wherein the sealed container comprises a multi-layer laminate of an inner contact

layer, an outer layer; and a barrier layer disposed between the contact layer and outer layer.

[00940] Embodiment 567. The method of any of embodiments 562 to 564 wherein the sealed container comprises a multi-layer laminate of an inner contact layer, an outer layer; and an oxygen-barrier layer disposed between the contact layer and outer layer.

[00941] Embodiment 568. The method of any of embodiments 562 to 564 wherein the sealed container comprises a multi-layer laminate of an inner contact layer, an outer layer; and a moisture-barrier layer disposed between the contact layer and outer layer.

[00942] Embodiment 569. The method of any of embodiments 562 to 564 wherein the sealed container comprises a multi-layer laminate of an inner contact layer, an outer layer; and an oxygen-barrier layer and a moisture-barrier layer disposed between the contact layer and outer layer.

[00943] Embodiment 570. The method of any of embodiments 562 to 564 wherein the sealed container comprises a multi-layer laminate of an inner contact layer, an outer layer; and an oxygen-scavenging layer disposed between the contact layer and the outer layer.

[00944] Embodiment 571. A composition for use in a method of treating metabolic acidosis in an adult human patient wherein in said treatment 0.1 – 12 g of said composition is administered to the patient per day, said composition being a nonabsorbable composition having the capacity to remove protons from the patient, wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 2.5 mEq/g in a Simulated Small Intestine Inorganic Buffer ("SIB") assay.

[00945] Embodiment 572. A composition for use in a method of treating metabolic acidosis in an adult human patient, said patient having a serum bicarbonate level of less than 20 mEq/L prior to treatment, said composition being a nonabsorbable composition having the capacity to remove protons from the patient.

[00946] Embodiment 573. The composition for use according to embodiment 572, wherein the patient's serum bicarbonate level is less than 19 mEq/L prior to treatment.

[00947] Embodiment 574. The composition for use according to embodiment 572, wherein the patient's serum bicarbonate level is less than 18 mEq/L prior to treatment.

[00948] Embodiment 575. The composition for use according to embodiment 572, wherein the patient's serum bicarbonate level is less than 17 mEq/L prior to treatment.

[00949] Embodiment 576. The composition for use according to embodiment 572, wherein the patient's serum bicarbonate level is less than 16 mEq/L prior to treatment.

[00950] Embodiment 577. The composition for use according to embodiment 572, wherein the patient's serum bicarbonate level is less than 15 mEq/L prior to treatment.

[00951] Embodiment 578. The composition for use according to embodiment 572, wherein the patient's serum bicarbonate level is less than 14 mEq/L prior to treatment.

[00952] Embodiment 579. The composition for use according to embodiment 572, wherein the patient's serum bicarbonate level is less than 13 mEq/L prior to treatment.

[00953] Embodiment 580. The composition for use according to embodiment 572, wherein the patient's serum bicarbonate level is less than 12 mEq/L prior to treatment.

[00954] Embodiment 581. The composition for use according to embodiment 572, wherein the patient's serum bicarbonate level is less than 11 mEq/L prior to treatment.

[00955] Embodiment 582. The composition for use according to embodiment 572, wherein the patient's serum bicarbonate level is less than 10 mEq/L prior to treatment.

[00956] Embodiment 583. The composition for use according to embodiment 572 to 582 wherein said patient's serum bicarbonate value is increased by at least 1 mEq/L over 15 days of treatment.

[00957] Embodiment 584. The composition of embodiment 572 to 583 wherein in said treatment 0.1 – 12 g of said polymer is administered to the patient per day.

[00958] Embodiment 585. The composition of any one of embodiments 572 to 584 wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 2.5 mEq/g in a Simulated Small Intestine Inorganic Buffer ("SIB") assay.

[00959] Embodiment 586. A composition for use in a method of treating metabolic acidosis in an adult human patient by increasing that patient's serum bicarbonate value by at least 1 mEq/L over 15 days of treatment, said composition being a nonabsorbable composition having the capacity to remove protons from the patient.

[00960] Embodiment 587. The composition of embodiment 571 to 586 wherein in said treatment 0.1 – 12 g of said polymer is administered to the patient per day.

[00961] Embodiment 588. The composition of any one of embodiments 572 to 587 wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 2.5 mEq/g in a Simulated Small Intestine Inorganic Buffer ("SIB") assay.

[00962] Embodiment 589. The composition according to any one of embodiments 586 to 588 wherein the patient's serum bicarbonate level value is increased by at least 1mEq/L over 15 days of treatment.

[00963] Embodiment 590. The composition for use according to any one of embodiments 586 to 589, wherein the increase in serum bicarbonate level is at least 1.5 mEq/L.

[00964] Embodiment 591. The composition for use according to any one of embodiments 586 to 590, wherein the increase in serum bicarbonate level is at least 2 mEq/L.

[00965] Embodiment 592. The composition for use according to any one of embodiments 586 to 591, wherein the increase in serum bicarbonate level is at least 2.5 mEq/L.

[00966] Embodiment 593. The composition for use according to any one of embodiments 586 to 592, wherein the increase in serum bicarbonate level is at least 3 mEq/L.

[00967] Embodiment 594. The composition for use according to any one of embodiments 586 to 593, wherein the increase in serum bicarbonate level is at least 3.5 mEq/L.

[00968] Embodiment 595. The composition for use according to any one of embodiments 586 to 594, wherein the increase in serum bicarbonate level is at least 4 mEq/L.

[00969] Embodiment 596. The composition for use according to any one of embodiments 586 to 595, wherein the increase in serum bicarbonate level is at least 4.5 mEq/L.

[00970] Embodiment 597. The composition for use according to any one of embodiments 586 to 596, wherein the increase in serum bicarbonate level is at least 5 mEq/L.

[00971] Embodiment 598. The composition for use according to embodiment any one of embodiments 586 to 597, wherein the increase is observed during 14 days of treatment.

[00972] Embodiment 599. The composition for use according to embodiment any one of embodiments 586 to 598, wherein the increase is observed during 13 days of treatment.

[00973] Embodiment 600. The composition for use according to embodiment any one of embodiments 586 to 599, wherein the increase is observed during 12 days of treatment.

[00974] Embodiment 601. The composition for use according to embodiment any one of embodiments 586 to 600, wherein the increase is observed during 11 days of treatment.

[00975] Embodiment 602. The composition for use according to embodiment any one of embodiments 586 to 601, wherein the increase is observed during 10 days of treatment.

[00976] Embodiment 603. The composition for use according to embodiment any one of embodiments 586 to 602, wherein the increase is observed during 9 days of treatment.

[00977] Embodiment 604. The composition for use according to embodiment any one of embodiments 586 to 603, wherein the increase is observed during 8 days of treatment.

[00978] Embodiment 605. The composition for use according to embodiment any one of embodiments 586 to 604, wherein the increase is observed during 7 days of treatment.

[00979] Embodiment 606. The composition for use according to embodiment any one of embodiments 586 to 605, wherein the increase is observed during 6 days of treatment.

[00980] Embodiment 607. The composition for use according to embodiment any one of embodiments 586 to 606, wherein the increase is observed during 5 days of treatment.

[00981] Embodiment 608. The composition for use according to embodiment any one of embodiments 586 to 607, wherein the increase is observed during 4 days of treatment.

[00982] Embodiment 609. The composition for use according to embodiment any one of embodiments 586 to 608, wherein the increase is observed during 3 days of treatment.

[00983] Embodiment 610. The composition for use according to embodiment any one of embodiments 586 to 609, wherein the increase is observed during 2 days of treatment.

[00984] Embodiment 611. The composition for use according to embodiment any one of embodiments 586 to 610, wherein the increase is observed during 1 day of treatment.

[00985] Embodiment 612. The composition for use according to any one of embodiments 571 to 611 wherein the specified number of days of treatment are the first days of treatment with the composition.

[00986] Embodiment 613. The composition for use according to embodiment 572 – 601, wherein in said treatment 0.1 – 12 g of said polymer is administered to the patient per day.

[00987] Embodiment 614. The composition for use according to embodiment 613, wherein in said treatment 1 – 11 g of said polymer is administered to the patient per day.

[00988] Embodiment 615. The composition for use according to embodiment 613, wherein in said treatment 2 – 10 g of said polymer is administered to the patient per day.

[00989] Embodiment 616. The composition for use according to embodiment 613, wherein in said treatment 3 – 9 g of said polymer is administered to the patient per day.

[00990] Embodiment 617. The composition for use according to embodiment 613, wherein in said treatment 3 – 8 g of said polymer is administered to the patient per day.

[00991] Embodiment 618. The composition for use according to embodiment 613, wherein in said treatment 3 – 7 g of said polymer is administered to the patient per day.

[00992] Embodiment 619. The composition for use according to embodiment 613, wherein in said treatment 3 – 6 g of said polymer is administered to the patient per day.

[00993] Embodiment 620. The composition for use according to embodiment 613, wherein in said treatment 3.5 – 5.5 g of said polymer is administered to the patient per day.

[00994] Embodiment 621. The composition for use according to embodiment 613, wherein in said treatment 4 – 5 g of said polymer is administered to the patient per day.

[00995] Embodiment 622. The composition for use according to embodiment 613, wherein in said treatment 1 – 3 g of said polymer is administered to the patient per day.

[00996] Embodiment 623. The composition for use according to embodiment 571 or 572, wherein about 0.5 g of the composition is administered to the patient per day.

[00997] Embodiment 624. The composition for use according to embodiment 571 or 572, wherein about 1 g of the composition is administered to the patient per day.

[00998] Embodiment 625. The composition for use according to embodiment 571 or 572, wherein about 1.5 g of the composition is administered to the patient per day.

[00999] Embodiment 626. The composition for use according to embodiment 571 or 572, wherein about 2 g of the composition is administered to the patient per day.

[001000] Embodiment 627. The composition for use according to embodiment 571 or 572, wherein about 2.5 g of the composition is administered to the patient per day.

[001001] Embodiment 628. The composition for use according to embodiment 571 or 572, wherein about 3 g of the composition is administered to the patient per day.

[001002] Embodiment 629. The composition for use according to embodiment 571 or 572, wherein about 3.5 g of the composition is administered to the patient per day.

[001003] Embodiment 630. The composition for use according to embodiment 571 or 572, wherein about 4.0 g of the composition is administered to the patient per day.

[001004] Embodiment 631. The composition for use according to embodiment 571 or 572, wherein about 4.5 g of the composition is administered to the patient per day.

[001005] Embodiment 632. The composition for use according to embodiment 571 or 572, wherein about 5.0 g of the composition is administered to the patient per day.

[001006] Embodiment 633. The composition for use according to any one of embodiments 571 to 632, wherein the chloride ion binding capacity in a Simulated Small Intestine Inorganic Buffer ("SIB") assay is at least 3 mEq/g.

[001007] Embodiment 634. The composition for use according to any one of embodiments 571 to 633, wherein the chloride ion binding capacity in a Simulated Small Intestine Inorganic Buffer ("SIB") assay is at least 3.5 mEq/g.

[001008] Embodiment 635. The composition for use according to any one of embodiments 571 to 634, wherein the chloride ion binding capacity in a Simulated Small Intestine Inorganic Buffer ("SIB") assay is at least 4 mEq/g.

[001009] Embodiment 636. The composition for use according to any one of embodiments 571 to 635, wherein the chloride ion binding capacity in a Simulated Small Intestine Inorganic Buffer ("SIB") assay is at least 4.5 mEq/g.

[001010] Embodiment 637. The composition for use according to any one of embodiments 571 to 636, wherein the chloride ion binding capacity in a Simulated Small Intestine Inorganic Buffer ("SIB") assay is at least 5 mEq/g.

[001011] Embodiment 638. The composition for use according any one of embodiments 571 to 637, wherein the chloride ion binding capacity in a SIB assay is less than 10 mEq/g.

[001012] Embodiment 639. The composition for use according any one of embodiments 571 to 638, wherein the chloride ion binding capacity in a SIB assay is less than 9 mEq/g.

[001013] Embodiment 640. The composition for use according any one of embodiments 571 to 639, wherein the chloride ion binding capacity in a SIB assay is less than 8 mEq/g.

[001014] Embodiment 641. The composition for use according any one of embodiments 571 to 640, wherein the chloride ion binding capacity in a SIB assay is less than 7 mEq/g.

[001015] Embodiment 642. The composition for use according any one of embodiments 571 to 641, wherein the chloride ion binding capacity in a SIB assay is less than 6 mEq/g.

[001016] Embodiment 643. The composition for use according any one of embodiments 571 to 642, wherein the chloride ion binding capacity in a SIB assay is less than 5 mEq/g.

[001017] Embodiment 644. A composition for use in a method of treating metabolic acidosis in an adult human patient wherein in said treatment >12 – 100g of said composition is administered to the patient per day, said composition being a nonabsorbable composition having the capacity to remove protons from the patient, wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of less than 2.5 mEq/g in a Simulated Small Intestine Inorganic Buffer ("SIB") assay.

[001018] Embodiment 645. The composition according to embodiments 644 wherein the patient's serum bicarbonate value is increased by at least 1mEq/L over 15 days of treatment.

[001019] Embodiment 646. A composition for use in a method of treating metabolic acidosis in an adult human patient by increasing that patient's serum bicarbonate value by at least 1 mEq/L over 15 days of treatment, wherein in said treatment >12 – 100g of said polymer is administered to the patient per day, said composition being a nonabsorbable composition having the capacity to remove protons from the patient, wherein the nonabsorbable composition is characterized by a chloride ion binding capacity of at least 2.5 mEq/g in a Simulated Small Intestine Inorganic Buffer ("SIB") assay.

[001020] Embodiment 647. The composition for use according to embodiment 645 or 646, wherein the increase in serum bicarbonate level is at least 1 mEq/L.

[001021] Embodiment 648. The composition for use according to embodiment 645 or 646, wherein the increase in serum bicarbonate level is at least 1.5 mEq/L.

[001022] Embodiment 649. The composition for use according to embodiment 645 or 646, wherein the increase in serum bicarbonate level is at least 2 mEq/L.

[001023] Embodiment 650. The composition for use according to embodiment 645 or 646, wherein the increase in serum bicarbonate level is at least 2.5 mEq/L.

[001024] Embodiment 651. The composition for use according to embodiment 645 or 646, wherein the increase in serum bicarbonate level is at least 3 mEq/L.

[001025] Embodiment 652. The composition for use according to embodiment 645 or 646, wherein the increase in serum bicarbonate level is at least 3.5 mEq/L.

[001026] Embodiment 653. The composition for use according to embodiment 645 or 646, wherein the increase in serum bicarbonate level is at least 4 mEq/L.

[001027] Embodiment 654. The composition for use according to embodiment 645 or 646, wherein the increase in serum bicarbonate level is at least 4.5 mEq/L.

[001028] Embodiment 655. The composition for use according to embodiment 645 or 646, wherein the increase in serum bicarbonate level is at least 5 mEq/L.

[001029] Embodiment 656. The composition for use according to embodiment 645 or 646, wherein the increase is observed during 14 days of treatment.

[001030] Embodiment 657. The composition for use according to embodiment 645 or 646, wherein the increase is observed during 13 days of treatment.

[001031] Embodiment 658. The composition for use according to embodiment 645 or 646, wherein the increase is observed during 12 days of treatment.

[001032] Embodiment 659. The composition for use according to embodiment 645 or 646, wherein the increase is observed during 11 days of treatment.

[001033] Embodiment 660. The composition for use according to embodiment 645 or 646, wherein the increase is observed during 10 days of treatment.

[001034] Embodiment 661. The composition for use according to embodiment 645 or 646, wherein the increase is observed during 9 days of treatment.

[001035] Embodiment 662. The composition for use according to embodiment 645 or 646, wherein the increase is observed during 8 days of treatment.

[001036] Embodiment 663. The composition for use according to embodiment 645 or 646, wherein the increase is observed during 7 days of treatment.

[001037] Embodiment 664. The composition for use according to embodiment 645 or 646, wherein the increase is observed during 6 days of treatment.

[001038] Embodiment 665. The composition for use according to embodiment 645 or 646, wherein the increase is observed during 5 days of treatment.

[001039] Embodiment 666. The composition for use according to embodiment 645 or 646, wherein the increase is observed during 4 days of treatment.

[001040] Embodiment 667. The composition for use according to embodiment 645 or 646, wherein the increase is observed during 3 days of treatment.

[001041] Embodiment 668. The composition for use according to embodiment 645 or 646, wherein the increase is observed during 2 days of treatment.

[001042] Embodiment 669. The composition for use according to embodiment 645 or 646, wherein the increase is observed during 1 day of treatment.

[001043] Embodiment 670. The composition for use according to any one of embodiments 644 to 654 wherein the specified number of days of treatment are the first days of treatment with the composition.

[001044] Embodiment 671. A composition for use according to embodiment 644 to 670 wherein 12 – 100 g is administered to the patient per day.

[001045] Embodiment 672. A composition for use according to embodiment 644 to 671 wherein 20 – 90 g is administered to the patient per day.

[001046] Embodiment 673. A composition for use according to embodiment 644 to 672 wherein 20 – 80 g is administered to the patient per day.

[001047] Embodiment 674. A composition for use according to embodiment 644 to 673 wherein 20 – 70 g is administered to the patient per day.

[001048] Embodiment 675. A composition for use according to embodiment 644 to 674 wherein 20 – 60 g is administered to the patient per day.

[001049] Embodiment 676. A composition for use according to embodiment 644 to 675 wherein 20 – 50 g is administered to the patient per day.

[001050] Embodiment 677. A composition for use according to embodiment 644 to 676 wherein 20 – 40 g is administered to the patient per day.

[001051] Embodiment 678. A composition for use according to embodiment 644 to 677 wherein 20 – 35 g is administered to the patient per day.

[001052] Embodiment 679. A composition for use according to embodiment 644 to 678 wherein 20 – 30 g is administered to the patient per day.

[001053] Embodiment 680. A composition for use according to embodiment 644 to 679 wherein 20 – 25 g is administered to the patient per day.

[001054] Embodiment 681. The composition for use according to any one of embodiments 644 to 680, wherein the chloride ion binding capacity in a Simulated Small Intestine Inorganic Buffer (“SIB”) assay is less than 2 mEq/g.

[001055] Embodiment 682. The composition for use according to any one of embodiments 644 to 681, wherein the chloride ion binding capacity in a Simulated Small Intestine Inorganic Buffer (“SIB”) assay is less than 1.5 mEq/g.

[001056] Embodiment 683. The composition for use according to any one of embodiments 644 to 682, wherein the chloride ion binding capacity in a Simulated Small Intestine Inorganic Buffer ("SIB") assay is less than 1 mEq/g.

[001057] Embodiment 684. The composition for use according to any one of embodiments 644 to 683, wherein the chloride ion binding capacity in a Simulated Small Intestine Inorganic Buffer ("SIB") assay is less than 0.75 mEq/g.

[001058] Embodiment 685. The composition for use according to any one of embodiments 644 to 684, wherein the chloride ion binding capacity in a Simulated Small Intestine Inorganic Buffer ("SIB") assay is greater than 0.5 mEq/g.

[001059] Embodiment 686. The composition for use according to any one of embodiments 644 to 685, wherein the chloride ion binding capacity in a Simulated Small Intestine Inorganic Buffer ("SIB") assay is greater than 1 mEq/g.

[001060] Embodiment 687. The composition for use according to any one of embodiments 644 to 686, wherein the chloride ion binding capacity in a Simulated Small Intestine Inorganic Buffer ("SIB") assay is greater than 1.5 mEq/g.

[001061] Embodiment 688. The composition for use according to any one of embodiments 644 to 687, wherein the chloride ion binding capacity in a Simulated Small Intestine Inorganic Buffer ("SIB") assay is greater than 2 mEq/g.

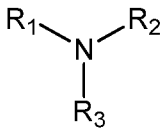
[001062] Embodiment 689. The composition for use according to any preceding embodiment wherein the composition is administered once per day in order to provide the total specified daily dose.

[001063] Embodiment 690. The composition for use according to any preceding embodiment wherein the composition is administered twice per day in order to provide the total specified daily dose.

[001064] Embodiment 691. The composition for use according to any preceding embodiment wherein the composition is administered three times per day in order to provide the total specified daily dose.

[001065] Embodiment 692. The composition for use according to any preceding enumerated embodiment wherein said composition is administered orally.

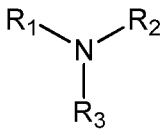
[001066] Embodiment 693. The composition for use according to any one of embodiments 571 to 692 wherein the composition is a pharmaceutical composition comprising a proton-binding, crosslinked amine polymer comprising the residue of an amine corresponding to Formula 1:



Formula 1

wherein R_1, R_2 and R_3 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen, and the crosslinked amine polymer has (i) an equilibrium proton binding capacity of at least 5 mmol/g and a chloride ion binding capacity of at least 5 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C, and (ii) an equilibrium swelling ratio in deionized water of about 2 or less.

[001067] Embodiment 694. The composition for use according to any one of embodiments 571 to 692 wherein the composition is a pharmaceutical composition comprising a proton-binding, crosslinked amine polymer comprising the residue of an amine corresponding to Formula 1:



Formula 1

wherein R_1, R_2 and R_3 are independently hydrogen, hydrocarbyl, substituted hydrocarbyl provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen, the crosslinked amine polymer has an equilibrium swelling ratio in deionized water of about 5 or less, and the crosslinked amine polymer binds a molar ratio of chloride ions to interfering ions of at least 0.35:1, respectively, in an interfering ion buffer at 37 °C wherein the interfering ions are phosphate ions and the interfering ion buffer is a buffered solution at pH 5.5 of 36mM chloride and 20mM phosphate.

[001068] Embodiment 695. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical

composition of embodiment 682 wherein the crosslinked amine polymer has an equilibrium chloride binding capacity of at least 7.5 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C.

[001069] Embodiment 696. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 682 wherein the crosslinked amine polymer has an equilibrium chloride binding capacity of at least 10 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C.

[001070] Embodiment 697. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 683 wherein the crosslinked amine polymer has an equilibrium swelling ratio in deionized water of about 4 or less.

[001071] Embodiment 698. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 683 wherein the crosslinked amine polymer has an equilibrium swelling ratio in deionized water of about 3 or less.

[001072] Embodiment 699. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 683 wherein the crosslinked amine polymer has an equilibrium swelling ratio in deionized water of about 2 or less.

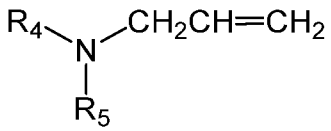
[001073] Embodiment 700. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein R_1, R_2 and R_3 are independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic provided, however, each of R_1, R_2 and R_3 is not hydrogen.

[001074] Embodiment 701. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein R_1, R_2 and R_3 are

independently hydrogen, aliphatic or heteroaliphatic provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen.

[001075] Embodiment 702. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the crosslinked amine polymer is prepared by substitution polymerization of the amine with a polyfunctional crosslinker, optionally also comprising amine moieties.

[001076] Embodiment 703. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any of embodiments 693 to 701 wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 1a and the crosslinked amine polymer is prepared by radical polymerization of an amine corresponding to Formula 1a:



Formula 1a

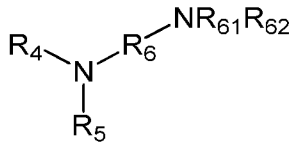
wherein R_4 and R_5 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl.

[001077] Embodiment 704. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 703 wherein R_4 and R_5 are independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic.

[001078] Embodiment 705. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 703 wherein R_4 and R_5 are independently hydrogen, aliphatic or heteroaliphatic.

[001079] Embodiment 706. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any of embodiments 693 to 701 wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 1b and the

crosslinked amine polymer is prepared by substitution polymerization of the amine corresponding to Formula 1b with a polyfunctional crosslinker:



Fromula 1b

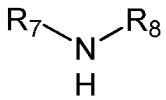
wherein R_4 and R_5 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl, R_6 is aliphatic and R_{61} and R_{62} are independently hydrogen, aliphatic, or heteroaliphatic.

[001080] Embodiment 707. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 706 wherein R_4 and R_5 are independently hydrogen, saturated hydrocarbon, unsaturated aliphatic, aryl, heteroaryl, heteroalkyl, or unsaturated heteroaliphatic.

[001081] Embodiment 708. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 706 wherein R_4 and R_5 are independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic.

[001082] Embodiment 709. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 706 wherein R_4 and R_5 are independently hydrogen, allyl, or aminoalkyl.

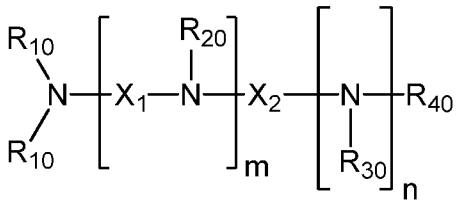
[001083] Embodiment 710. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 1c:



Formula 1c

wherein R_7 is hydrogen, aliphatic or heteroaliphatic and R_8 is aliphatic or heteroaliphatic.

[001084] Embodiment 711. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any of embodiments 693 to 701 wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 2:

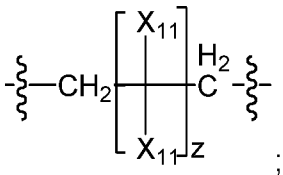


Formula 2

wherein

m and n are independently non-negative integers;

R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl;

X_1 is  ;

X_2 is hydrocarbyl or substituted hydrocarbyl;

each X_{11} is independently hydrogen, hydrocarbyl, substituted hydrocarbyl, hydroxy, or amino; and

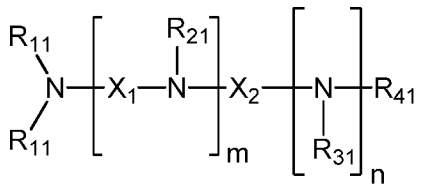
z is a non-negative number.

[001085] Embodiment 712. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 711 wherein R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, aliphatic, aryl, heteroaliphatic, or heteroaryl, m and z are independently 0-3 and n is 0 or 1.

[001086] Embodiment 713. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 711 or 712 wherein X_2 is aliphatic or heteroaliphatic.

[001087] Embodiment 714. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 711, 712 or 713 wherein m is 1-3 and X_{11} is hydrogen, aliphatic or heteroaliphatic.

[001088] Embodiment 715. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any of embodiments 693 to 701 wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 2a:



Formula 2a

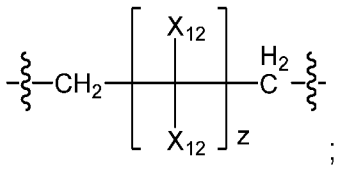
wherein

m and n are independently non-negative integers;

each R_{11} is independently hydrogen, hydrocarbyl, heteroaliphatic, or heteroaryl;

R_{21} and R_{31}, are independently hydrogen or heteroaliphatic;

R_{41} is hydrogen, substituted hydrocarbyl, or hydrocarbyl;

X_1 is  ;

X_2 is alkyl or substituted hydrocarbyl;

each X_{12} is independently hydrogen, hydroxy, amino, aminoalkyl, boronic acid or halo; and

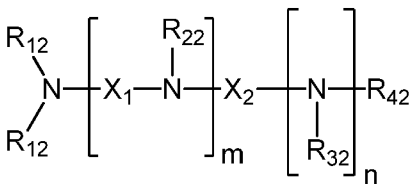
z is a non-negative number.

[001089] Embodiment 716. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 715 wherein m and z are independently 0-3 and n is 0 or 1.

[001090] Embodiment 717. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 715 or 716 wherein R_{11} is independently hydrogen, aliphatic, aminoalkyl, haloalkyl, or heteroaryl, R_{21} and R_{31} are independently hydrogen or heteroaliphatic and R_{41} is hydrogen, aliphatic, aryl, heteroaliphatic, or heteroaryl.

[001091] Embodiment 718. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 715 or 716 wherein each R_{11} is hydrogen, aliphatic, aminoalkyl, or haloalkyl, R_{21} and R_{31} are hydrogen or aminoalkyl, and R_{41} is hydrogen, aliphatic, or heteroaliphatic.

[001092] Embodiment 719. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any of embodiments 693 to 701 wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 2b:



Formula 2b

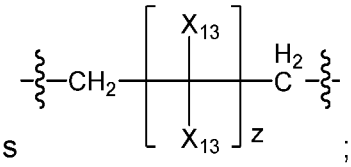
wherein

m and n are independently non-negative integers;

each R_{12} is independently hydrogen, substituted hydrocarbyl, or hydrocarbyl;

R_{22} and R_{32} are independently hydrogen substituted hydrocarbyl, or hydrocarbyl;

R_{42} is hydrogen, hydrocarbyl or substituted hydrocarbyl;

X_1 is  ;

X_2 is alkyl, aminoalkyl, or alkanol;

each X_{13} is independently hydrogen, hydroxy, alicyclic, amino, aminoalkyl, halogen, alkyl, heteroaryl, boronic acid or aryl;

z is a non-negative number; and

the amine corresponding to Formula 2b comprises at least one allyl group.

[001093] Embodiment 720. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 719 wherein m and z are independently 0-3 and n is 0 or 1.

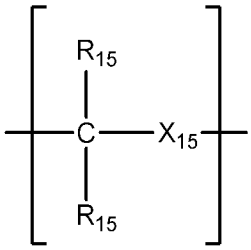
[001094] Embodiment 721. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 719 or 720 wherein R_{12} or R_{42} independently comprise at least one allyl or vinyl moiety.

[001095] Embodiment 722. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 719 or 720 wherein (i) m is a positive integer and R_{12}, R_{22} and R_{42}, in combination comprise at least two allyl or vinyl moieties or (ii) n is a positive integer and R_{12}, R_{32} and R_{42}, in combination, comprise at least two allyl or vinyl moieties.

[001096] Embodiment 723. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 719 or 720 wherein the crosslinked amine polymer comprises the residue of an amine appearing in Table A.

[001097] Embodiment 724. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 719, 720 or 723 wherein the crosslinked amine polymer is crosslinked with a crosslinking agent appearing in Table B.

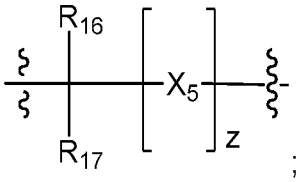
[001098] Embodiment 725. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the crosslinked amine polymer comprises a repeat unit corresponding to Formula 3:



Formula 3

wherein

R_{15}, R_{16} and R_{17} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, hydroxyl, amino, boronic acid or halo;

X_{15} is 

;

X_5 is hydrocarbyl, substituted hydrocarbyl, oxo (-O-), or amino; and

z is a non-negative number.

[001099] Embodiment 726. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 725 wherein R_{15}, R_{16} and R_{17} are independently aliphatic or heteroaliphatic.

[001100] Embodiment 727. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 725 or 726 wherein X_5 is oxo, amino, alkylamino, ethereal, alkanol, or haloalkyl.

[001101] Embodiment 728. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any of embodiments 693 to 701 wherein the crosslinked amine polymer is prepared by (i) substitution polymerization of polyfunctional reagents at

least one of which comprises amine moieties, (2) radical polymerization of a monomer comprising at least one amine moiety or nitrogen containing moiety, or (3) crosslinking of an amine-containing intermediate with a crosslinking agent, optionally containing amine moieties.

[001102] Embodiment 729. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 728 wherein the crosslinked amine polymer is a crosslinked homopolymer or a crosslinked copolymer.

[001103] Embodiment 730. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 728 wherein the crosslinked amine polymer comprises free amine moieties, separated by the same or varying lengths of repeating linker units.

[001104] Embodiment 731. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 728 wherein the crosslinked amine polymer is prepared by polymerizing an amine-containing monomer with a crosslinking agent in a substitution polymerization reaction.

[001105] Embodiment 732. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 731 wherein the amine-containing monomer is a linear amine possessing at least two reactive amine moieties to participate in the substitution polymerization reaction.

[001106] Embodiment 733. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 731 or 732 wherein the amine-containing monomer is 1,3-Bis[bis(2-aminoethyl)amino]propane, 3-Amino-1-{[2-(bis{2-[bis(3-aminopropyl)amino]ethyl}amino)ethyl](3-aminopropyl)amino}propane, 2-[Bis(2-aminoethyl)amino]ethanamine, Tris(3-aminopropyl)amine, 1,4-Bis[bis(3-aminopropyl)amino]butane, 1,2-Ethanediamine, 2-Amino-1-(2-aminoethylamino)ethane, 1,2-Bis(2-aminoethylamino)ethane, 1,3-Propanediamine, 3,3'-Diaminodipropylamine, 2,2-dimethyl-1,3-propanediamine, 2-methyl-1,3-

propanediamine, N,N'-dimethyl-1,3-propanediamine, N-methyl-1,3-diaminopropane, 3,3'-diamino-N-methyldipropylamine, 1,3-diaminopentane, 1,2-diamino-2-methylpropane, 2-methyl-1,5-diaminopentane, 1,2-diaminopropane, 1,10-diaminodecane, 1,8-diaminooctane, 1,9-diaminooctane, 1,7-diaminoheptane, 1,6-diaminohexane, 1,5-diaminopentane, 3-bromopropylamine hydrobromide, N,2-dimethyl-1,3-propanediamine, N-isopropyl-1,3-diaminopropane, N,N'-bis(2-aminoethyl)-1,3-propanediamine, N,N'-bis(3-aminopropyl)ethylenediamine, N,N'-bis(3-aminopropyl)-1,4-butanediamine tetrahydrochloride, 1,3-diamino-2-propanol, N-ethylethylenediamine, 2,2'-diamino-N-methyldiethylamine, N,N'-diethylethylenediamine, N-isopropylethylenediamine, N-methylethylenediamine, N,N'-di-tert-butylethylenediamine, N,N'-diisopropylethylenediamine, N,N'-dimethylethylenediamine, N-butylethylenediamine, 2-(2-aminoethylamino)ethanol, 1,4,7,10,13,16-hexaazacyclooctadecane, 1,4,7,10-tetraazacyclododecane, 1,4,7-triazacyclononane, N,N'-bis(2-hydroxyethyl)ethylenediamine, piperazine, bis(hexamethylene)triamine, N-(3-hydroxypropyl)ethylenediamine, N-(2-Aminoethyl)piperazine, 2-Methylpiperazine, Homopiperazine, 1,4,8,11-Tetraazacyclotetradecane, 1,4,8,12-Tetraazacyclopentadecane, 2-(Aminomethyl)piperidine, or 3-(Methylamino)pyrrolidino.

[001107] Embodiment 734. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any of embodiments 728, 730, 732, and 733 wherein the crosslinking agent is selected from the group consisting of dihaloalkanes, haloalkyloxiranes, alkyloxirane sulfonates, di(haloalkyl)amines, tri(haloalkyl) amines, diepoxides, triepoxides, tetraepoxides, bis (halomethyl)benzenes, tri(halomethyl)benzenes, tetra(halomethyl)benzenes, epihalohydrins such as epichlorohydrin and epibromohydrin poly(epichlorohydrin), (iodomethyl)oxirane, glycidyl tosylate, glycidyl 3-nitrobenzenesulfonate, 4-tosyloxy-1,2-epoxybutane, bromo-1,2-epoxybutane, 1,2-dibromoethane, 1,3-dichloropropane, 1,2- dichloroethane, l-bromo-2-chloroethane, 1,3- dibromopropane, bis(2-chloroethyl)amine, tris(2- chloroethyl)amine, and bis(2-chloroethyl)methylamine, 1,3-butadiene diepoxide, 1,5-hexadiene diepoxide, diglycidyl ether, 1,2,7,8-diepoxyoctane, 1,2,9,10-diepoxydecane, ethylene glycol diglycidyl ether, propylene glycol diglycidyl ether, 1,4-butanediol diglycidyl ether, 1,2 ethanedioldiglycidyl ether, glycerol diglycidyl ether, 1,3-diglycidyl glyceryl ether, N,N-

diglycidylaniline, neopentyl glycol diglycidyl ether, diethylene glycol diglycidyl ether, 1,4-bis(glycidyloxy)benzene, resorcinol digylcidyl ether, 1,6-hexanediol diglycidyl ether, trimethylolpropane diglycidyl ether, 1,4-cyclohexanedimethanol diglycidyl ether, 1,3-bis-(2,3-epoxypropyloxy)-2-(2,3-dihydroxypropyloxy)propane, 1,2-cyclohexanedicarboxylic acid diglycidyl ester, 2,2'-bis(glycidyloxy) diphenylmethane, bisphenol F diglycidyl ether, 1,4-bis(2',3'epoxypropyl)perfluoro-n-butane, 2,6-di(oxiran-2-ylmethy1)- 1,2,3,5,6,7-hexahydropyrrolo[3,4-f]isoindol-1,3,5,7- tetraone, bisphenol A diglycidyl ether, ethyl 5-hydroxy-6,8- di(oxiran-2-ylmethyl)-4-oxo-4-h-chromene-2-carboxylate, bis[4-(2,3-epoxy-propylthio)phenyl]-sulfide, 1,3-bis(3-glycidoxypropyl) tetramethyldisiloxane, 9,9-bis[4-(glycidyloxy)phenyl]fluorine, triepoxyisocyanurate, glycerol triglycidyl ether, N,N-diglycidyl-4-glycidyloxyaniline, isocyanuric acid (S,S,S)-triglycidyl ester, isocyanuric acid (R,R,R)-triglycidyl ester, triglycidyl isocyanurate, trimethylolpropane triglycidyl ether, glycerol propoxylate triglycidyl ether, triphenylolmethane triglycidyl ether, 3,7,14-tris[[3-(epoxypropoxy)propyl]dimethylsilyloxy]-1,3,5,7,9,11,14- heptacyclopentyltricyclo [7,3,3,15, 11]heptasiloxane, 4,4 'methylenebis(N,N-diglycidylaniline), bis(halomethyl)benzene, bis(halomethyl)biphenyl and bis(halomethyl)naphthalene, toluene diisocyanate, acrylol chloride, methyl acrylate, ethylene bisacrylamide, pyrometallic dianhydride, succinyl dichloride, dimethylsuccinate, 3-chloro-1-(3-chloropropylamino-2-propanol, 1,2-bis(3-chloropropylamino)ethane, Bis(3-chloropropyl)amine, 1,3-Dichloro-2-propanol, 1,3-Dichloropropane, 1-chloro-2,3-epoxypropane, tris[(2-oxiranyl)methyl]amine, and combinations thereof.

[001108] Embodiment 735. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 728 wherein the preparation of the crosslinked amine polymer comprises radical polymerization of an amine monomer comprising at least one amine moiety or nitrogen containing moiety.

[001109] Embodiment 736. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the crosslinked amine polymer has an equilibrium swelling ratio in deionized water of about 1.5 or less.

[001110] Embodiment 737. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the crosslinked amine polymer has an equilibrium swelling ratio in deionized water of about 1 or less.

[001111] Embodiment 738. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the crosslinked amine polymer has a chloride ion to phosphate ion binding molar ratio of at least 0.5:1, respectively, in an aqueous simulated small intestine inorganic buffer ("SIB") containing 36 mM NaCl, 20 mM NaH_2PO_4, and 50 mM 2-(N-morpholino)ethanesulfonic acid (MES) buffered to pH 5.5 and at 37 °C.

[001112] Embodiment 739. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the crosslinked amine polymer has a chloride ion to phosphate ion binding molar ratio of at least 1:1, respectively, in an aqueous simulated small intestine inorganic buffer ("SIB") containing 36 mM NaCl, 20 mM NaH_2PO_4, and 50 mM 2-(N-morpholino)ethanesulfonic acid (MES) buffered to pH 5.5 and at 37 °C.

[001113] Embodiment 740. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the crosslinked amine polymer has a chloride ion to phosphate ion binding molar ratio of at least 2:1, respectively, in an aqueous simulated small intestine inorganic buffer ("SIB") containing 36 mM NaCl, 20 mM NaH_2PO_4, and 50 mM 2-(N-morpholino)ethanesulfonic acid (MES) buffered to pH 5.5 and at 37 °C.

[001114] Embodiment 741. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the crosslinked amine polymer has a proton binding capacity of at least 10 mmol/g and a chloride ion binding capacity of at least 10 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C.

[001115] Embodiment 742. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the crosslinked amine polymer has an equilibrium proton binding capacity of at least 12 mmol/g and a chloride ion binding capacity of at least 12 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C.

[001116] Embodiment 743. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the crosslinked amine polymer has an equilibrium proton binding capacity of at least 14 mmol/g and a chloride ion binding capacity of at least 14 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C.

[001117] Embodiment 744. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the percentage of quaternized amines is less than 40%.

[001118] Embodiment 745. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the percentage of quaternized amines is less than 30%.

[001119] Embodiment 746. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the percentage of quaternized amines is less than 20%.

[001120] Embodiment 747. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the percentage of quaternized amines is less than 10%.

[001121] Embodiment 748. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the percentage of quaternized amines is less than 5%.

[001122] Embodiment 749. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the crosslinked amine polymer is a gel or a bead having a mean particle size of 40 to 180 micrometers.

[001123] Embodiment 750. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the crosslinked amine polymer is a gel or a bead having a mean particle size of 60 to 160 micrometers.

[001124] Embodiment 751. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the crosslinked amine polymer is a gel or a bead having a mean particle size of 80 to 140 micrometers.

[001125] Embodiment 752. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any one of embodiments 749 to 751 wherein less than about 0.5 volume percent of the particles have a diameter of less than about 10 micrometers.

[001126] Embodiment 753. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any one of embodiments 749 to 751 wherein less than about 5 volume percent of the particles have a diameter of less than about 20 micrometers.

[001127] Embodiment 754. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any one of embodiments 749 to 751 wherein less than about 0.5 volume percent of the particles have a diameter of less than about 20 micrometers.

[001128] Embodiment 755. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any one of embodiments 749 to 751 wherein less than about 5 volume percent of the particles have a diameter of less than about 30 micrometers.

[001129] Embodiment 756. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment in a dosage unit form.

[001130] Embodiment 757. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of embodiment 756 wherein the dosage unit form is a capsule, tablet or sachet dosage form.

[001131] Embodiment 758. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any preceding enumerated embodiment wherein the pharmaceutical composition comprises a pharmaceutically acceptable carrier, excipient, or diluent.

[001132] Embodiment 759. The composition for use according to any one of embodiments 571 to 692 wherein the composition is a method of treating and acid/base disorder in an animal including a human by removing HCl through oral administration of a pharmaceutical composition of any of the preceding enumerated embodiments.

[001133] Embodiment 760. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the method of treatment of embodiment 759 wherein the acid/base disorder is metabolic acidosis.

[001134] Embodiment 761. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the method of treatment of embodiment 759 wherein the pH is controlled or normalized.

[001135] Embodiment 762. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the method of treatment of embodiment 759 wherein the serum bicarbonate is controlled or normalized.

[001136] Embodiment 763. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the method of treatment of embodiment 759 wherein less than 1g of sodium or potassium is administered per day.

[001137] Embodiment 764. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the method of treatment of

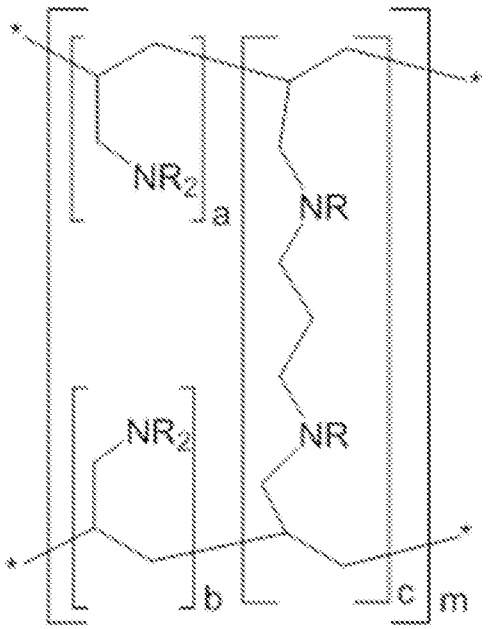
embodiment 759 wherein less than 0.5g of sodium or potassium is administered per day.

[001138] Embodiment 765. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the method of treatment of embodiment 759 wherein less than 0.1g of sodium or potassium is administered per day.

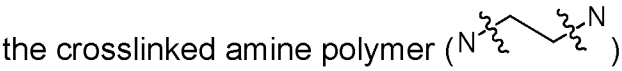
[001139] Embodiment 766. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the method of treatment of embodiment 759 wherein no sodium or potassium is administered.

[001140] Embodiment 767. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the pharmaceutical composition of any of embodiments 682-755 wherein a dose of the pharmaceutical composition is titrated based on the serum bicarbonate values of a patient in need of treatment or other indicators of acidosis.

[001141] Embodiment 768. The composition for use according to any one of embodiments 571 to 692 wherein the composition is a polymer comprising a structure corresponding to Formula 4:



Formula 4

wherein each R is independently hydrogen or an ethylene crosslink between two nitrogen atoms of the crosslinked amine polymer () and a, b, c, and m are integers.

[001142] Embodiment 769. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the polymer of embodiment 768 wherein m is a large integer indicating an extended polymer network.

[001143] Embodiment 770. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the polymer of embodiment 768 or 769 wherein a ratio of the sum of a and b to c (*i.e.*, a+b:c) is in the range of about 1:1 to 5:1.

[001144] Embodiment 771. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the polymer of embodiment 768 or 769 wherein a ratio of the sum of a and b to c (*i.e.*, a+b:c) is in the range of about 1.5:1 to 4:1.

[001145] Embodiment 772. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the polymer of embodiment 768 or 769 wherein a ratio of the sum of a and b to c (*i.e.*, a+b:c) is in the range of about 1.75:1 to 3:1.

[001146] Embodiment 773. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the polymer of embodiment 768 or 769 wherein a ratio of the sum of a and b to c (*i.e.*, a+b:c) is in the range of about 2:1 to 2.5:1.

[001147] Embodiment 774. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the polymer of embodiment 768 or 769 wherein the sum of a and b is 57 and c is 24.

[001148] Embodiment 775. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the polymer of any of embodiments 768 or 774 wherein 50-95% of the R substituents are hydrogen and 5-50% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001149] Embodiment 776. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the polymer of any of embodiments 768 or 774 wherein 55-90% of the R substituents are hydrogen and 10-45% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001150] Embodiment 777. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the polymer of any of embodiments 768 or 774 wherein 60-90% of the R substituents are hydrogen and 10-40% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001151] Embodiment 778. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the polymer of any of embodiments 768 to 774 wherein 65-90% of the R substituents are hydrogen and 10-35% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001152] Embodiment 779. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the polymer of any of embodiments 768 to 774 wherein 70-90% of the R substituents are hydrogen and 10-30% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001153] Embodiment 780. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the polymer of any of embodiments 768 to 774 wherein 75-85% of the R substituents are hydrogen and 15-25% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001154] Embodiment 781. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the polymer of any of embodiments 768 to 774 wherein 80-85% of the R substituents are hydrogen and 15-20% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001155] Embodiment 782. The composition for use according to any one of embodiments 571 to 692 wherein the composition is the polymer of any of

embodiments 768 to 774 wherein about 81% of the R substituents are hydrogen and about 19% are an ethylene crosslink.

[001156] Embodiment 783. The composition for use according to any one of embodiments 571 to 592 wherein the method of treatment further includes the feature or features set out in any one of embodiments 1 to 570, or part thereof.

[001157] Embodiment 784. A composition for use in a method of treating metabolic acidosis in an adult human patient wherein said treatment is administered to the patient less frequently than once per day, said composition being a nonabsorbable composition having the capacity to remove protons from the patient.

[001158] Embodiment 785. The composition of embodiment 784, wherein the composition is administered on a regular schedule.

[001159] Embodiment 786. The composition of embodiment 784, wherein the regular schedule is once every two days.

[001160] Embodiment 787. The composition of embodiment 785, wherein the regular schedule is once every three days.

[001161] Embodiment 788. The composition of embodiment 785, wherein the regular schedule is twice a week.

[001162] Embodiment 789. The composition of embodiment 785, wherein the regular schedule is three times a week.

[001163] Embodiment 790. The composition of embodiment 785, wherein the regular schedule is four times a week.

[001164] Embodiment 791. The composition of any one of embodiments 784 to 790 wherein the composition is as defined in any preceding enumerated embodiment.

[001165] Embodiment 792. The composition of any one of embodiments 784 to 791 wherein the method of treatment is as defined in any preceding enumerated embodiment.

[001166] Embodiment 793. A method of increasing serum bicarbonate levels in an individual afflicted with an acid-base disorder, the method comprising

oral administration of a pharmaceutical composition to increase the individual's serum bicarbonate levels wherein:

(i) the pharmaceutical composition binds a target species in the individual's digestive system when given orally, the target species being selected from the group consisting of protons, strong acids, and conjugate bases of strong acids and

(ii) the pharmaceutical composition increases the serum bicarbonate level by at least 1 mEq/l in a placebo controlled study, said increase being the difference between the cohort average serum bicarbonate level in a first cohort at the end of the study, relative to the cohort average serum bicarbonate level in a second cohort at the end of the study, wherein the first cohort's subjects receive the pharmaceutical composition and the second cohort's subjects receive a placebo, wherein the first and second cohorts each comprise at least 25 subjects, each cohort is prescribed the same diet during the study and the study lasts at least two weeks.

[001167] Embodiment 794. The method of embodiment 793 wherein the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 100 g/day.

[001168] Embodiment 795. The method of embodiment 793 wherein the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 50 g/day.

[001169] Embodiment 796. The method of embodiment 793 wherein the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 30 g/day.

[001170] Embodiment 797. The method of embodiment 793 wherein the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 25 g/day.

[001171] Embodiment 798. The method of embodiment 793 wherein the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 20 g/day.

[001172] Embodiment 799. The method of embodiment 793 wherein the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 15 g/day.

[001173] Embodiment 800. The method of embodiment 793 wherein the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 10 g/day.

[001174] Embodiment 801. The method of embodiment 793 wherein the first cohort receives a daily dose of the pharmaceutical composition that does not exceed 5 g/day.

[001175] Embodiment 802. The method of any of embodiments 793 to 801 wherein the target species is protons.

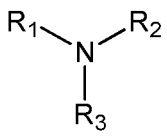
[001176] Embodiment 803. The method of any of embodiments 793 to 801 wherein the target species is chloride ions.

[001177] Embodiment 804. The method of any of embodiments 793 to 801 wherein the target species is a strong acid.

[001178] Embodiment 805. The method of any of embodiments 793 to 801 wherein the target species is HCl.

[001179] Embodiment 806. The method of any of embodiments 793 to 805 wherein the pharmaceutical composition is not absorbed when ingested.

[001180] Embodiment 807. The method of any of embodiments 793 to 806 wherein the composition is a pharmaceutical composition comprising a proton-binding, crosslinked amine polymer comprising the residue of an amine corresponding to Formula 1:

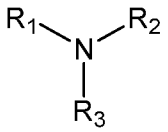


Formula 1

wherein R_1, R_2 and R_3 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen, and the crosslinked amine polymer has (i) an equilibrium proton binding capacity of at least 5 mmol/g and a chloride ion binding capacity of at least 5 mmol/g in an

aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C, and (ii) an equilibrium swelling ratio in deionized water of about 2 or less.

[001181] Embodiment 808. The method of any of embodiments 793 to 806 wherein the composition is a pharmaceutical composition comprising a proton-binding, crosslinked amine polymer comprising the residue of an amine corresponding to Formula 1:



Formula 1

wherein R_1, R_2 and R_3 are independently hydrogen, hydrocarbyl, substituted hydrocarbyl provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen, the crosslinked amine polymer has an equilibrium swelling ratio in deionized water of about 5 or less, and the crosslinked amine polymer binds a molar ratio of chloride ions to interfering ions of at least 0.35:1, respectively, in an interfering ion buffer at 37 °C wherein the interfering ions are phosphate ions and the interfering ion buffer is a buffered solution at pH 5.5 of 36mM chloride and 20mM phosphate.

[001182] Embodiment 809. The method of embodiments 807 or 808 wherein the crosslinked amine polymer has an equilibrium chloride binding capacity of at least 7.5 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C.

[001183] Embodiment 810. The method of embodiments 807 or 808 wherein the crosslinked amine polymer has an equilibrium chloride binding capacity of at least 10 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C.

[001184] Embodiment 811. The method of embodiments 807 or 808 wherein the crosslinked amine polymer has an equilibrium swelling ratio in deionized water of about 4 or less.

[001185] Embodiment 812. The method of embodiments 807 or 808 wherein the crosslinked amine polymer has an equilibrium swelling ratio in deionized water of about 3 or less.

[001186] Embodiment 813. The method of embodiments 807 or 808 wherein the crosslinked amine polymer has an equilibrium swelling ratio in deionized water of about 2 or less.

[001187] Embodiment 814. The method of any of embodiments 807 to 813 wherein R_1, R_2 and R_3 are independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic provided, however, each of R_1, R_2 and R_3 is not hydrogen.

[001188] Embodiment 815. The method of any of embodiments 807 to 813 wherein R_1, R_2 and R_3 are independently hydrogen, aliphatic or heteroaliphatic provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen.

[001189] Embodiment 816. The method of any of embodiments 807 to 813 wherein the crosslinked amine polymer is prepared by substitution polymerization of the amine with a polyfunctional crosslinker, optionally also comprising amine moieties.

[001190] Embodiment 817. The method of any of embodiments 807 to 816 wherein the potential renal acid load (PRAL value) of the diet is, on average, 0.82 mEq/d).

[001191] Embodiment 818. The method of any of embodiments 807 to 817 wherein eligible subjects for the study have chronic kidney disease (CKD Stage 3 – 4; eGFR 20 – <60 mL/min/1.73m^2) and a baseline serum bicarbonate value at the start of the study between 12 and 20 mEq/L.

[001192] Embodiment 819. The method of any of embodiments 807 to 818 wherein the pharmaceutical composition increases the serum bicarbonate level by at least 2 mEq/l in the placebo controlled study.

[001193] Embodiment 820. The method of any of embodiments 807 to 818 wherein the pharmaceutical composition increases the serum bicarbonate level by at least 3 mEq/l in the placebo controlled study.

[001194] Embodiment 821. The method or composition of any preceding enumerated embodiment wherein the individual or adult human patient has chronic kidney disease.

[001195] Embodiment 822. The method or composition of any preceding enumerated embodiment wherein the individual or adult human patient is not yet in need for kidney replacement therapy (dialysis or transplant).

[001196] Embodiment 823. The method or composition of any preceding enumerated embodiment wherein the individual or adult human patient has not yet reached end stage renal disease ("ESRD").

[001197] Embodiment 824. The method or composition of any preceding enumerated embodiment wherein the individual or adult human patient has a mGFR of at least 15 mL/min/1.73 m^2.

[001198] Embodiment 825. The method or composition of any preceding enumerated embodiment wherein the individual or adult human patient has an eGFR of at least 15 mL/min/1.73 m^2.

[001199] Embodiment 826. The method or composition of any preceding enumerated embodiment wherein the individual or adult human patient has a mGFR of at least 30 mL/min/1.73 m^2.

[001200] Embodiment 827. The method or composition of any preceding enumerated embodiment wherein the individual or adult human patient has an eGFR of at least 30 mL/min/1.73 m^2.

[001201] Embodiment 828. The method or composition of any preceding enumerated embodiment wherein the individual or adult human patient has a mGFR of less than 45 mL/min/1.73 m^2 for at least three months.

[001202] Embodiment 829. The method or composition of any preceding enumerated embodiment wherein the individual or adult human patient has an eGFR of less than 45 mL/min/1.73 m^2 for at least three months.

[001203] Embodiment 830. The method or composition of any preceding enumerated embodiment wherein the individual or adult human patient has a mGFR of less than 60 mL/min/1.73 m^2 for at least three months.

[001204] Embodiment 831. The method or composition of any preceding enumerated embodiment wherein the individual or adult human patient has an eGFR of less than 60 mL/min/1.73 m^2 for at least three months.

[001205] Embodiment 832. The method or composition of any preceding enumerated embodiment wherein the individual or adult human patient has Stage 3A CKD, Stage 3B CKD, or Stage 4 CKD.

[001206] Embodiment 833. A method of treating an individual afflicted with an acid-base disorder characterized by a baseline serum bicarbonate value of less than 22 mEq/l, the method comprising oral administration of a daily dose of a pharmaceutical composition containing a nonabsorbable composition;

wherein said oral administration increases the individual's serum bicarbonate value from baseline to an increased serum bicarbonate value that exceeds the baseline serum bicarbonate value by at least 1 mEq/l; and

wherein the treatment enables the increased serum bicarbonate value to be sustained over a prolonged period of at least one week, at least one month, at least two months, at least three months, at least six months, or at least one year.

[001207] Embodiment 834. The method or pharmaceutical composition of embodiment 833, wherein the method or pharmaceutical composition is one of any preceding enumerated embodiments.

[001208] Embodiment 835. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by at least 1 mEq/L.

[001209] Embodiment 836. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by at least 2 mEq/L.

[001210] Embodiment 837. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by at least 3 mEq/L.

[001211] Embodiment 838. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by at least 4 mEq/L.

[001212] Embodiment 839. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by at least 5 mEq/L.

[001213] Embodiment 840. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by 1-2 mEq/L.

[001214] Embodiment 841. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by 1-3 mEq/L.

[001215] Embodiment 842. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by 1-4 mEq/L.

[001216] Embodiment 843. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by 1-5 mEq/L.

[001217] Embodiment 844. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by 2-3 mEq/L.

[001218] Embodiment 845. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by 2-4 mEq/L.

[001219] Embodiment 846. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by 2-5 mEq/L.

[001220] Embodiment 846. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by 3-4 mEq/L.

[001221] Embodiment 847. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by 3-5 mEq/L.

[001222] Embodiment 848. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by 4-5 mEq/L.

[001223] Embodiment 849. The method of any preceding enumerated embodiment wherein the treatment decreases the individual's anion gap by less than 1 mEq/L (e.g. 0.5 mEq/L, or 0.75 mEq/L).

[001224] Embodiment 850. A method of improving the quality of life of a patient afflicted with chronic kidney disease and an acid-base disorder characterized by a baseline serum bicarbonate value of ≤22 mEq/L, the method comprising oral administration of a pharmaceutical composition capable of increasing and maintaining the patient's serum bicarbonate above 20 mEq/L for a period of at least twelve weeks, the pharmaceutical composition having the capacity to bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids.

[001225] Embodiment 851. A method of improving the quality of life of a patient afflicted with chronic kidney disease and an acid-base disorder, the method comprising oral administration of a pharmaceutical composition having: (a) the capacity to selectively bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay, wherein the improvement in quality of life is statistically significant compared to a placebo control group for a period of at least twelve weeks as assessed by a Quality of Life (QoL) questionnaire.

[001226] Embodiment 852. A method of improving quality of life of a patient afflicted with chronic kidney disease and an acid-base disorder, wherein the patient has a baseline serum bicarbonate value of ≤22 mEq/L, comprising orally administering to the patient an effective amount of TRC101 once daily for a period of time sufficient to statistically significantly increase the patient's quality of life compared to a placebo control.

[001227] Embodiment 853. A method of improving quality of life of a patient afflicted with metabolic acidosis disease, the method comprising administering to the patient a daily dose of a nonabsorbed crosslinked amine polymer, which daily dose: (a) is sufficient to increase the patient's serum bicarbonate concentration by at least 1 mEq/L; (b) results in a sustained serum bicarbonate increase of at least 1 mEq/L over a period of at least twelve weeks; and (c) is sufficient to improve the patient's

quality of life compared to a placebo control group over the period, wherein the improvement in quality of life is statistically significant.

[001228] Embodiment 854. A pharmaceutical composition for improving the quality of life of a human patient afflicted with chronic kidney disease and an acid-base disorder, the patient having a baseline serum bicarbonate level of ≤22 mEq/L prior to treatment, the composition being a nonabsorbable composition having the capacity to: (a) remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) improve the patient's quality of life compared to a placebo control in a statistically significant manner over at least a twelve-week period.

[001229] Embodiment 855. A pharmaceutical composition for improving the quality of life of a human patient suffering from a disease or disorder by increasing that patient's serum bicarbonate value by at least 1 mEq/L over at least twelve weeks of treatment, the composition: (a) being a nonabsorbable composition having the capacity to remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (b) characterized by a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (c) having the capacity to improve the patient's quality of life compared to a placebo control in a statistically significant manner over at least the twelve-week period.

[001230] Embodiment 856. A pharmaceutical composition for improving the quality of life of a human patient suffering from metabolic acidosis disease, wherein: (a) an effective amount of the pharmaceutical composition is administered to the patient per day over at least a twelve-week period; (b) the pharmaceutical composition is nonabsorbable with the capacity to remove from the patient a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (c) the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (d) the improvement in quality of life compared to a placebo control is statistically significant over the twelve-week period.

[001231] Embodiment 857. A method of improving the physical function of a patient afflicted with chronic kidney disease and an acid-base disorder

characterized by a baseline serum bicarbonate value of ≤22 mEq/L, the method comprising oral administration of a pharmaceutical composition capable of increasing and maintaining the patient's serum bicarbonate above 20 mEq/L for a period of at least twelve weeks, the pharmaceutical composition having the capacity to bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids.

[001232] Embodiment 858. A method of improving the physical function of a patient afflicted with chronic kidney disease and an acid-base disorder, the method comprising oral administration of a pharmaceutical composition having: (a) the capacity to selectively bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay, wherein the improvement in physical function is statistically significant compared to a placebo control group at least twelve weeks after initiation of treatment as assessed by the patient's answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF).

[001233] Embodiment 859. A method of improving the physical function of a patient afflicted with chronic kidney disease and an acid-base disorder, wherein the patient has a baseline serum bicarbonate value of ≤22 mEq/L, comprising orally administering to the patient an effective amount of TRC101 once daily for a period of time sufficient to statistically significantly increase the patient's physical function score based on answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF) compared to the patient's baseline physical function score.

[001234] Embodiment 860. A method of improving the physical function of a patient afflicted with metabolic acidosis disease, the method comprising administering to the patient a daily dose of a nonabsorbed crosslinked amine polymer, which daily dose: (a) is sufficient to increase the patient's serum bicarbonate concentration by at least 1 mEq/L; (b) results in a sustained serum bicarbonate increase of at least 1 mEq/L over a period of at least twelve weeks; and (c) is sufficient to improve the physical function score of the patient compared to a placebo control group at the end of the period, wherein the improvement in the physical function score is statistically significant.

[001235] Embodiment 861. A pharmaceutical composition for improving the physical function score of a human patient afflicted with chronic kidney disease and an acid-base disorder, the patient having a baseline serum bicarbonate level of ≤22 mEq/L prior to treatment, the composition being a nonabsorbable composition having the capacity to: (a) remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) improve the patient's physical function score based on answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF) compared to a placebo control in a statistically significant manner at the end of at least a twelve-week period.

[001236] Embodiment 862. A pharmaceutical composition for improving the physical function score of a human patient suffering from a disease or disorder by increasing that patient's serum bicarbonate value by at least 1 mEq/L over at least twelve weeks of treatment, the composition: (a) being a nonabsorbable composition having the capacity to remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (b) characterized by a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (c) having the capacity to improve the patient's physical function score based on answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF) compared to a placebo control in a statistically significant manner at the end of an at least the twelve-week period.

[001237] Embodiment 863. A pharmaceutical composition for improving the physical function score of a human patient suffering from metabolic acidosis disease, wherein: (a) an effective amount of the pharmaceutical composition is administered to the patient per day over at least a twelve-week period; (b) the pharmaceutical composition is nonabsorbable with the capacity to remove from the patient a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (c) the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (d) the improvement in physical function score is a statistically significant improvement over a baseline physical function score based on answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF) compared to a placebo control at the end of the at least twelve-week period.

[001238] Embodiment 864. A method of slowing the progression of kidney disease in a patient afflicted with chronic kidney disease and an acid-base disorder characterized by a baseline serum bicarbonate value of ≤22 mEq/L, the method comprising oral administration of a pharmaceutical composition capable of increasing and maintaining the patient's serum bicarbonate above 20 mEq/L for a period of at least twelve weeks, the pharmaceutical composition having the capacity to bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids.

[001239] Embodiment 865. A method of slowing the progression of kidney disease in a patient afflicted with chronic kidney disease and an acid-base disorder, wherein the patient has a baseline serum bicarbonate value of ≤22 mEq/L, comprising orally administering to the patient an effective amount of TRC101 once daily for a period of time sufficient to increase the patient's serum bicarbonate by at least 1 mEq/L.

[001240] Embodiment 866. A method of slowing the progression of kidney disease in a patient afflicted with chronic kidney disease and metabolic acidosis disease, the method comprising administering to the patient a daily dose of a nonabsorbed crosslinked amine polymer, which daily dose: (a) is sufficient to increase the patient's serum bicarbonate concentration by at least 1 mEq/L; (b) results in a sustained serum bicarbonate increase of at least 1 mEq/L over a period of at least twelve weeks; and (c) is sufficient to slow the progression of kidney disease.

[001241] Embodiment 867. A pharmaceutical composition for slowing the progression of kidney disease in a human patient afflicted with chronic kidney disease and an acid-base disorder, the patient having a baseline serum bicarbonate level of ≤22 mEq/L prior to treatment, the composition being a nonabsorbable composition having the capacity to: (a) remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) slow the progression of kidney disease in a human patient over at least a twelve-week period.

[001242] Embodiment 868. A pharmaceutical composition for slowing the progression of kidney disease in a human patient afflicted with chronic kidney

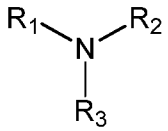
disease and an acid-base disorder by increasing that patient's serum bicarbonate value by at least 1 mEq/L over at least twelve weeks of treatment, the composition: (a) being a nonabsorbable composition having the capacity to remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (b) characterized by a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (c) having the capacity to slow the progression of kidney disease over at least the twelve-week period.

[001243] Embodiment 869. A pharmaceutical composition for slowing the progression of kidney disease in a human patient also suffering from metabolic acidosis disease, wherein: (a) an effective amount of the pharmaceutical composition is administered to the patient per day over at least a twelve-week period; (b) the pharmaceutical composition is nonabsorbable with the capacity to remove from the patient a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (c) the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (d) the progression of kidney disease in the patient is slowed over the twelve-week period compared to a placebo control group not receiving the pharmaceutical composition.

[001244] Embodiment 870. A pharmaceutical composition for use in a method of treating an acid-base disorder in a patient, wherein the method of treatment improves the quality of life of the patient.

[001245] Embodiment 871. A pharmaceutical composition for use in a method of treating an acid-base disorder in a patient, wherein the method of treatment improves the physical function of the patient.

[001246] Embodiment 872. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a proton-binding, crosslinked amine polymer comprising the residue of an amine corresponding to Formula 1:



Formula 1

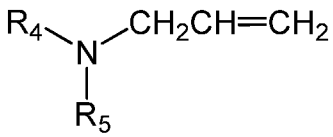
[001247] wherein R_1, R_2 and R_3 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen.

[001248] Embodiment 872. The method/composition of embodiment 871 wherein R_1, R_2 and R_3 are independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic provided, however, each of R_1, R_2 and R_3 is not hydrogen.

[001249] Embodiment 873. The method/composition of any of embodiments 871 to 872 wherein R_1, R_2 and R_3 are independently hydrogen, aliphatic or heteroaliphatic provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen.

[001250] Embodiment 874. The method/composition of any of embodiments 871 to 873 wherein the crosslinked amine polymer is prepared by substitution polymerization of the amine with a polyfunctional crosslinker, optionally also comprising amine moieties.

[001251] Embodiment 875. The method/composition of any of embodiments 871 to 874 wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 1a and the crosslinked amine polymer is prepared by radical polymerization of an amine corresponding to Formula 1a:



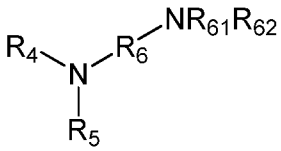
Formula 1a

wherein R_4 and R_5 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl.

[001252] Embodiment 876. The method/composition of embodiment 875 wherein R_4 and R_5 are independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic.

[001253] Embodiment 877. The method/composition of embodiment 875 wherein R_4 and R_5 are independently hydrogen, aliphatic or heteroaliphatic.

[001254] Embodiment 878. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a crosslinked amine polymer containing the residue of an amine corresponding to Formula 1b and the crosslinked amine polymer is prepared by substitution polymerization of the amine corresponding to Formula 1b with a polyfunctional crosslinker:



Fromula 1b

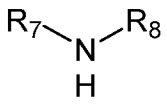
wherein R_4 and R_5 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl, R_6 is aliphatic and R_{61} and R_{62} are independently hydrogen, aliphatic, or heteroaliphatic.

[001255] Embodiment 879. The method/composition of embodiment 878 wherein R_4 and R_5 are independently hydrogen, saturated hydrocarbon, unsaturated aliphatic, aryl, heteroaryl, heteroalkyl, or unsaturated heteroaliphatic.

[001256] Embodiment 880. The method/composition of embodiment 878 wherein R_4 and R_5 are independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic.

[001257] Embodiment 881. The method/composition of embodiment 878 wherein R_4 and R_5 are independently hydrogen, allyl, or aminoalkyl.

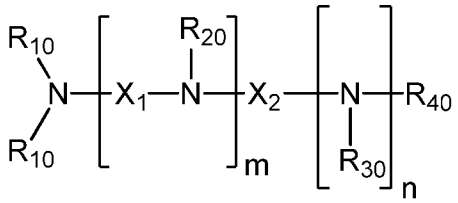
[001258] Embodiment 882. The method/composition according to any one of embodiments 871 to 881 wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 1c:



Formula 1c

wherein R_7 is hydrogen, aliphatic or heteroaliphatic and R_8 is aliphatic or heteroaliphatic.

[001259] Embodiment 883. The method/composition according to any one of the preceding enumerated embodiments wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 2:

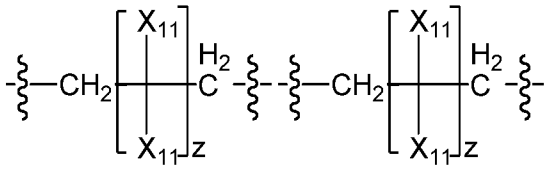


Formula 2

wherein

m and n are independently non-negative integers;

R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl;

X_1 is  ;

X_2 is hydrocarbyl or substituted hydrocarbyl;

each X_{11} is independently hydrogen, hydrocarbyl, substituted hydrocarbyl, hydroxy, or amino; and

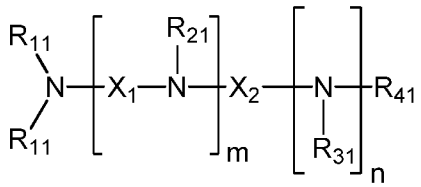
z is a non-negative number.

[001260] Embodiment 884. The method/composition according to embodiment 883 wherein R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, aliphatic, aryl, heteroaliphatic, or heteroaryl, m and z are independently 0-3 and n is 0 or 1.

[001261] Embodiment 885. The method/composition according to embodiment 883 wherein X_2 is aliphatic or heteroaliphatic.

[001262] Embodiment 886. The method/composition according to embodiment 883, wherein m is 1-3 and X_{11} is hydrogen, aliphatic or heteroaliphatic.

[001263] Embodiment 887. The method/composition according to embodiment 883, wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 2a:



Formula 2a

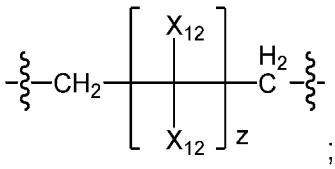
wherein

m and n are independently non-negative integers;

each R_{11} is independently hydrogen, hydrocarbyl, heteroaliphatic, or heteroaryl;

R_{21} and R_{31}, are independently hydrogen or heteroaliphatic;

R_{41} is hydrogen, substituted hydrocarbyl, or hydrocarbyl;

X_1 is  ;

X_2 is alkyl or substituted hydrocarbyl;

each X_{12} is independently hydrogen, hydroxy, amino, aminoalkyl, boronic acid or halo; and

z is a non-negative number.

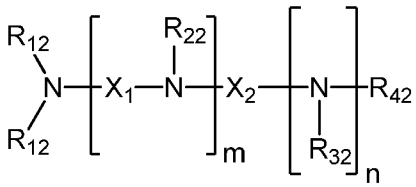
[001264] Embodiment 888. The method/composition according to embodiment 887, wherein m and z are independently 0-3 and n is 0 or 1.

[001265] Embodiment 889. The method/composition according to any one of embodiments 887 to 888 wherein R_{11} is independently hydrogen, aliphatic,

aminoalkyl, haloalkyl, or heteroaryl, R_{21} and R_{31} are independently hydrogen or heteroaliphatic and R_{41} is hydrogen, aliphatic, aryl, heteroaliphatic, or heteroaryl.

[001266] Embodiment 890. The method/composition according to any one of embodiments 887 to 889 each R_{11} is hydrogen, aliphatic, aminoalkyl, or haloalkyl, R_{21} and R_{31} are hydrogen or aminoalkyl, and R_{41} is hydrogen, aliphatic, or heteroaliphatic.

[001267] Embodiment 891. The method/composition according to any one of embodiments 887 to 890 wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 2b:



Formula 2b

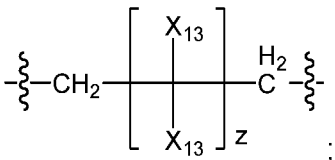
wherein

m and n are independently non-negative integers;

each R_{12} is independently hydrogen, substituted hydrocarbyl, or hydrocarbyl;

R_{22} and R_{32} are independently hydrogen substituted hydrocarbyl, or hydrocarbyl;

R_{42} is hydrogen, hydrocarbyl or substituted hydrocarbyl;

X_1 is  ;

X_2 is alkyl, aminoalkyl, or alkanol;

each X_{13} is independently hydrogen, hydroxy, alicyclic, amino, aminoalkyl, halogen, alkyl, heteroaryl, boronic acid or aryl;

z is a non-negative number; and

the amine corresponding to Formula 2b comprises at least one allyl group.

[001268] Embodiment 892. The method/composition according to embodiment 891, wherein m and z are independently 0-3 and n is 0 or 1.

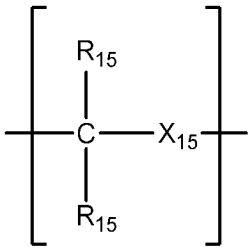
[001269] Embodiment 893. The method/composition according to any one of embodiments 891 to 892 wherein R_{12} or R_{42} independently comprise at least one allyl or vinyl moiety.

[001270] Embodiment 894. The method/composition according to any one of embodiments 891 to 893 wherein (i) m is a positive integer and R_{12}, R_{22} and R_{42}, in combination comprise at least two allyl or vinyl moieties or (ii) n is a positive integer and R_{12}, R_{32} and R_{42}, in combination, comprise at least two allyl or vinyl moieties.

[001271] Embodiment 895. The method/composition according to any preceding enumerated embodiment wherein the crosslinked amine polymer comprises the residue of an amine appearing in Table A.

[001272] Embodiment 896. The method/composition according to any preceding enumerated embodiment wherein the crosslinked amine polymer is crosslinked with a crosslinking agent appearing in Table B.

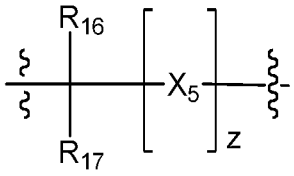
[001273] Embodiment 897. The method/composition according to any preceding enumerated embodiment wherein the crosslinked amine polymer comprises a repeat unit corresponding to Formula 3:



Formula 3

wherein

R_{15}, R_{16} and R_{17} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, hydroxyl, amino, boronic acid or halo;

X_{15} is 

;

X_5 is hydrocarbyl, substituted hydrocarbyl, oxo (O), or amino; and

z is a non-negative number.

[001274] Embodiment 898. The method/composition according to embodiment 897 wherein R_{15}, R_{16} and R_{17} are independently aliphatic or heteroaliphatic.

[001275] Embodiment 899. The method/composition according to any one of embodiments 897 to 898 wherein X_5 is oxo, amino, alkylamino, ethereal, alkanol, or haloalkyl.

[001276] Embodiment 900. The method/composition according to any one of embodiments 897 to 899 wherein the crosslinked amine polymer is prepared by (i) substitution polymerization of polyfunctional reagents at least one of which comprises amine moieties, (2) radical polymerization of a monomer comprising at least one amine moiety or nitrogen containing moiety, or (3) crosslinking of an amine-containing intermediate with a crosslinking agent, optionally containing amine moieties.

[001277] Embodiment 901. The method/composition according to any preceding enumerated embodiment wherein the crosslinked amine polymer is a crosslinked homopolymer or a crosslinked copolymer.

[001278] Embodiment 902. The method/composition according to according to any preceding enumerated embodiment wherein the crosslinked amine polymer comprises free amine moieties, separated by the same or varying lengths of repeating linker units.

[001279] Embodiment 903. The method/composition according to any preceding enumerated embodiment wherein the crosslinked amine polymer is prepared by polymerizing an amine-containing monomer with a crosslinking agent in a substitution polymerization reaction.

[001280] Embodiment 904. The method/composition according to any preceding enumerated embodiment wherein the amine-containing monomer is a linear amine possessing at least two reactive amine moieties to participate in the substitution polymerization reaction.

[001281] Embodiment 905. The method/composition according to any preceding enumerated embodiment wherein the amine-containing monomer is 1,3-

Bis[bis(2-aminoethyl)amino]propane, 3-Amino-1-{[2-(bis{2-[bis(3-aminopropyl)amino]ethyl}amino)ethyl](3-aminopropyl)amino}propane, 2-[Bis(2-aminoethyl)amino]ethanamine, Tris(3-aminopropyl)amine, 1,4-Bis[bis(3-aminopropyl)amino]butane, 1,2-Ethanediamine, 2-Amino-1-(2-aminoethylamino)ethane, 1,2-Bis(2-aminoethylamino)ethane, 1,3-Propanediamine, 3,3'-Diaminodipropylamine, 2,2-dimethyl-1,3-propanediamine, 2-methyl-1,3-propanediamine, N,N'-dimethyl-1,3-propanediamine, N-methyl-1,3-diaminopropane, 3,3'-diamino-N-methyldipropylamine, 1,3-diaminopentane, 1,2-diamino-2-methylpropane, 2-methyl-1,5-diaminopentane, 1,2-diaminopropane, 1,10-diaminodecane, 1,8-diaminooctane, 1,9-diaminooctane, 1,7-diaminoheptane, 1,6-diaminohexane, 1,5-diaminopentane, 3-bromopropylamine hydrobromide, N,2-dimethyl-1,3-propanediamine, N-isopropyl-1,3-diaminopropane, N,N'-bis(2-aminoethyl)-1,3-propanediamine, N,N'-bis(3-aminopropyl)ethylenediamine, N,N'-bis(3-aminopropyl)-1,4-butanediamine tetrahydrochloride, 1,3-diamino-2-propanol, N-ethylethylenediamine, 2,2'-diamino-N-methyldiethylamine, N,N'-diethylethylenediamine, N-isopropylethylenediamine, N-methylethylenediamine, N,N'-di-tert-butylethylenediamine, N,N'-diisopropylethylenediamine, N,N'-dimethylethylenediamine, N-butylethylenediamine, 2-(2-aminoethylamino)ethanol, 1,4,7,10,13,16-hexaazacyclooctadecane, 1,4,7,10-tetraazacyclododecane, 1,4,7-triazacyclononane, N,N'-bis(2-hydroxyethyl)ethylenediamine, piperazine, bis(hexamethylene)triamine, N-(3-hydroxypropyl)ethylenediamine, N-(2-Aminoethyl)piperazine, 2-Methylpiperazine, Homopiperazine, 1,4,8,11-Tetraazacyclotetradecane, 1,4,8,12-Tetraazacyclopentadecane, 2-(Aminomethyl)piperidine, or 3-(Methylamino)pyrrolidino.

[001282] Embodiment 906. The method/composition according to any preceding enumerated embodiment wherein the crosslinking agent is selected from the group consisting of dihaloalkanes, haloalkyloxiranes, alkyloxirane sulfonates, di(haloalkyl)amines, tri(haloalkyl) amines, diepoxides, triepoxides, tetraepoxides, bis (halomethyl)benzenes, tri(halomethyl)benzenes, tetra(halomethyl)benzenes, epihalohydrins such as epichlorohydrin and epibromohydrin poly(epichlorohydrin), (iodomethyl)oxirane, glycidyl tosylate, glycidyl 3-nitrobenzenesulfonate, 4-tosyloxy-1,2-epoxybutane, bromo-1,2-epoxybutane, 1,2-dibromoethane, 1,3-dichloropropane, 1,2- dichloroethane, l-bromo-2-chloroethane, 1,3- dibromopropane, bis(2-

chloroethyl)amine, tris(2- chloroethyl)amine, and bis(2-chloroethyl)methylamine, 1,3-butadiene diepoxide, 1,5-hexadiene diepoxide, diglycidyl ether, 1,2,7,8-diepoxyoctane, 1,2,9,10-diepoxydecane, ethylene glycol diglycidyl ether, propylene glycol diglycidyl ether, 1,4-butanediol diglycidyl ether, 1,2 ethanedioldiglycidyl ether, glycerol diglycidyl ether, 1,3-diglycidyl glyceryl ether, N,N-diglycidylaniline, neopentyl glycol diglycidyl ether, diethylene glycol diglycidyl ether, 1,4-bis(glycidyloxy)benzene, resorcinol digylcidyl ether, 1,6-hexanediol diglycidyl ether, trimethylolpropane diglycidyl ether, 1,4-cyclohexanedimethanol diglycidyl ether, 1,3-bis-(2,3-epoxypropyloxy)-2-(2,3-dihydroxypropy loxy)propane, 1,2-cyclohexanedicarboxylic acid diglycidyl ester, 2,2'-bis(glycidyloxy) diphenylmethane, bisphenol F diglycidyl ether, 1,4-bis(2',3'epoxypropyl)perfluoro-n-butane, 2,6-di(oxiran-2-ylmethy1)-1,2,3,5,6,7-hexahydropyrrolo[3,4-f]isoindol-1,3,5,7- tetraone, bisphenol A diglycidyl ether, ethyl 5-hydroxy-6,8- di(oxiran-2-ylmethyl)-4-oxo-4-h-chromene-2-carboxylate, bis[4-(2,3-epoxy-propylthio)phenyl]-sulfide, 1,3-bis(3-glycidoxypropyl) tetramethyldisiloxane, 9,9-bis[4-(glycidyloxy)phenyl]fluorine, triepoxyisocyanurate, glycerol triglycidyl ether, N,N-diglycidyl-4-glycidyloxyaniline, isocyanuric acid (S,S,S)-triglycidyl ester, isocyanuric acid (R,R,R)-triglycidyl ester, triglycidyl isocyanurate, trimethylolpropane triglycidyl ether, glycerol propoxylate triglycidyl ether, triphenylolmethane triglycidyl ether, 3,7,14-tris[[3-(epoxypropoxy)propyl]dimethylsilyloxy]-1,3,5,7,9,11,14- heptacyclopentyltricyclo [7,3,3,15, 11]heptasiloxane, 4,4 'methylenebis(N,N-diglycidylaniline), bis(halomethyl)benzene, bis(halomethyl)biphenyl and bis(halomethyl)naphthalene, toluene diisocyanate, acrylol chloride, methyl acrylate, ethylene bisacrylamide, pyrometallic dianhydride, succinyl dichloride, dimethylsuccinate, 3-chloro-1-(3-chloropropylamino-2-propanol, 1,2-bis(3-chloropropylamino)ethane, Bis(3-chloropropyl)amine, 1,3-Dichloro-2-propanol, 1,3-Dichloropropane, 1-chloro-2,3-epoxypropane, tris[(2-oxiranyl)methyl]amine, and combinations thereof.

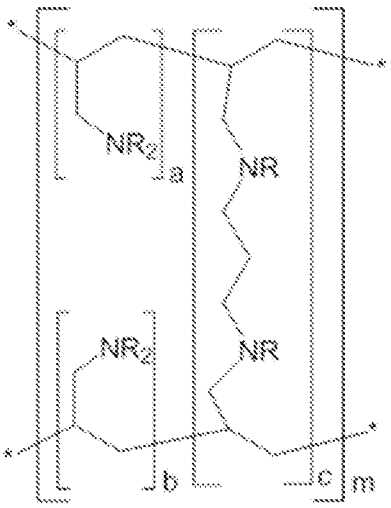
[001283] Embodiment 907. The method/composition according to any preceding enumerated embodiment wherein the preparation of the crosslinked amine polymer comprises radical polymerization of an amine monomer comprising at least one amine moiety or nitrogen containing moiety.

[001284] Embodiment 908. The method/composition according to any preceding enumerated embodiment wherein the crosslinked amine polymer has an equilibrium swelling ratio in deionized water of about 1.5 or less.

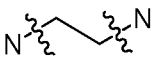
[001285] Embodiment 909. The method/composition according to any preceding enumerated embodiment wherein the crosslinked amine polymer has an equilibrium swelling ratio in deionized water of about 1 or less.

[001286] Embodiment 910. The method/composition according to any preceding enumerated embodiment wherein the crosslinked amine polymer has a chloride ion to phosphate ion binding molar ratio of at least 0.5:1, respectively, in an aqueous simulated small intestine inorganic buffer ("SIB") containing 36 mM NaCl, 20 mM NaH2PO4, and 50 mM 2-(N-morpholino)ethanesulfonic acid (MES) buffered to pH 5.5 and at 37 °C.

[001287] Embodiment 911. The method/composition according to any preceding enumerated embodiment wherein the pharmaceutical composition comprises a polymer comprising a structure corresponding to Formula 4:



Formula 4

wherein each R is independently hydrogen or an ethylene crosslink between two nitrogen atoms of the crosslinked amine polymer () and a, b, c, and m are integers.

[001288] Embodiment 912. The method/composition according to embodiment 911 wherein m is a large integer indicating an extended polymer network.

[001289] Embodiment 913. The method/composition according to embodiment 911 or 912 wherein a ratio of the sum of a and b to c (i.e., a+b:c) is in the range of about 1:1 to 5:1.

[001290] Embodiment 914. The method/composition according to any one of embodiments 9111 to 913 wherein a ratio of the sum of a and b to c (i.e., a+b:c) is in the range of about 1.5:1 to 4:1.

[001291] Embodiment 915. The method/composition according to any one of embodiments 911 to 914 wherein a ratio of the sum of a and b to c (i.e., a+b:c) is in the range of about 1.75:1 to 3:1.

[001292] Embodiment 916. The method/composition according to any one of embodiments 911 to 915 wherein a ratio of the sum of a and b to c (i.e., a+b:c) is in the range of about 2:1 to 2.5:1.

[001293] Embodiment 917. The method/composition according to any one of embodiments 911 to 916 wherein the sum of a and b is 57 and c is 24.

[001294] Embodiment 918. The method/composition according to any preceding enumerated embodiment wherein 50-95% of the R substituents are hydrogen and 5-50% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001295] Embodiment 919. The method/composition according to any preceding enumerated embodiment wherein 55-90% of the R substituents are hydrogen and 10-45% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001296] Embodiment 920. The method/composition according to any preceding enumerated embodiment wherein 60-90% of the R substituents are hydrogen and 10-40% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001297] Embodiment 921. The method/composition according to any preceding enumerated embodiment wherein 65-90% of the R substituents are hydrogen and 10-35% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001298] Embodiment 922. The method/composition according to any one of embodiments 911 to 921 wherein the R substituents are hydrogen and 10-30% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001299] Embodiment 923. The method/composition according to any preceding enumerated embodiment wherein the composition is the polymer of any of embodiments 768 to 774 wherein 75-85% of the R substituents are hydrogen and 15-25% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001300] Embodiment 924. The method/composition according to any preceding enumerated embodiment wherein the R substituents are hydrogen and 15-20% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001301] Embodiment 925. The method/composition according to any preceding enumerated embodiment wherein the R substituents are hydrogen and about 19% are an ethylene crosslink.

[001302] Embodiment 926. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 1 mEq/g in a SIB assay.

[001303] Embodiment 927. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 1.5 mEq/g in a SIB assay.

[001304] Embodiment 928. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 2 mEq/g in a SIB assay.

[001305] Embodiment 929. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 2.5 mEq/g in a SIB assay.

[001306] Embodiment 930. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 3 mEq/g in a SIB assay.

[001307] Embodiment 931. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 3.5 mEq/g in a SIB assay.

[001308] Embodiment 932. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 4 mEq/g in a SIB assay.

[001309] Embodiment 933. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 4.5 mEq/g in a SIB assay.

[001310] Embodiment 934. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 5 mEq/g in a SIB assay.

[001311] Embodiment 935. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 5.5 mEq/g in a SIB assay.

[001312] Embodiment 936. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 6 mEq/g in a SIB assay.

[001313] Embodiment 937. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.1:1, respectively.

[001314] Embodiment 938. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.2:1, respectively.

[001315] Embodiment 939. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.25:1, respectively.

[001316] Embodiment 940. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.3:1, respectively.

[001317] Embodiment 941. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.35:1, respectively.

[001318] Embodiment 942. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.4:1, respectively.

[001319] Embodiment 943. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.45:1, respectively.

[001320] Embodiment 944. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.5:1, respectively.

[001321] Embodiment 945. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 2:3, respectively.

[001322] Embodiment 946. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.75:1, respectively.

[001323] Embodiment 947. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.9:1, respectively.

[001324] Embodiment 948. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 1:1, respectively.

[001325] Embodiment 949. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 1.25:1, respectively.

[001326] Embodiment 950. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 1.5:1, respectively.

[001327] Embodiment 951. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 1.75:1, respectively.

[001328] Embodiment 952. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 2:1, respectively.

[001329] Embodiment 953. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 2.25:1, respectively.

[001330] Embodiment 954. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 2.5:1, respectively.

[001331] Embodiment 955. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 2.75:1, respectively.

[001332] Embodiment 956. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 3:1, respectively.

[001333] Embodiment 957. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 4:1, respectively.

[001334] Embodiment 958. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 5:1, respectively.

[001335] Embodiment 959. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 6:1, respectively.

[001336] Embodiment 960. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 7:1, respectively.

[001337] Embodiment 961. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 8:1, respectively.

[001338] Embodiment 962. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 9:1, respectively.

[001339] Embodiment 963. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 10:1, respectively.

[001340] Embodiment 964. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 12.5:1, respectively.

[001341] Embodiment 965. The method/composition of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 15:1, respectively.

[001342] Embodiment 966. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition has an equilibrium chloride binding capacity of at least 5 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C.

[001343] Embodiment 967. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition has an equilibrium chloride binding capacity of at least 7.5 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C.

[001344] Embodiment 968. The method/composition of any preceding enumerated embodiment wherein the pharmaceutical composition has an equilibrium chloride binding capacity of at least 10 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C.

[001345] Embodiment 969. The method/composition of any preceding enumerated embodiment, wherein the pharmaceutical composition increases the serum bicarbonate level by at least 1 mEq/L in a placebo controlled study, said increase being the difference between the cohort average serum bicarbonate level in a first cohort at the end of the study, relative to the cohort average serum bicarbonate level in a second cohort at the end of the study, wherein the first cohort's subjects receive the pharmaceutical composition and the second cohort's subjects receive a placebo, wherein the first and second cohorts each comprise a patient

population sufficient in size to evaluate statistically significant serum bicarbonate level differences between the cohorts over the period.

[001346] Embodiment 970. The method/composition of any preceding enumerated embodiment, wherein the pharmaceutical composition increases the serum bicarbonate level by at least 2 mEq/L in a placebo controlled study, said increase being the difference between the cohort average serum bicarbonate level in a first cohort at the end of the study, relative to the cohort average serum bicarbonate level in a second cohort at the end of the study, wherein the first cohort's subjects receive the pharmaceutical composition and the second cohort's subjects receive a placebo, wherein the first and second cohorts each comprise a patient population sufficient in size to evaluate statistically significant serum bicarbonate level differences between the cohorts over the period.

[001347] Embodiment 971. The method/composition of any preceding enumerated embodiment, wherein the pharmaceutical composition increases the serum bicarbonate level by at least 2.5 mEq/L in a placebo controlled study, said increase being the difference between the cohort average serum bicarbonate level in a first cohort at the end of the study, relative to the cohort average serum bicarbonate level in a second cohort at the end of the study, wherein the first cohort's subjects receive the pharmaceutical composition and the second cohort's subjects receive a placebo, wherein the first and second cohorts each comprise a patient population sufficient in size to evaluate statistically significant serum bicarbonate level differences between the cohorts over the period.

[001348] Embodiment 972. The method/composition of any preceding enumerated embodiment, wherein the pharmaceutical composition has the capacity to change the patient's baseline serum bicarbonate level by at least 2 mEq/L in at the end of an at least twelve week placebo controlled study.

[001349] Embodiment 973. The method/composition of any preceding enumerated embodiment, wherein the pharmaceutical composition has the capacity to change the patient's baseline serum bicarbonate level by at least 3 mEq/L in at the end of an at least twelve week placebo controlled study.

[001350] Embodiment 974. The method/composition of any preceding enumerated embodiment, wherein the pharmaceutical composition has the capacity

to change the patient's baseline serum bicarbonate level by at least 4 mEq/L in at the end of an at least twelve week placebo controlled study.

[001351] Embodiment 975. The method/composition of any preceding enumerated embodiment, wherein the patient population for each cohort is at least 25 patients.

[001352] Embodiment 976. The method/composition of any preceding enumerated embodiment, wherein the patient population for each cohort is at least 50 patients.

[001353] Embodiment 977. The method/composition of any preceding enumerated embodiment, wherein the patient population for each cohort is at least 100 patients.

[001354] Embodiment 978. The method/composition of any preceding enumerated embodiment, wherein the patient population for each cohort is at least 150 patients.

[001355] Embodiment 979. The method/composition of any preceding enumerated embodiment, wherein the patient population for each cohort is at least 200 patients.

[001356] Embodiment 980. The method/composition of any preceding enumerated embodiment, wherein improvement in quality of life or physical function is assessed by a questionnaire answered by a first cohort at the end of the period, relative to a second cohort who answered the same questionnaire at the end of the period, wherein the first cohort's subjects receive the pharmaceutical composition and the second cohort's subjects receive a placebo.

[001357] Embodiment 981. The method/composition of any preceding enumerated embodiment, wherein improvement in quality of life or physical function is assessed by a questionnaire, which is a clinically validated assessment for evaluating a patient's physical and mental health.

[001358] Embodiment 982. The method/composition of any preceding enumerated embodiment, wherein the questionnaire comprises questions concerning parameters selected from the group consisting of symptoms/problems related to the disease/condition, effects of the disease/condition, burden of the

disease/condition, work status, cognitive function, quality of social interaction, sleep, social support, physical functioning, pain, general health, emotional well-being, social function, energy/fatigue, and combinations thereof.

[001359] Embodiment 983. The method/composition of any preceding enumerated embodiment, wherein the questionnaire comprises questions concerning how the patient's health limits the patient's ability to engage in physical activities selected from the group: vigorous activities; moderate activities; lifting or carrying groceries; climbing several flights of stairs; climbing one flight of stairs; bending, kneeling or stooping; walking more than one mile; walking several blocks; walking one block; and bathing or dressing.

[001360] Embodiment 984. The method/composition of any preceding enumerated embodiment, wherein the patient achieves at least about a 10% improvement on the quality of life scale relative to the placebo control.

[001361] Embodiment 985. The method/composition of any preceding enumerated embodiment, wherein the patient achieves at least about a 25% improvement on the quality of life scale relative to the placebo control.

[001362] Embodiment 986. The method/composition of any preceding enumerated embodiment, wherein the patient achieves at least about a 50% improvement on the quality of life scale relative to the placebo control.

[001363] Embodiment 987. The method/composition of any preceding enumerated embodiment, wherein the patient achieves at least about a 75% improvement on the quality of life scale relative to the placebo control.

[001364] Embodiment 988. The method/composition of any preceding enumerated embodiment, wherein the improvement of the physical function comprises: (a) an improvement in the patient's baseline physical function score of at least 1.5 points based on the patient's answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF); (b) an improvement in the patient's baseline repeated chair stand times of at least -1.5 seconds; or (c) an improvement in the patient's baseline physical function score of at least 1.5 points based on the patient's answers to question 3 of the KDQOL-SF and an improvement in the patient's baseline repeated chair stand times of at least -1.5 seconds. In one aspect of this and other embodiments, the improvement in the patient's baseline repeated chair

stand times is seen after treatment for a period of at least about 52 weeks, at least about 40 weeks, at least about 26 weeks, or at least about 12 weeks. In another aspect of this and other embodiments, the improvement in patient's baseline repeated chair stand times is seen after treatment for a period of at least about 12 weeks and a period of at least about 40 weeks. In another aspect of this and other embodiments, the improvement in patient's baseline repeated chair stand times is seen after treatment for a period of at least about 12 weeks and a period of at least about 52 weeks. In another aspect of this and other embodiments, the improvement in patient's baseline repeated chair stand times is seen after treatment for a period of at least about 12 weeks, a period of at least about 40 weeks and a period of at least about 52 weeks. In another aspect of this and other embodiments, in the Repeated Chair Stand Test, after about twelve weeks of treatment, there is a trend toward significance for the difference between treated and placebo-treated patients. In a further aspect of this and other embodiments, improvement in the patient's baseline repeated chair stand times is at least about 0.5, 0.75, 1.0, 1.1, 1.2, 1.3, or 1.4 seconds. In another aspect of this and other embodiments, the improvement in the patient's baseline physical function score is based on the patient's performance in the Single Chair Stand and/or Repeated Chair Stand protocols as depicted in Fig. 22. In another aspect of this and other embodiments, the patient's KDQOL-SF score is calculated as follows: 1 (limited a lot) = 0; 2 (limited a little) = 50; 3 (not limited) = 100. Total score = sum of all 10, divided by 10.

[001365] Embodiment 989. The method/composition of any preceding enumerated embodiment, wherein the improvement in the quality of life of the patient comprises a decrease or prevention of further bone loss and/or a decrease or prevention of further muscle loss in the patient.

[001366] Embodiment 990. The method of any preceding enumerated embodiment, wherein the improvement in physical function score further includes an improvement in the patient's baseline repeated chair stand times compared to a placebo control of at least -1.5 seconds over the period. In one aspect of this and other embodiments, the improvement in the patient's baseline repeated chair stand is seen after treatment for a period of at least about 52 weeks, at least about 40 weeks, at least about 26 weeks, or at least about 12 weeks. In another aspect of this and other embodiments, the improvement in the patient's baseline repeated

chair stand is seen after treatment for a period of at least about 12 weeks and at least about 40 weeks. In another aspect of this and other embodiments, the improvement in the patient's baseline repeated chair stand is seen after treatment for a period of at least about 12 weeks and at least about 52 weeks. In another aspect of this and other embodiments, the improvement in the patient's baseline repeated chair stand is seen after treatment for a period of at least about 12 weeks, at least about 40 weeks and at least about 52 weeks. In another aspect of this and other embodiments, in the Repeated Chair Stand Test, after about twelve weeks of treatment, there is a trend toward significance for the difference between treated and placebo-treated patients. In another aspect of this and other embodiments, in the Repeated Chair Stand Test, after about twelve weeks of treatment, there is a trend toward significance for the difference between treated and placebo-treated patients. In a further aspect of this and other embodiments, improvement in the patient's baseline repeated chair stand times is at least about 0.5, 0.75, 1.0, 1.1, 1.2, 1.3, or 1.4 seconds. In another aspect of this and other embodiments, the improvement in the patient's baseline physical function score is based on the patient's performance in the Single Chair Stand and/or Repeated Chair Stand protocols as depicted in Fig. 22. In another aspect of this and other embodiments, the patient's KDQOL-SF score is calculated as follows: 1 (limited a lot) = 0; 2 (limited a little) = 50; 3 (not limited) = 100. Total score = sum of all 10, divided by 10.

[001367] Embodiment 991. The method/composition of any preceding enumerated embodiment, wherein the patient achieves at least about a 1.5 point improvement on the KDQOL-SF scale relative to the placebo control.

[001368] Embodiment 992. The method/composition of any preceding enumerated embodiment, wherein the patient achieves at least about a 3.0 point improvement on the KDQOL-SF scale relative to the placebo control.

[001369] Embodiment 993. The method/composition of any preceding enumerated embodiment, wherein the patient achieves at least about a 4.5 point improvement on the KDQOL-SF scale relative to the placebo control.

[001370] Embodiment 994. The method/composition of any preceding enumerated embodiment, wherein the patient achieves at least about a 6.0 point improvement on the KDQOL-SF scale relative to the placebo control.

[001371] Embodiment 995. The method/composition of any preceding enumerated embodiment, wherein the disease or disorder is characterized by a baseline serum bicarbonate value of less than 18 mEq/L.

[001372] Embodiment 996. The method/composition of any preceding enumerated embodiment, wherein the disease or disorder is characterized by a baseline serum bicarbonate value of at least 12 mEq/L.

[001373] Embodiment 997. The method/composition of any preceding enumerated embodiment, wherein the disease or disorder is characterized by a baseline serum bicarbonate value of at least 15 mEq/L.

[001374] Embodiment 998. The method/composition of any preceding enumerated embodiment, wherein the patient's baseline serum bicarbonate value increases by at least 1 mEq/L during the period.

[001375] Embodiment 999. The method/composition of any preceding enumerated embodiment, wherein the patient's baseline serum bicarbonate value increases by at least 2 mEq/L during the period.

[001376] Embodiment 1000. The method/composition of any preceding enumerated embodiment, wherein the patient's baseline serum bicarbonate value increases by at least 3 mEq/L during the period.

[001377] Embodiment 1001. The method/composition of any preceding enumerated embodiment, wherein a daily dose of the pharmaceutical composition is administered to the patient and the daily dose has the capacity to remove at least about 10 mEq/day, at least about 15 mEq/day, at least about 20 mEq/day, at least about 25 mEq/day, or at least about 30 mEq/day of the target species.

[001378] Embodiment 1002. The method/composition of any preceding enumerated embodiment, wherein a daily dose of the pharmaceutical composition is administered to the patient and the daily dose has the capacity to remove less than 50 mEq/day or less than 35 mEq/day of the target species.

[001379] Embodiment 1003. The method/composition of any preceding enumerated embodiment, wherein the period is at least three weeks, at least one month, at least two months, at least six months, at least 12 months, at least 18 months, or at least 24 months.

[001380] Embodiment 1004. The method/composition of any preceding enumerated embodiment, wherein the pharmaceutical composition has the capacity to bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids.

[001381] Embodiment 1005. The method/composition of any preceding enumerated embodiment, wherein the conjugate base of a strong acid is selected from the group consisting of chloride, bisulfate and sulfate ions.

[001382] Embodiment 1006. The method/composition of any preceding enumerated embodiment, wherein the target species comprises chloride ions.

[001383] Embodiment 1007. The method/composition of any preceding enumerated embodiment, wherein the target species comprises hydrochloric acid.

[001384] Embodiment 62A. The method/composition of any preceding enumerated embodiment, wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 1 mEq/g in a SIB assay.

[001385] Embodiment 1008. The method/composition of any preceding enumerated embodiment, wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 1.5 mEq/g in a SIB assay.

[001386] Embodiment 1009. The method/composition of any preceding enumerated embodiment, wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 2 mEq/g in a SIB assay.

[001387] Embodiment 1010. The method/composition of any preceding enumerated embodiment, wherein the pharmaceutical composition has the capacity to bind chloride and phosphate ions in a SIB assay at a ratio that is at least 0.25:1, respectively.

[001388] Embodiment 1011. The method/composition of any preceding enumerated embodiment, wherein the pharmaceutical composition has the capacity to bind chloride and phosphate ions in a SIB assay at a ratio that is at least 0.5:1, respectively.

[001389] Embodiment 1012. The method/composition of any preceding enumerated embodiment, wherein the pharmaceutical composition has the capacity

to bind chloride and phosphate ions in a SIB assay at a ratio that is at least 1:1, respectively.

[001390] Embodiment 1013. The method/composition of any preceding enumerated embodiment, wherein the effective amount of the pharmaceutical composition or TRC101 comprises at least about 1 gm/day.

[001391] Embodiment 1014. The method/composition of any preceding enumerated embodiment, wherein the effective amount of the pharmaceutical composition or TRC101 comprises from about 1-9 gm/day.

[001392] Embodiment 1015. The method/composition of any preceding enumerated embodiment, wherein the effective amount of the pharmaceutical composition or TRC101 comprises about 4-6 gm/day.

[001393] Embodiment 1016. The method/composition of any preceding enumerated embodiment, wherein the effective amount of the pharmaceutical composition or TRC101 comprises about 6 gm/day.

[001394] Embodiment 1017. The method/composition of any preceding enumerated embodiment, wherein the effective amount of the pharmaceutical composition or TRC101 is administered to the patient in an oral dosage form once-a-day.

[001395] Embodiment 1018. The method/composition of any preceding enumerated embodiment, wherein the effective amount of the pharmaceutical composition or TRC101 is adjusted to maintain the patient's serum bicarbonate level in a range between 22-29 mEq/L.

[001396] Embodiment 1019. The method/composition of any preceding enumerated embodiment, wherein the improvement in the patient's baseline repeated chair stand times represents an improvement for at least one repetition.

[001397] Embodiment 1020. The method/composition of any preceding enumerated embodiment, wherein the improvement in the patient's baseline repeated chair stand times represents an improvement for at least two repetitions.

[001398] Embodiment 1021. The method/composition of any preceding enumerated embodiment, wherein the improvement in the patient's baseline repeated chair stand times represents an improvement for at least three repetitions.

[001399] Embodiment 1022. The method/composition of any preceding enumerated embodiment, wherein the improvement in the patient's baseline repeated chair stand times represents an improvement for at least four repetitions.

[001400] Embodiment 1023. The method/composition of any preceding enumerated embodiment, wherein the improvement in the patient's baseline repeated chair stand times represents an improvement for at least five repetitions.

[001401] Embodiment 1024. The method/composition of any preceding enumerated embodiment, wherein the improvement in the patient's baseline physical function score is based on the patient's answers to at least one question to Question 3 the of KDQOL-SF as depicted in Fig. 21.

[001402] Embodiment 1025. The method/composition of any preceding enumerated embodiment, wherein the improvement in the patient's baseline physical function score is based on the patient's answers to at least five questions to Question 3 the of KDQOL-SF as depicted in Fig. 21.

[001403] Embodiment 1026. The method/composition of any preceding enumerated embodiment, wherein the improvement in the patient's baseline physical function score is based on the patient's answers to at least seven questions to Question 3 of the KDQOL-SF as depicted in Fig. 21.

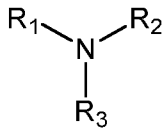
[001404] Embodiment 1027. The method/composition of any preceding enumerated embodiment, wherein the improvement in the patient's baseline physical function score is based on the patient's answers to all questions to Question 3 of the KDQOL-SF as depicted in Fig. 21.

[001405] Embodiment 1028. A pharmaceutical composition for use in a method of treating an acid-base disorder in a patient, wherein the method of treatment improves the quality of life of the patient.

[001406] Embodiment 1029. A pharmaceutical composition for use in a method of treating an acid-base disorder in a patient, wherein the method of treatment improves the physical function of the patient.

[001407] Embodiment 1030. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising

a proton-binding, crosslinked amine polymer comprising the residue of an amine corresponding to Formula 1:



Formula 1

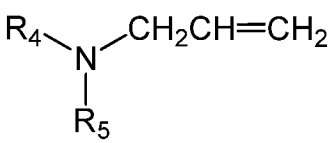
wherein R_1, R_2 and R_3 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen.

[001408] Embodiment 1031. The pharmaceutical composition for use in a method of treating an acid-base disorder of embodiment 1030 wherein R_1, R_2 and R_3 are independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic provided, however, each of R_1, R_2 and R_3 is not hydrogen.

[001409] Embodiment 1032. The pharmaceutical composition for use in a method of treating an acid-base disorder of any of embodiments 1030 to 1031 wherein R_1, R_2 and R_3 are independently hydrogen, aliphatic or heteroaliphatic provided, however, at least one of R_1, R_2 and R_3 is other than hydrogen.

[001410] Embodiment 1033. The pharmaceutical composition for use in a method of treating an acid-base disorder of any of embodiments 1030 to 1032 wherein the crosslinked amine polymer is prepared by substitution polymerization of the amine with a polyfunctional crosslinker, optionally also comprising amine moieties.

[001411] Embodiment 1034. The pharmaceutical composition for use in a method of treating an acid-base disorder of any of embodiments 1030 to 1033 wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 1a and the crosslinked amine polymer is prepared by radical polymerization of an amine corresponding to Formula 1a:



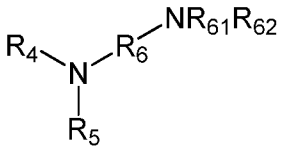
Formula 1a

wherein R_4 and R_5 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl.

[001412] Embodiment 1035. The pharmaceutical composition for use in a method of treating an acid-base disorder of embodiment 1034 wherein R_4 and R_5 are independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic.

[001413] Embodiment 1036. The pharmaceutical composition for use in a method of treating an acid-base disorder of embodiment 1034 wherein R_4 and R_5 are independently hydrogen, aliphatic or heteroaliphatic.

[001414] Embodiment 1037. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition is a nonabsorbable composition comprising a crosslinked amine polymer containing the residue of an amine corresponding to Formula 1b and the crosslinked amine polymer is prepared by substitution polymerization of the amine corresponding to Formula 1b with a polyfunctional crosslinker:



Fromula 1b

wherein R_4 and R_5 are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl, R_6 is aliphatic and R_{61} and R_{62} are independently hydrogen, aliphatic, or heteroaliphatic.

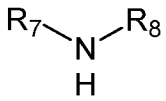
[001415] Embodiment 1038. The pharmaceutical composition for use in a method of treating an acid-base disorder of embodiment 1037 wherein R_4 and R_5 are independently hydrogen, saturated hydrocarbon, unsaturated aliphatic, aryl, heteroaryl, heteroalkyl, or unsaturated heteroaliphatic.

[001416] Embodiment 1039. The pharmaceutical composition for use in a method of treating an acid-base disorder of embodiment 1037 wherein R_4 and R_5 are

independently hydrogen, alkyl, alkenyl, allyl, vinyl, aryl, aminoalkyl, alkanol, haloalkyl, hydroxyalkyl, ethereal, heteroaryl or heterocyclic.

[001417] Embodiment 1040. The pharmaceutical composition for use in a method of treating an acid-base disorder of embodiment 1037 wherein R_4 and R_5 are independently hydrogen, allyl, or aminoalkyl.

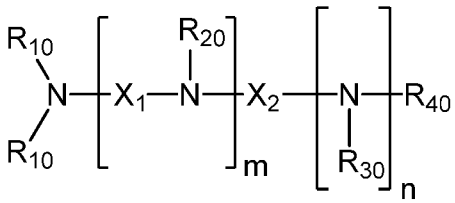
[001418] Embodiment 1041. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any one of embodiments 2E1 to 1040 wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 1c:



Formula 1c

wherein R_7 is hydrogen, aliphatic or heteroaliphatic and R_8 is aliphatic or heteroaliphatic.

[001419] Embodiment 1042. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any one of the preceding enumerated embodiments wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 2:

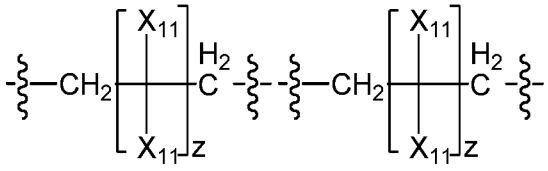


Formula 2

wherein

m and n are independently non-negative integers;

R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, hydrocarbyl, or substituted hydrocarbyl;

X_1 is  ;

X_2 is hydrocarbyl or substituted hydrocarbyl;

each X_{11} is independently hydrogen, hydrocarbyl, substituted hydrocarbyl, hydroxy, or amino; and

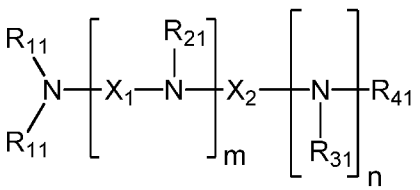
z is a non-negative number.

[001420] Embodiment 1043. The pharmaceutical composition for use in a method of treating an acid-base disorder according to embodiment 1042 wherein R_{10}, R_{20}, R_{30}, and R_{40} are independently hydrogen, aliphatic, aryl, heteroaliphatic, or heteroaryl, m and z are independently 0-3 and n is 0 or 1.

[001421] Embodiment 1044. The pharmaceutical composition for use in a method of treating an acid-base disorder according to embodiment wherein X_2 is aliphatic or heteroaliphatic.

[001422] Embodiment 1045. The pharmaceutical composition for use in a method of treating an acid-base disorder according to embodiment 1042, wherein m is 1-3 and X_{11} is hydrogen, aliphatic or heteroaliphatic.

[001423] Embodiment 1046. The pharmaceutical composition for use in a method of treating an acid-base disorder according to embodiment 1042, wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 2a:



Formula 2a

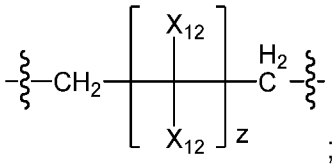
wherein

m and n are independently non-negative integers;

each R_{11} is independently hydrogen, hydrocarbyl, heteroaliphatic, or heteroaryl;

R_{21} and R_{31}, are independently hydrogen or heteroaliphatic;

R_{41} is hydrogen, substituted hydrocarbyl, or hydrocarbyl;

X_1 is  ;

X_2 is alkyl or substituted hydrocarbyl;

each X_{12} is independently hydrogen, hydroxy, amino, aminoalkyl, boronic acid or halo; and

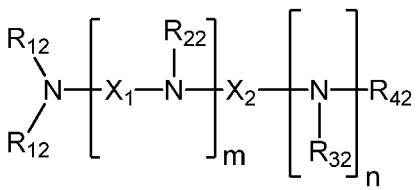
z is a non-negative number.

[001424] Embodiment 1047. The pharmaceutical composition for use in a method of treating an acid-base disorder according to embodiment 1046, wherein m and z are independently 0-3 and n is 0 or 1.

[001425] Embodiment 1048. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any one of embodiments 1046 to 1047 wherein R_{11} is independently hydrogen, aliphatic, aminoalkyl, haloalkyl, or heteroaryl, R_{21} and R_{31} are independently hydrogen or heteroaliphatic and R_{41} is hydrogen, aliphatic, aryl, heteroaliphatic, or heteroaryl.

[001426] Embodiment 1049. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any one of embodiments 1046 to 1048 each R_{11} is hydrogen, aliphatic, aminoalkyl, or haloalkyl, R_{21} and R_{31} are hydrogen or aminoalkyl, and R_{41} is hydrogen, aliphatic, or heteroaliphatic.

[001427] Embodiment 1050. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any one of embodiments 1046 to 1049 wherein the crosslinked amine polymer comprises the residue of an amine corresponding to Formula 2b:



Formula 2b

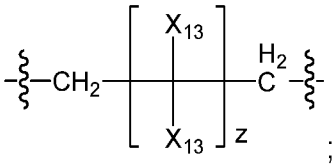
wherein

m and n are independently non-negative integers;

each R_{12} is independently hydrogen, substituted hydrocarbyl, or hydrocarbyl;

R_{22} and R_{32} are independently hydrogen substituted hydrocarbyl, or hydrocarbyl;

R_{42} is hydrogen, hydrocarbyl or substituted hydrocarbyl;

X_1 is  ;

X_2 is alkyl, aminoalkyl, or alkanol;

each X_{13} is independently hydrogen, hydroxy, alicyclic, amino, aminoalkyl, halogen, alkyl, heteroaryl, boronic acid or aryl;

z is a non-negative number; and

the amine corresponding to Formula 2b comprises at least one allyl group.

[001428] Embodiment 1051. The pharmaceutical composition for use in a method of treating an acid-base disorder according to embodiment 1050, wherein m and z are independently 0-3 and n is 0 or 1.

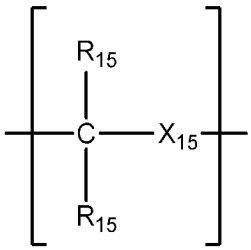
[001429] Embodiment 1052. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any one of embodiments 1050 to 1051 wherein R_{12} or R_{42} independently comprise at least one allyl or vinyl moiety.

[001430] Embodiment 1053. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any one of embodiments 1050 to 1052 wherein (i) m is a positive integer and R_{12}, R_{22} and R_{42}, in combination comprise at least two allyl or vinyl moieties or (ii) n is a positive integer and R_{12}, R_{32} and R_{42}, in combination, comprise at least two allyl or vinyl moieties.

[001431] Embodiment 1054. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein the crosslinked amine polymer comprises the residue of an amine appearing in Table A.

[001432] Embodiment 1055. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein the crosslinked amine polymer is crosslinked with a crosslinking agent appearing in Table B.

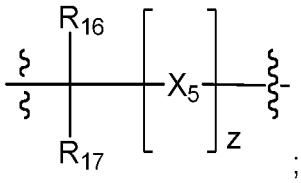
[001433] Embodiment 1056. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein the crosslinked amine polymer comprises a repeat unit corresponding to Formula 3:



Formula 3

wherein

R_{15}, R_{16} and R_{17} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, hydroxyl, amino, boronic acid or halo;

X_{15} is 

;

X_5 is hydrocarbyl, substituted hydrocarbyl, oxo (O), or amino; and

z is a non-negative number.

[001434] Embodiment 1057. The pharmaceutical composition for use in a method of treating an acid-base disorder according to embodiment 1056 wherein R_{15}, R_{16} and R_{17} are independently aliphatic or heteroaliphatic.

[001435] Embodiment 1058. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any one of embodiments 1056 to 1057 wherein X_5 is oxo, amino, alkylamino, ethereal, alkanol, or haloalkyl.

[001436] Embodiment 1059. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any one of embodiments 1056

to 1058 wherein the crosslinked amine polymer is prepared by (i) substitution polymerization of polyfunctional reagents at least one of which comprises amine moieties, (2) radical polymerization of a monomer comprising at least one amine moiety or nitrogen containing moiety, or (3) crosslinking of an amine-containing intermediate with a crosslinking agent, optionally containing amine moieties.

[001437] Embodiment 1060. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein the crosslinked amine polymer is a crosslinked homopolymer or a crosslinked copolymer.

[001438] Embodiment 1061. The pharmaceutical composition for use in a method of treating an acid-base disorder according to according to any preceding enumerated embodiment wherein the crosslinked amine polymer comprises free amine moieties, separated by the same or varying lengths of repeating linker units.

[001439] Embodiment 1062. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein the crosslinked amine polymer is prepared by polymerizing an amine-containing monomer with a crosslinking agent in a substitution polymerization reaction.

[001440] Embodiment 1063. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein the amine-containing monomer is a linear amine possessing at least two reactive amine moieties to participate in the substitution polymerization reaction.

[001441] Embodiment 1064. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein the amine-containing monomer is 1,3-Bis[bis(2-aminoethyl)amino]propane, 3-Amino-1-{[2-(bis{2-[bis(3-aminopropyl)amino]ethyl}amino)ethyl](3-aminopropyl)amino}propane, 2-[Bis(2-aminoethyl)amino]ethanamine, Tris(3-aminopropyl)amine, 1,4-Bis[bis(3-aminopropyl)amino]butane, 1,2-Ethanediamine, 2-Amino-1-(2-aminoethylamino)ethane, 1,2-Bis(2-aminoethylamino)ethane, 1,3-Propanediamine, 3,3'-Diaminodipropylamine, 2,2-dimethyl-1,3-propanediamine, 2-methyl-1,3-

propanediamine, N,N'-dimethyl-1,3-propanediamine, N-methyl-1,3-diaminopropane, 3,3'-diamino-N-methyldipropylamine, 1,3-diaminopentane, 1,2-diamino-2-methylpropane, 2-methyl-1,5-diaminopentane, 1,2-diaminopropane, 1,10-diaminodecane, 1,8-diaminooctane, 1,9-diaminooctane, 1,7-diaminoheptane, 1,6-diaminohexane, 1,5-diaminopentane, 3-bromopropylamine hydrobromide, N,2-dimethyl-1,3-propanediamine, N-isopropyl-1,3-diaminopropane, N,N'-bis(2-aminoethyl)-1,3-propanediamine, N,N'-bis(3-aminopropyl)ethylenediamine, N,N'-bis(3-aminopropyl)-1,4-butanediamine tetrahydrochloride, 1,3-diamino-2-propanol, N-ethylethylenediamine, 2,2'-diamino-N-methyldiethylamine, N,N'-diethylethylenediamine, N-isopropylethylenediamine, N-methylethylenediamine, N,N'-di-tert-butylethylenediamine, N,N'-diisopropylethylenediamine, N,N'-dimethylethylenediamine, N-butylethylenediamine, 2-(2-aminoethylamino)ethanol, 1,4,7,10,13,16-hexaazacyclooctadecane, 1,4,7,10-tetraazacyclododecane, 1,4,7-triazacyclononane, N,N'-bis(2-hydroxyethyl)ethylenediamine, piperazine, bis(hexamethylene)triamine, N-(3-hydroxypropyl)ethylenediamine, N-(2-Aminoethyl)piperazine, 2-Methylpiperazine, Homopiperazine, 1,4,8,11-Tetraazacyclotetradecane, 1,4,8,12-Tetraazacyclopentadecane, 2-(Aminomethyl)piperidine, or 3-(Methylamino)pyrrolidino.

[001442] Embodiment 1065. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein the crosslinking agent is selected from the group consisting of dihaloalkanes, haloalkyloxiranes, alkyloxirane sulfonates, di(haloalkyl)amines, tri(haloalkyl) amines, diepoxides, triepoxides, tetraepoxides, bis (halomethyl)benzenes, tri(halomethyl)benzenes, tetra(halomethyl)benzenes, epihalohydrins such as epichlorohydrin and epibromohydrin poly(epichlorohydrin), (iodomethyl)oxirane, glycidyl tosylate, glycidyl 3-nitrobenzenesulfonate, 4-tosyloxy-1,2-epoxybutane, bromo-1,2-epoxybutane, 1,2-dibromoethane, 1,3-dichloropropane, 1,2- dichloroethane, l-bromo-2-chloroethane, 1,3- dibromopropane, bis(2-chloroethyl)amine, tris(2- chloroethyl)amine, and bis(2-chloroethyl)methylamine, 1,3-butadiene diepoxide, 1,5-hexadiene diepoxide, diglycidyl ether, 1,2,7,8-diepoxyoctane, 1,2,9,10-diepoxydecane, ethylene glycol diglycidyl ether, propylene glycol diglycidyl ether, 1,4-butanediol diglycidyl ether, 1,2 ethanedioldiglycidyl ether, glycerol diglycidyl ether, 1,3-diglycidyl glyceryl ether, N,N-diglycidylaniline, neopentyl

glycol diglycidyl ether, diethylene glycol diglycidyl ether, 1,4-bis(glycidyloxy)benzene, resorcinol digylcidyl ether, 1,6-hexanediol diglycidyl ether, trimethylolpropane diglycidyl ether, 1,4-cyclohexanedimethanol diglycidyl ether, 1,3-bis-(2,3-epoxypropyloxy)-2-(2,3-dihydroxypropy loxy)propane, 1,2-cyclohexanedicarboxylic acid diglycidyl ester, 2,2'-bis(glycidyloxy) diphenylmethane, bisphenol F diglycidyl ether, 1,4-bis(2',3'epoxypropyl)perfluoro-n-butane, 2,6-di(oxiran-2-ylmethy1)-1,2,3,5,6,7-hexahydropyrrolo[3,4-f]isoindol-1,3,5,7- tetraone, bisphenol A diglycidyl ether, ethyl 5-hydroxy-6,8- di(oxiran-2-ylmethyl)-4-oxo-4-h-chromene-2-carboxylate, bis[4-(2,3-epoxy-propylthio)phenyl]-sulfide, 1,3-bis(3-glycidoxypropyl) tetramethyldisiloxane, 9,9-bis[4-(glycidyloxy)phenyl]fluorine, triepoxyisocyanurate, glycerol triglycidyl ether, N,N-diglycidyl-4-glycidyloxyaniline, isocyanuric acid (S,S,S)-triglycidyl ester, isocyanuric acid (R,R,R)-triglycidyl ester, triglycidyl isocyanurate, trimethylolpropane triglycidyl ether, glycerol propoxylate triglycidyl ether, triphenylolmethane triglycidyl ether, 3,7,14-tris[[3-(epoxypropoxy)propyl]dimethylsilyloxy]-1,3,5,7,9,11,14- heptacyclopentyltricyclo [7,3,3,15, 11]heptasiloxane, 4,4 'methylenebis(N,N-diglycidylaniline), bis(halomethyl)benzene, bis(halomethyl)biphenyl and bis(halomethyl)naphthalene, toluene diisocyanate, acrylol chloride, methyl acrylate, ethylene bisacrylamide, pyrometallic dianhydride, succinyl dichloride, dimethylsuccinate, 3-chloro-1-(3-chloropropylamino-2-propanol, 1,2-bis(3-chloropropylamino)ethane, Bis(3-chloropropyl)amine, 1,3-Dichloro-2-propanol, 1,3-Dichloropropane, 1-chloro-2,3-epoxypropane, tris[(2-oxiranyl)methyl]amine, and combinations thereof.

[001443] Embodiment 1066. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein the preparation of the crosslinked amine polymer comprises radical polymerization of an amine monomer comprising at least one amine moiety or nitrogen containing moiety.

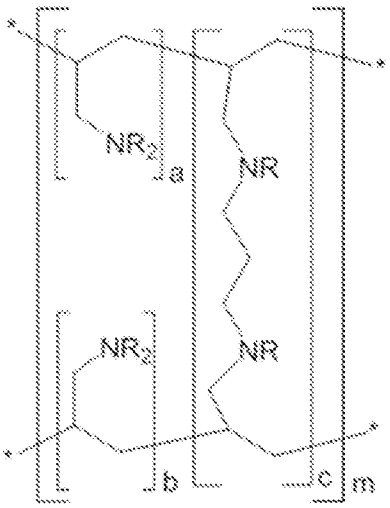
[001444] Embodiment 1067. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein the crosslinked amine polymer has an equilibrium swelling ratio in deionized water of about 1.5 or less.

[001445] Embodiment 1068. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated

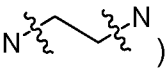
embodiment wherein the crosslinked amine polymer has an equilibrium swelling ratio in deionized water of about 1 or less.

[001446] Embodiment 1069. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein the crosslinked amine polymer has a chloride ion to phosphate ion binding molar ratio of at least 0.5:1, respectively, in an aqueous simulated small intestine inorganic buffer ("SIB") containing 36 mM NaCl, 20 mM NaH_2PO_4, and 50 mM 2-(N-morpholino)ethanesulfonic acid (MES) buffered to pH 5.5 and at 37 °C.

[001447] Embodiment 1070. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein the pharmaceutical composition comprises a polymer comprising a structure corresponding to Formula 4:



Formula 4

wherein each R is independently hydrogen or an ethylene crosslink between two nitrogen atoms of the crosslinked amine polymer () and a, b, c, and m are integers.

[001448] Embodiment 1071. The pharmaceutical composition for use in a method of treating an acid-base disorder according to embodiment 1070 wherein m is a large integer indicating an extended polymer network.

[001449] Embodiment 1072. The pharmaceutical composition for use in a method of treating an acid-base disorder according to embodiment 1070 or 1071

wherein a ratio of the sum of a and b to c (i.e., a+b:c) is in the range of about 1:1 to 5:1.

[001450] Embodiment 1073. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any one of embodiments 1070 to 1072 wherein a ratio of the sum of a and b to c (i.e., a+b:c) is in the range of about 1.5:1 to 4:1.

[001451] Embodiment 1074. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any one of embodiments 1070 to 1073 wherein a ratio of the sum of a and b to c (i.e., a+b:c) is in the range of about 1.75:1 to 3:1.

[001452] Embodiment 1075. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any one of embodiments 1070 to 1074 wherein a ratio of the sum of a and b to c (i.e., a+b:c) is in the range of about 2:1 to 2.5:1.

[001453] Embodiment 1076. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any one of embodiments 1070 to 1075 wherein the sum of a and b is 57 and c is 24.

[001454] Embodiment 1077. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein 50-95% of the R substituents are hydrogen and 5-50% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001455] Embodiment 1078. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein 55-90% of the R substituents are hydrogen and 10-45% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001456] Embodiment 1079. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein 60-90% of the R substituents are hydrogen and 10-40% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001457] Embodiment 1080. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated

embodiment wherein 65-90% of the R substituents are hydrogen and 10-35% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001458] Embodiment 1081. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any one of embodiments 1070 to 1082 wherein the R substituents are hydrogen and 10-30% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001459] Embodiment 1082. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein the composition is the polymer of any of embodiments 768 to 774 wherein 75-85% of the R substituents are hydrogen and 15-25% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001460] Embodiment 1083. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein the R substituents are hydrogen and 15-20% are an ethylene crosslink between two nitrogens of the crosslinked amine polymer.

[001461] Embodiment 1084. The pharmaceutical composition for use in a method of treating an acid-base disorder according to any preceding enumerated embodiment wherein the R substituents are hydrogen and about 19% are an ethylene crosslink.

[001462] Embodiment 1085. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 1 mEq/g in a SIB assay.

[001463] Embodiment 1086. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 1.5 mEq/g in a SIB assay.

[001464] Embodiment 1087. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 2 mEq/g in a SIB assay.

[001465] Embodiment 1088. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 2.5 mEq/g in a SIB assay.

[001466] Embodiment 1089. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 3 mEq/g in a SIB assay.

[001467] Embodiment 1090. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 3.5 mEq/g in a SIB assay.

[001468] Embodiment 1091. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 4 mEq/g in a SIB assay.

[001469] Embodiment 1092. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 4.5 mEq/g in a SIB assay.

[001470] Embodiment 1093. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 5 mEq/g in a SIB assay.

[001471] Embodiment 1094. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 5.5 mEq/g in a SIB assay.

[001472] Embodiment 1095. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 6 mEq/g in a SIB assay.

[001473] Embodiment 1096. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.1:1, respectively.

[001474] Embodiment 1097. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.2:1, respectively.

[001475] Embodiment 1098. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.25:1, respectively.

[001476] Embodiment 1099. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.3:1, respectively.

[001477] Embodiment 1100. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.35:1, respectively.

[001478] Embodiment 1101. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.4:1, respectively.

[001479] Embodiment 1102. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment

wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.45:1, respectively.

[001480] Embodiment 1103. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.5:1, respectively.

[001481] Embodiment 1104. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 2:3, respectively.

[001482] Embodiment 1105. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.75:1, respectively.

[001483] Embodiment 1106. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 0.9:1, respectively.

[001484] Embodiment 1107. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 1:1, respectively.

[001485] Embodiment 1108. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a

ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 1.25:1, respectively.

[001486] Embodiment 1109. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 1.5:1, respectively.

[001487] Embodiment 1110. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 1.75:1, respectively.

[001488] Embodiment 1111. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 2:1, respectively.

[001489] Embodiment 1112. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 2.25:1, respectively.

[001490] Embodiment 1113. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 2.5:1, respectively.

[001491] Embodiment 1114. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 2.75:1, respectively.

[001492] Embodiment 1115. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 3:1, respectively.

[001493] Embodiment 1116. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 4:1, respectively.

[001494] Embodiment 1117. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 5:1, respectively.

[001495] Embodiment 1118. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 6:1, respectively.

[001496] Embodiment 1119. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 7:1, respectively.

[001497] Embodiment 1120. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 8:1, respectively.

[001498] Embodiment 1121. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment

wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 9:1, respectively.

[001499] Embodiment 1122. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 10:1, respectively.

[001500] Embodiment 1123. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 12.5:1, respectively.

[001501] Embodiment 1124. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the binding capacity of the pharmaceutical composition is characterized by a ratio of the amount of bound chloride to bound phosphate in a SIB assay of at least 15:1, respectively.

[001502] Embodiment 1125. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition has an equilibrium chloride binding capacity of at least 5 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C.

[001503] Embodiment 1126. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition has an equilibrium chloride binding capacity of at least 7.5 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C.

[001504] Embodiment 1127. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment wherein the pharmaceutical composition has an equilibrium chloride binding capacity

of at least 10 mmol/g in an aqueous simulated gastric fluid buffer ("SGF") containing 35 mM NaCl and 63 mM HCl at pH 1.2 and 37 °C.

[001505] Embodiment 1128. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment, wherein the acid-base disorder is metabolic acidosis.

[001506] Embodiment 1129. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment, wherein the patient is afflicted with chronic kidney disease.

[001507] Embodiment 1130. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment, wherein the pharmaceutical composition comprises a polymer as defined anywhere in the description.

[001508] Embodiment 1131. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment, wherein the acid-based disorder is characterized by a baseline serum bicarbonate value of less than about 21 mEq/l.

[001509] Embodiment 1132. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment, wherein the acid-based disorder is characterized by a baseline serum bicarbonate value of less than about 20 mEq/l.

[001510] Embodiment 1133. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment, wherein the acid-based disorder is characterized by a baseline serum bicarbonate value of less than about 19 mEq/l.

[001511] Embodiment 1134. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment, wherein the acid-based disorder is characterized by a baseline serum bicarbonate value of less than about 18 mEq/l.

[001512] Embodiment 1135. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment,

wherein the acid-based disorder is characterized by a baseline serum bicarbonate value of less than about 17 mEq/l.

[001513] Embodiment 1136. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment, wherein the acid-based disorder is characterized by a baseline serum bicarbonate value of less than about 16 mEq/l.

[001514] Embodiment 1137. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment, wherein the acid-based disorder is characterized by a baseline serum bicarbonate value of less than about 15 mEq/l.

[001515] Embodiment 1138. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment, wherein the acid-based disorder is characterized by a baseline serum bicarbonate value of less than about 14 mEq/l.

[001516] Embodiment 1139. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment, wherein the acid-based disorder is characterized by a baseline serum bicarbonate value of less than about 13 mEq/l.

[001517] Embodiment 1140. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment, wherein the acid-based disorder is characterized by a baseline serum bicarbonate value of less than about 12 mEq/l.

[001518] Embodiment 1141. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment, wherein the acid-based disorder is characterized by a baseline serum bicarbonate value of less than about 11 mEq/l.

[001519] Embodiment 1142. The pharmaceutical composition for use in a method of treating an acid-base disorder of any preceding enumerated embodiment, wherein the acid-based disorder is characterized by a baseline serum bicarbonate value of less than about 10 mEq/l.

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CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 302

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THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 302

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CLAIMS

What is claimed is:

1. A method of improving the quality of life of a patient afflicted with chronic kidney disease and an acid-base disorder characterized by a baseline serum bicarbonate value of ≤22 mEq/L, the method comprising oral administration of a pharmaceutical composition capable of increasing and maintaining the patient's serum bicarbonate above 20 mEq/L for a period of at least twelve weeks, the pharmaceutical composition having the capacity to bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids.

2. A method of improving the quality of life of a patient afflicted with chronic kidney disease and an acid-base disorder, the method comprising oral administration of a pharmaceutical composition having: (a) the capacity to selectively bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay, wherein the improvement in quality of life is statistically significant compared to a placebo control group for a period of at least twelve weeks as assessed by a Quality of Life (QoL) questionnaire.

3. A method of improving quality of life of a patient afflicted with chronic kidney disease and an acid-base disorder, wherein the patient has a baseline serum bicarbonate value of ≤22 mEq/L, comprising orally administering to the patient an effective amount of TRC101 once daily for a period of time sufficient to statistically significantly increase the patient's quality of life compared to a placebo control.

4. A method of improving quality of life of a patient afflicted with metabolic acidosis disease, the method comprising administering to the patient a daily dose of a nonabsorbed crosslinked amine polymer, which daily dose: (a) is sufficient to increase the patient's serum bicarbonate concentration by at least 1 mEq/L; (b) results in a sustained serum bicarbonate increase of at least 1 mEq/L over a period

of at least twelve weeks; and (c) is sufficient to improve the patient's quality of life compared to a placebo control group over the period, wherein the improvement in quality of life is statistically significant.

5. A pharmaceutical composition for improving the quality of life of a human patient afflicted with chronic kidney disease and an acid-base disorder, the patient having a baseline serum bicarbonate level of ≤22 mEq/L prior to treatment, the composition being a nonabsorbable composition having the capacity to: (a) remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) improve the patient's quality of life compared to a placebo control in a statistically significant manner over at least a twelve-week period.

6. A pharmaceutical composition for improving the quality of life of a human patient suffering from a disease or disorder by increasing that patient's serum bicarbonate value by at least 1 mEq/L over at least twelve weeks of treatment, the composition: (a) being a nonabsorbable composition having the capacity to remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (b) characterized by a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (c) having the capacity to improve the patient's quality of life compared to a placebo control in a statistically significant manner over at least the twelve-week period.

7. A pharmaceutical composition for improving the quality of life of a human patient suffering from metabolic acidosis disease, wherein: (a) an effective amount of the pharmaceutical composition is administered to the patient per day over at least a twelve-week period; (b) the pharmaceutical composition is nonabsorbable with the capacity to remove from the patient a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (c) the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (d)

the improvement in quality of life compared to a placebo control is statistically significant over the twelve-week period.

8. A method of improving the physical function of a patient afflicted with chronic kidney disease and an acid-base disorder characterized by a baseline serum bicarbonate value of ≤22 mEq/L, the method comprising oral administration of a pharmaceutical composition capable of increasing and maintaining the patient's serum bicarbonate above 20 mEq/L for a period of at least twelve weeks, the pharmaceutical composition having the capacity to bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids.

9. A method of improving the physical function of a patient afflicted with chronic kidney disease and an acid-base disorder, the method comprising oral administration of a pharmaceutical composition having: (a) the capacity to selectively bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay, wherein the improvement in physical function is statistically significant compared to a placebo control group at least twelve weeks after initiation of treatment as assessed by the patient's answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF).

10. A method of improving the physical function of a patient afflicted with chronic kidney disease and an acid-base disorder, wherein the patient has a baseline serum bicarbonate value of ≤22 mEq/L, comprising orally administering to the patient an effective amount of TRC101 once daily for a period of time sufficient to statistically significantly increase the patient's physical function score based on answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF) compared to the patient's baseline physical function score.

11. A method of improving the physical function of a patient afflicted with metabolic acidosis disease, the method comprising administering to the patient a daily dose of a nonabsorbed crosslinked amine polymer, which daily dose: (a) is sufficient to increase the patient's serum bicarbonate concentration by at least 1 mEq/L; (b) results in a sustained serum bicarbonate increase of at least 1 mEq/L over a period of at least twelve weeks; and (c) is sufficient to improve the physical function score of the patient compared to a placebo control group at the end of the period, wherein the improvement in the physical function score is statistically significant.

12. A pharmaceutical composition for improving the physical function score of a human patient afflicted with chronic kidney disease and an acid-base disorder, the patient having a baseline serum bicarbonate level of ≤22 mEq/L prior to treatment, the composition being a nonabsorbable composition having the capacity to: (a) remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) improve the patient's physical function score based on answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF) compared to a placebo control in a statistically significant manner at the end of at least a twelve-week period.

13. A pharmaceutical composition for improving the physical function score of a human patient suffering from a disease or disorder by increasing that patient's serum bicarbonate value by at least 1 mEq/L over at least twelve weeks of treatment, the composition: (a) being a nonabsorbable composition having the capacity to remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (b) characterized by a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (c) having the capacity to improve the patient's physical function score based on answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF) compared to a placebo control in a statistically significant manner at the end of an at least the twelve-week period.

14. A pharmaceutical composition for improving the physical function score of a human patient suffering from metabolic acidosis disease, wherein: (a) an effective amount of the pharmaceutical composition is administered to the patient per day over at least a twelve-week period; (b) the pharmaceutical composition is nonabsorbable with the capacity to remove from the patient a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (c) the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (d) the improvement in physical function score is a statistically significant improvement over a baseline physical function score based on answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF) compared to a placebo control at the end of the at least twelve-week period.

15. A method of slowing the progression of kidney disease in a patient afflicted with chronic kidney disease and an acid-base disorder characterized by a baseline serum bicarbonate value of ≤22 mEq/L, the method comprising oral administration of a pharmaceutical composition capable of increasing and maintaining the patient's serum bicarbonate above 20 mEq/L for a period of at least twelve weeks, the pharmaceutical composition having the capacity to bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids.

16. A method of slowing the progression of kidney disease in a patient afflicted with chronic kidney disease and an acid-base disorder, wherein the patient has a baseline serum bicarbonate value of ≤22 mEq/L, comprising orally administering to the patient an effective amount of TRC101 once daily for a period of time sufficient to increase the patient's serum bicarbonate by at least 1 mEq/L.

17. A method of slowing the progression of kidney disease in a patient afflicted with chronic kidney disease and metabolic acidosis disease, the method comprising administering to the patient a daily dose of a nonabsorbed crosslinked amine polymer, which daily dose: (a) is sufficient to increase the patient's serum

bicarbonate concentration by at least 1 mEq/L; (b) results in a sustained serum bicarbonate increase of at least 1 mEq/L over a period of at least twelve weeks; and (c) is sufficient to slow the progression of kidney disease.

18. A pharmaceutical composition for slowing the progression of kidney disease in a human patient afflicted with chronic kidney disease and an acid-base disorder, the patient having a baseline serum bicarbonate level of ≤22 mEq/L prior to treatment, the composition being a nonabsorbable composition having the capacity to: (a) remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; and (b) slow the progression of kidney disease in a human patient over at least a twelve-week period.

19. A pharmaceutical composition for slowing the progression of kidney disease in a human patient afflicted with chronic kidney disease and an acid-base disorder by increasing that patient's serum bicarbonate value by at least 1 mEq/L over at least twelve weeks of treatment, the composition: (a) being a nonabsorbable composition having the capacity to remove a target species from the patient selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (b) characterized by a target species binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (c) having the capacity to slow the progression of kidney disease over at least the twelve-week period.

20. A pharmaceutical composition for slowing the progression of kidney disease in a human patient also suffering from metabolic acidosis disease, wherein: (a) an effective amount of the pharmaceutical composition is administered to the patient per day over at least a twelve-week period; (b) the pharmaceutical composition is nonabsorbable with the capacity to remove from the patient a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids; (c) the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 3 mEq/g in a Simulated Small Intestine Inorganic Buffer (SIB) assay; and (d) the progression of kidney disease in the patient is slowed over the

twelve-week period compared to a placebo control group not receiving the pharmaceutical composition.

21. A pharmaceutical composition for use in a method of treating an acid-base disorder in a patient, wherein the method of treatment improves the quality of life of the patient.

22. A pharmaceutical composition for use in a method of treating an acid-base disorder in a patient, wherein the method of treatment improves the physical function of the patient.

23. The method/composition according to any one of the preceding claims, wherein the pharmaceutical composition increases the serum bicarbonate level by at least 1 mEq/L in a placebo controlled study, said increase being the difference between the cohort average serum bicarbonate level in a first cohort at the end of the study, relative to the cohort average serum bicarbonate level in a second cohort at the end of the study, wherein the first cohort's subjects receive the pharmaceutical composition and the second cohort's subjects receive a placebo, wherein the first and second cohorts each comprise a patient population sufficient in size to evaluate statistically significant serum bicarbonate level differences between the cohorts over the period.

24. The method/composition according to any one of the preceding claims, wherein the pharmaceutical composition increases the serum bicarbonate level by at least 2 mEq/L in a placebo controlled study, said increase being the difference between the cohort average serum bicarbonate level in a first cohort at the end of the study, relative to the cohort average serum bicarbonate level in a second cohort at the end of the study, wherein the first cohort's subjects receive the pharmaceutical composition and the second cohort's subjects receive a placebo, wherein the first and second cohorts each comprise a patient population sufficient in size to evaluate statistically significant serum bicarbonate level differences between the cohorts over the period.

25. The method/composition according to any one of the preceding claims, wherein the pharmaceutical composition increases the serum bicarbonate level by at least 2.5 mEq/L in a placebo controlled study, said increase being the difference between the cohort average serum bicarbonate level in a first cohort at the end of the study, relative to the cohort average serum bicarbonate level in a second cohort at the end of the study, wherein the first cohort's subjects receive the pharmaceutical composition and the second cohort's subjects receive a placebo, wherein the first and second cohorts each comprise a patient population sufficient in size to evaluate statistically significant serum bicarbonate level differences between the cohorts over the period.

26. The method/composition according to any one of the preceding claims, wherein the pharmaceutical composition has the capacity to change the patient's baseline serum bicarbonate level by at least 2 mEq/L in at the end of an at least twelve week placebo controlled study.

27. The method/composition according to any one of the preceding claims, wherein the pharmaceutical composition has the capacity to change the patient's baseline serum bicarbonate level by at least 3 mEq/L in at the end of an at least twelve week placebo controlled study.

28. The method/composition according to any one of the preceding claims, wherein the pharmaceutical composition has the capacity to change the patient's baseline serum bicarbonate level by at least 4 mEq/L in at the end of an at least twelve week placebo controlled study.

29. The method/composition according to any one of the preceding claims, wherein the patient population for each cohort is at least 25 patients.

30. The method/composition according to any one of the preceding claims, wherein the patient population for each cohort is at least 50 patients.

31. The method/composition according to any one of the preceding claims, wherein the patient population for each cohort is at least 100 patients.

32. The method/composition according to any one of the preceding claims, wherein the patient population for each cohort is at least 150 patients.

33. The method/composition according to any one of the preceding claims, wherein the patient population for each cohort is at least 200 patients.

34. The method/composition according to any one of the preceding claims, wherein improvement in quality of life or physical function is assessed by a questionnaire answered by a first cohort at the end of the period, relative to a second cohort who answered the same questionnaire at the end of the period, wherein the first cohort's subjects receive the pharmaceutical composition and the second cohort's subjects receive a placebo.

35. The method/composition according to any one of the preceding claims, wherein improvement in quality of life or physical function is assessed by a questionnaire, which is a clinically validated assessment for evaluating a patient's physical and mental health.

36. The method/composition according to any one of the preceding claims, wherein the questionnaire comprises questions concerning parameters selected from the group consisting of symptoms/problems related to the disease/condition, effects of the disease/condition, burden of the disease/condition, work status, cognitive function, quality of social interaction, sleep, social support, physical functioning, pain, general health, emotional well-being, social function, energy/fatigue, and combinations thereof.

37. The method/composition according to any one of the preceding claims, wherein the questionnaire comprises questions concerning how the patient's health limits the patient's ability to engage in physical activities selected from the group: vigorous activities; moderate activities; lifting or carrying groceries; climbing several flights of stairs; climbing one flight of stairs; bending, kneeling or stooping; walking more than one mile; walking several blocks; walking one block; and bathing or dressing.

38. The method/composition according to any one of the preceding claims, wherein the patient achieves at least about a 10% improvement on the quality of life scale relative to the placebo control.

39. The method/composition according to any one of the preceding claims, wherein the patient achieves at least about a 25% improvement on the quality of life scale relative to the placebo control.

40. The method/composition according to any one of the preceding claims, wherein the patient achieves at least about a 50% improvement on the quality of life scale relative to the placebo control.

41. The method/composition according to any one of the preceding claims, wherein the patient achieves at least about a 75% improvement on the quality of life scale relative to the placebo control.

42. The method/composition according to any one of the preceding claims, wherein the improvement of the physical function comprises: (a) an improvement in the patient's baseline physical function score of at least 1.5 points based on the patient's answers to question 3 of the Kidney Disease Quality of Life Short Form (KDQOL-SF); (b) an improvement in the patient's baseline repeated chair stand times of at least -1.5 seconds; or (c) an improvement in the patient's baseline physical function score of at least 1.5 points based on the patient's answers to

question 3 of the KDQOL-SF and an improvement in the patient's baseline repeated chair stand times of at least -1.5 seconds.

43. The method/composition according to any one of the preceding claims, wherein the improvement in the patient's baseline physical function score is based on the patient's performance in the Single Chair Stand and/or Repeated Chair Stand protocols as depicted in Fig. 22.

44. The method/composition according to any one of the preceding claims, wherein the improvement in the patient's baseline repeated chair stand times represents an improvement for at least one repetition.

45. The method/composition according to any one of the preceding claims, wherein the improvement in the patient's baseline repeated chair stand times represents an improvement for at least two repetitions.

46. The method/composition according to any one of the preceding claims, wherein the improvement in the patient's baseline repeated chair stand times represents an improvement for at least three repetitions.

47. The method/composition according to any one of the preceding claims, wherein the improvement in the patient's baseline repeated chair stand times represents an improvement for at least four repetitions.

48. The method/composition according to any one of the preceding claims, wherein the improvement in the patient's baseline repeated chair stand times represents an improvement for at least five repetitions.

49. The method/composition according to any one of the preceding claims, wherein the improvement in the patient's baseline physical function score is based on the patient's answers to at least one question to Question 3 the of KDQOL-SF as depicted in Fig. 21.

50. The method/composition according to any one of the preceding claims, wherein the improvement in the patient's baseline physical function score is based on the patient's answers to at least five questions to Question 3 the of KDQOL-SF as depicted in Fig. 21.

51. The method/composition according to any one of the preceding claims, wherein the improvement in the patient's baseline physical function score is based on the patient's answers to at least seven questions to Question 3 of the KDQOL-SF as depicted in Fig. 21.

52. The method/composition according to any one of the preceding claims, wherein the improvement in the patient's baseline physical function score is based on the patient's answers to all questions to Question 3 of the KDQOL-SF as depicted in Fig. 21.

53. The method/composition according to any one of the preceding claims, wherein the improvement in the quality of life of the patient comprises a decrease or prevention of further bone loss and/or a decrease or prevention of further muscle loss in the patient.

54. The method according to any one of the preceding claims, wherein the improvement in physical function score further includes an improvement in the patient's baseline repeated chair stand times compared to a placebo control of at least -1.5 seconds over the period.

55. The method/composition according to any one of the preceding claims, wherein the patient achieves at least about a 1.5 point improvement on the KDQOL-SF scale relative to the placebo control.

56. The method/composition according to any one of the preceding claims, wherein the patient achieves at least about a 3.0 point improvement on the KDQOL-SF scale relative to the placebo control.

57. The method/composition according to any one of the preceding claims, wherein the patient achieves at least about a 4.5 point improvement on the KDQOL-SF scale relative to the placebo control.

58. The method/composition according to any one of the preceding claims, wherein the patient achieves at least about a 6.0 point improvement on the KDQOL-SF scale relative to the placebo control.

59. The method/composition according to any one of the preceding claims, wherein the patient's KDQOL-SF score is calculated as follows: 1 (limited a lot) = 0; 2 (limited a little) = 50; 3 (not limited) = 100. Total score = sum of all 10, divided by 10.

60. The method/composition according to any one of the preceding claims, wherein the disease or disorder is characterized by a baseline serum bicarbonate value of less than 18 mEq/L.

61. The method/composition according to any one of the preceding claims, wherein the disease or disorder is characterized by a baseline serum bicarbonate value of at least 12 mEq/L.

62. The method/composition according to any one of the preceding claims, wherein the disease or disorder is characterized by a baseline serum bicarbonate value of at least 15 mEq/L.

63. The method/composition according to any one of the preceding claims, wherein the patient's baseline serum bicarbonate value increases by at least 1 mEq/L during the period.

64. The method/composition according to any one of the preceding claims, wherein the patient's baseline serum bicarbonate value increases by at least 2 mEq/L during the period.

65. The method/composition according to any one of the preceding claims, wherein the patient's baseline serum bicarbonate value increases by at least 3 mEq/L during the period.

66. The method/composition according to any one of the preceding claims, wherein a daily dose of the pharmaceutical composition is administered to the patient and the daily dose has the capacity to remove at least about 10 mEq/day, at least about 15 mEq/day, at least about 20 mEq/day, at least about 25 mEq/day, or at least about 30 mEq/day of the target species.

67. The method/composition according to any one of the preceding claims, wherein a daily dose of the pharmaceutical composition is administered to the patient and the daily dose has the capacity to remove less than 50 mEq/day or less than 35 mEq/day of the target species.

68. The method/composition according to any one of the preceding claims, wherein the period is at least three weeks, at least one month, at least two months, at least six months, at least 12 months, at least 18 months, or at least 24 months.

69. The method/composition according to any one of the preceding claims, wherein the pharmaceutical composition has the capacity to bind a target species selected from the group consisting of protons, strong acids, and conjugate bases of strong acids.

70. The method/composition according to any one of the preceding claims, wherein the conjugate base of a strong acid is selected from the group consisting of chloride, bisulfate and sulfate ions.

71. The method/composition according to any one of the preceding claims, wherein the target species comprises chloride ions.

72. The method/composition according to any one of the preceding claims, wherein the target species comprises hydrochloric acid.

73. The method/composition according to any one of the preceding claims, wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 1 mEq/g in a SIB assay.

74. The method/composition according to any one of the preceding claims, wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 1.5 mEq/g in a SIB assay.

75. The method/composition according to any one of the preceding claims, wherein the pharmaceutical composition is characterized by a chloride ion binding capacity of at least 2 mEq/g in a SIB assay.

76. The method/composition according to any one of the preceding claims, wherein the pharmaceutical composition has the capacity to bind chloride and phosphate ions in a SIB assay at a ratio that is at least 0.25:1, respectively.

77. The method/composition according to any one of the preceding claims, wherein the pharmaceutical composition has the capacity to bind chloride and phosphate ions in a SIB assay at a ratio that is at least 0.5:1, respectively.

78. The method/composition according to any one of the preceding claims, wherein the pharmaceutical composition has the capacity to bind chloride and phosphate ions in a SIB assay at a ratio that is at least 1:1, respectively.

79. The method/composition according to any one of the preceding claims, wherein the effective amount of the pharmaceutical composition or TRC101 comprises at least about 1 gm/day.

80. The method/composition according to any one of the preceding claims, wherein the effective amount of the pharmaceutical composition or TRC101 comprises from about 1-9 gm/day.

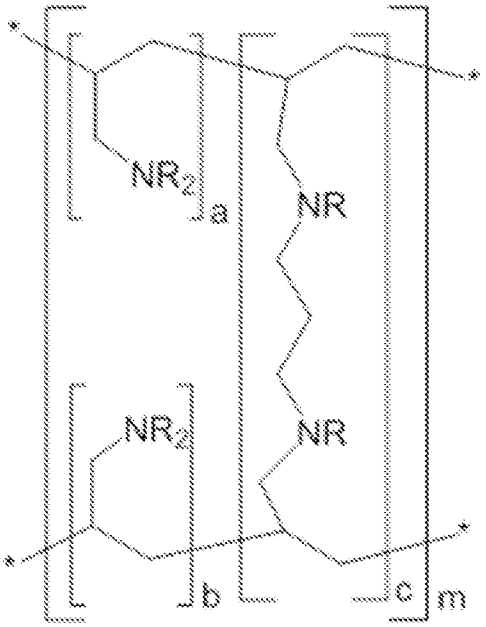
81. The method/composition according to any one of the preceding claims, wherein the effective amount of the pharmaceutical composition or TRC101 comprises about 4-6 gm/day.

82. The method/composition according to any one of the preceding claims, wherein the effective amount of the pharmaceutical composition or TRC101 comprises about 6 gm/day.

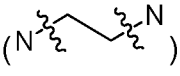
83. The method/composition according to any one of the preceding claims, wherein the effective amount of the pharmaceutical composition or TRC101 is administered to the patient in an oral dosage form once-a-day.

84. The method/composition according to any one of the preceding claims, wherein the effective amount of the pharmaceutical composition or TRC101 is adjusted to maintain the patient's serum bicarbonate level in a range between 22-29 mEq/L.

85. The method/composition according to any one of the preceding claims wherein the pharmaceutical composition comprises a polymer comprising a structure corresponding to Formula 4:



Formula 4

wherein each R is independently hydrogen or an ethylene crosslink between two nitrogen atoms of the crosslinked amine polymer () and a, b, c, and m are integers.

86. The method/composition according to any one of the preceding claims wherein the polymer comprises, 2-Propen-1-ylamine, 1,3-Bis(allylamino)propane and dichloroethane.

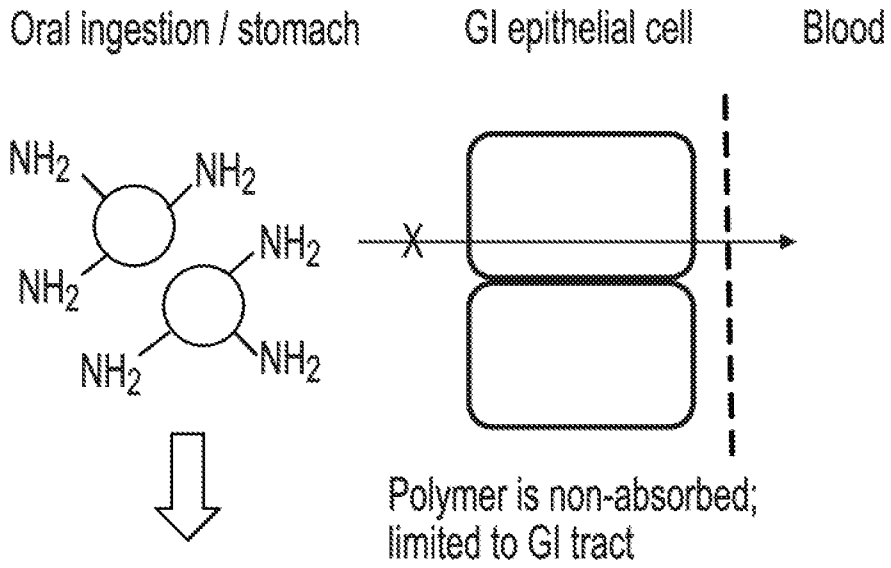

Oral ingestion / stomach
GI epithelial cell
Blood
NH2
NH2
NH2
NH2
NH2
NH2
X
Polymer is non-absorbed;
limited to GI tract

FIG. 1A

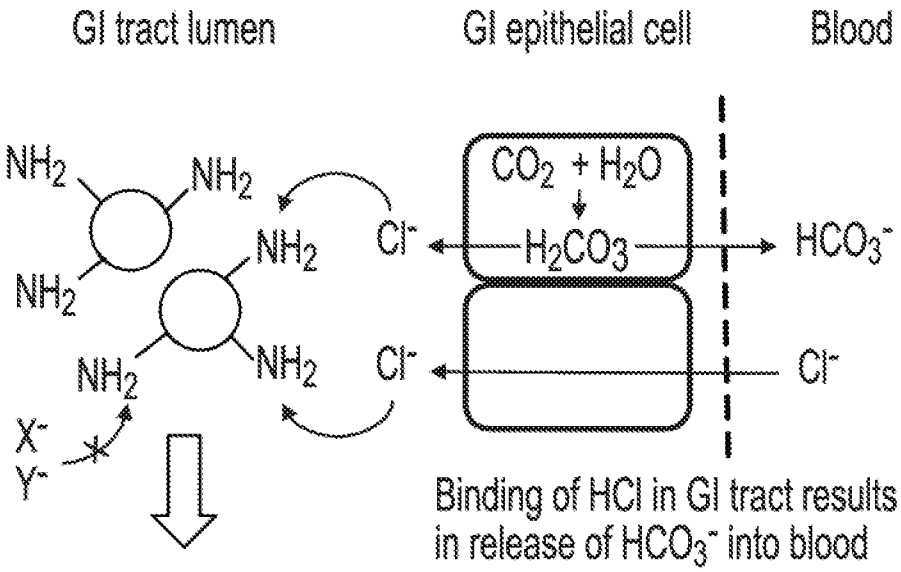

GI tract lumen
GI epithelial cell
Blood
NH2
NH2
NH2
NH2
NH2
NH2
X-
Y-
Cl-
Cl-
CO2 + H2O
H2CO3
HCO3-
Cl-
Binding of HCl in GI tract results
in release of HCO3- into blood

FIG. 1B

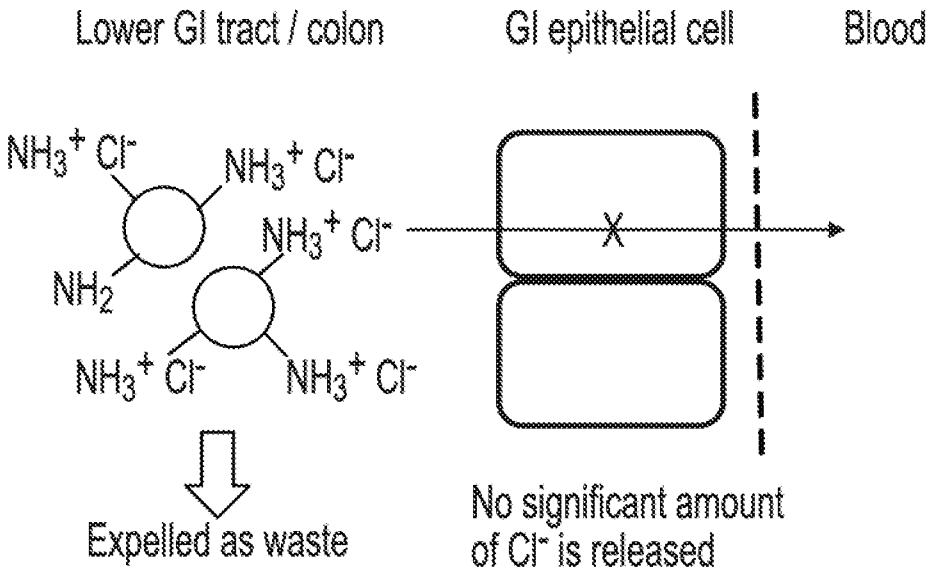

Lower GI tract / colon
GI epithelial cell
Blood
NH3+ Cl-
NH3+ Cl-
NH3+ Cl-
NH2
NH3+ Cl-
NH3+ Cl-
X
Expelled as waste
No significant amount
of Cl- is released

FIG. 1C

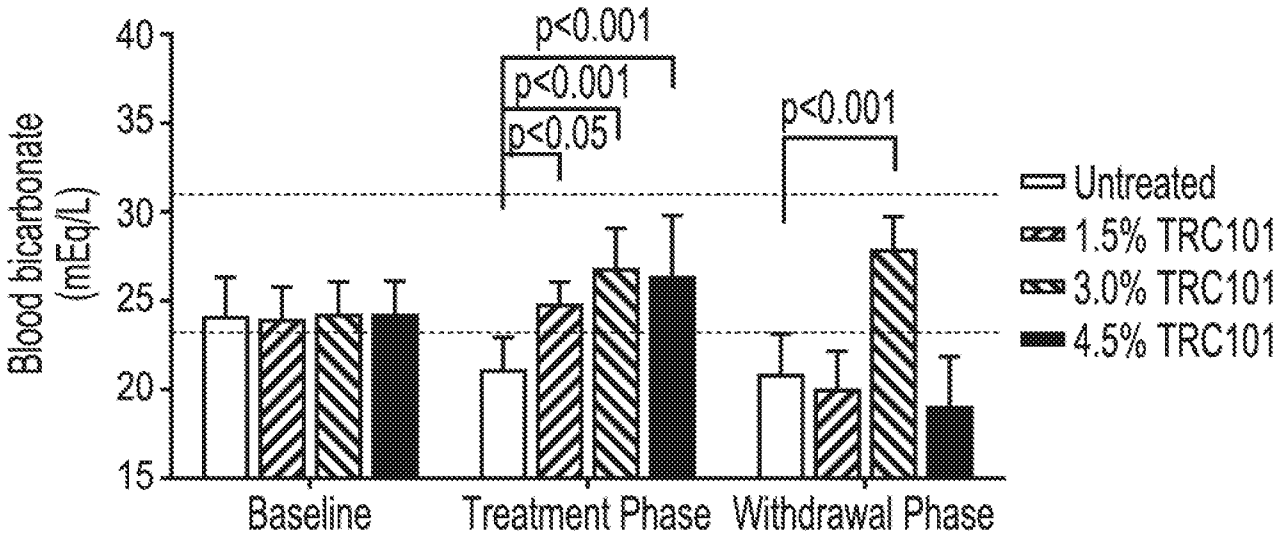


FIG. 2

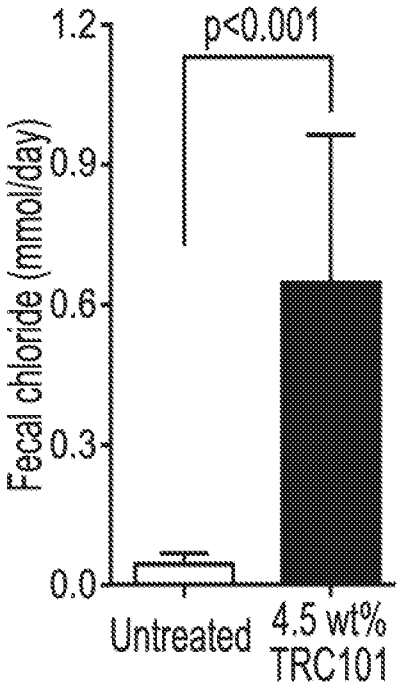


FIG. 3A

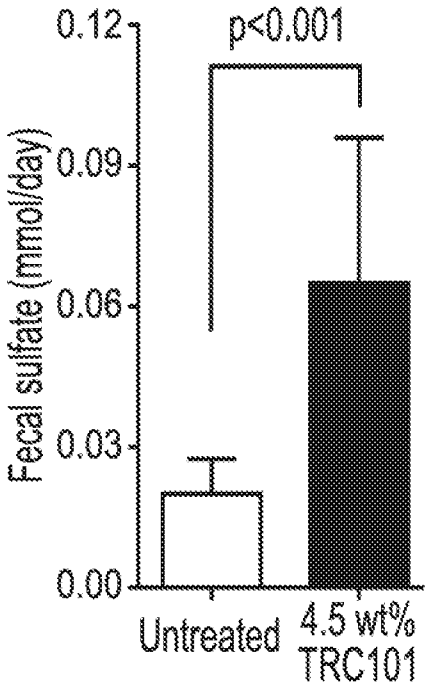


FIG. 3B

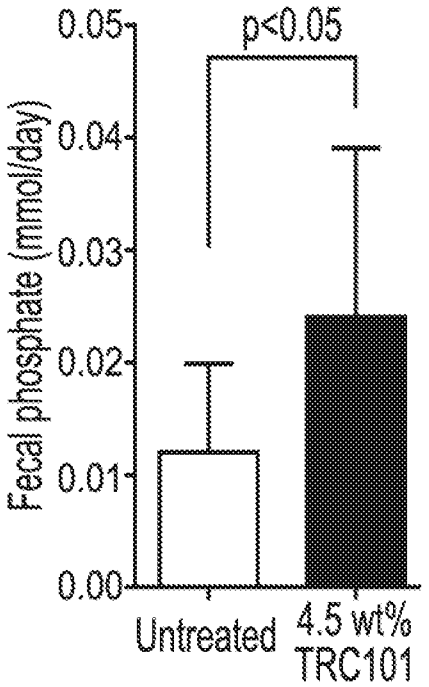


FIG. 3C

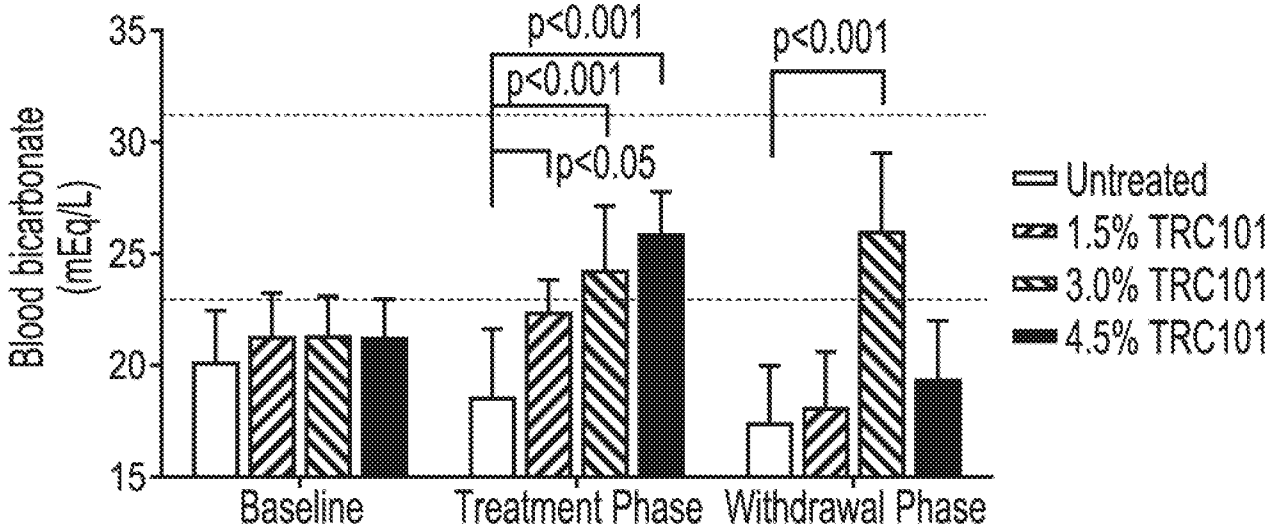


FIG. 4

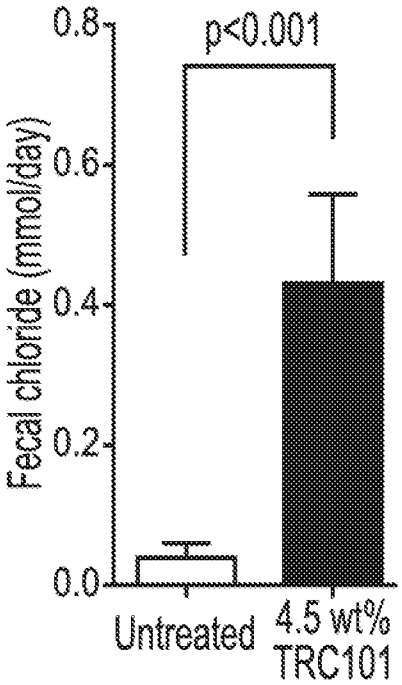


FIG. 5A

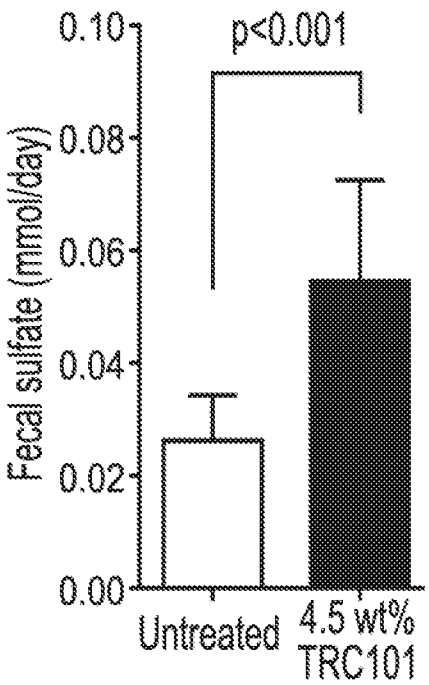


FIG. 5B

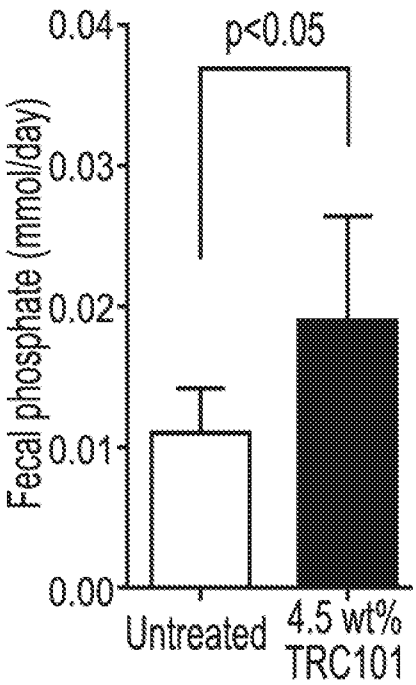


FIG. 5C

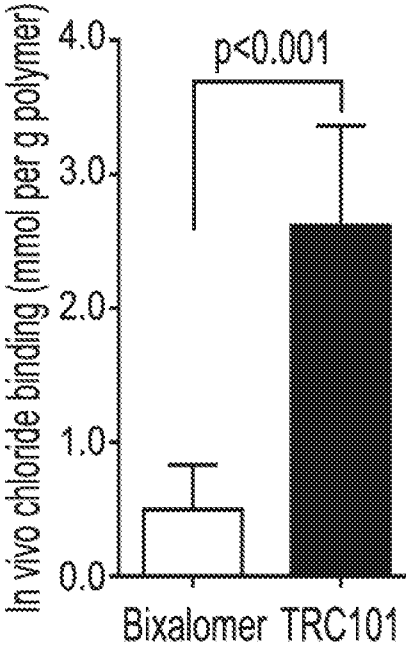


FIG. 6A

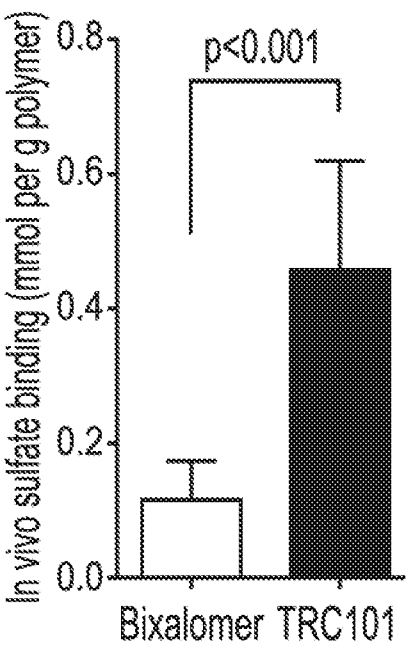


FIG. 6B

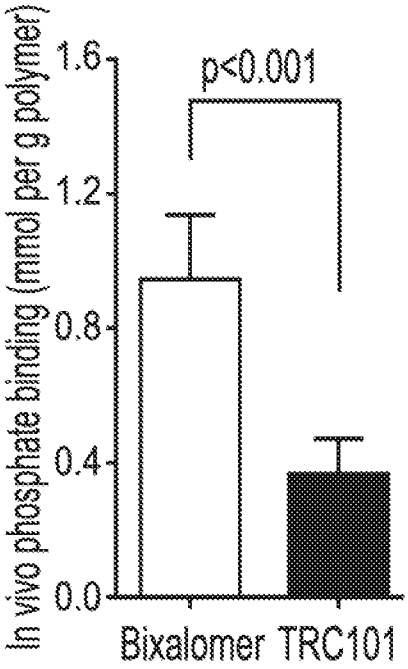


FIG. 6C

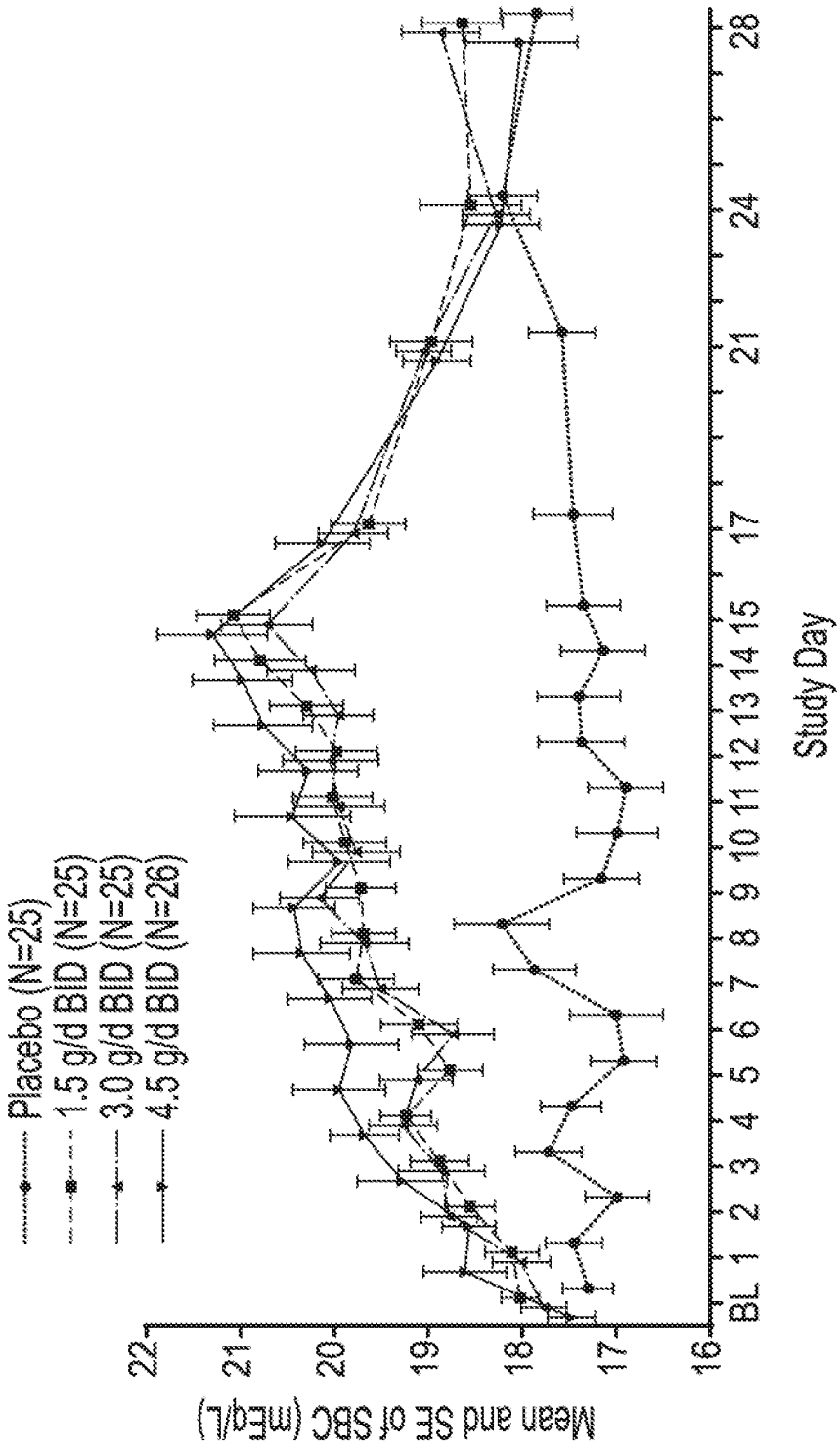

Placebo (N=25)
1.5 g/d BID (N=25)
3.0 g/d BID (N=25)
4.5 g/d BID (N=26)
Mean and SE of SBC (mEq/L)
22
21
20
19
18
17
16
BL 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 17 21 24 28
Study Day

FIG. 7

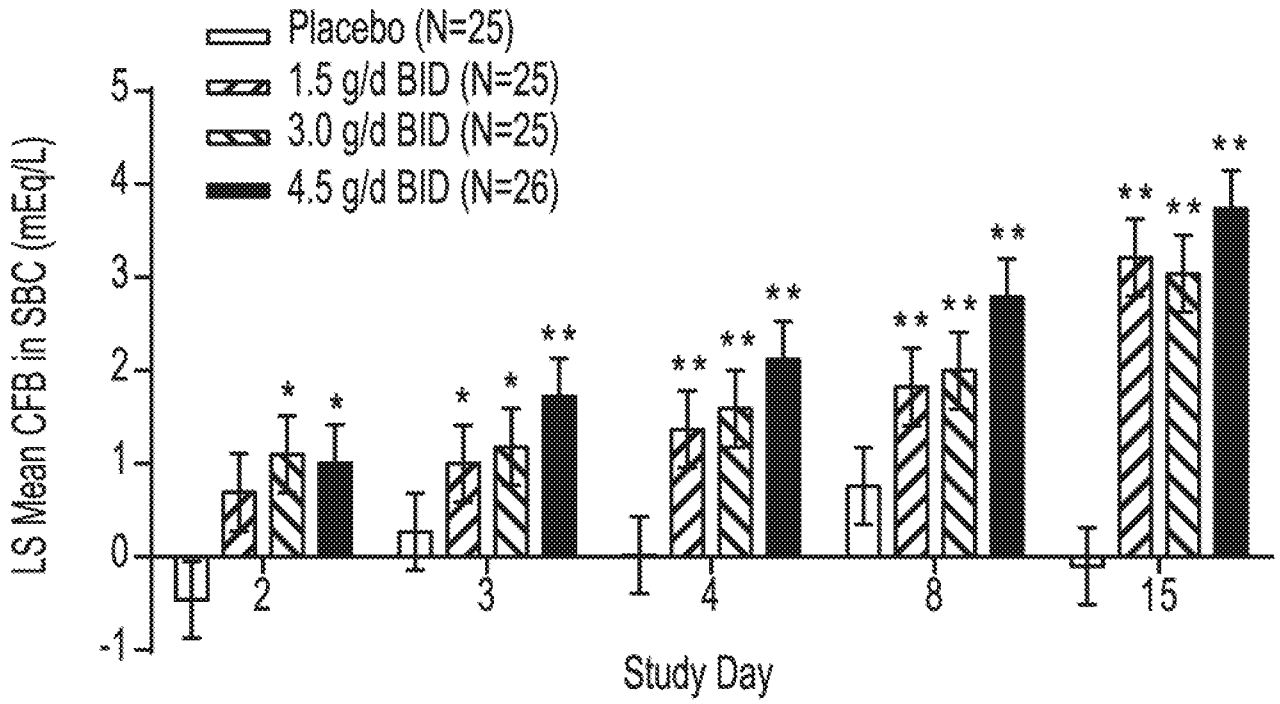

Placebo (N=25)
1.5 g/d BID (N=25)
3.0 g/d BID (N=25)
4.5 g/d BID (N=26)
LS Mean CFB in SBC (mEq/L)
5
4
3
2
1
0
-1
2
3
4
8
15
Study Day

FIG. 8

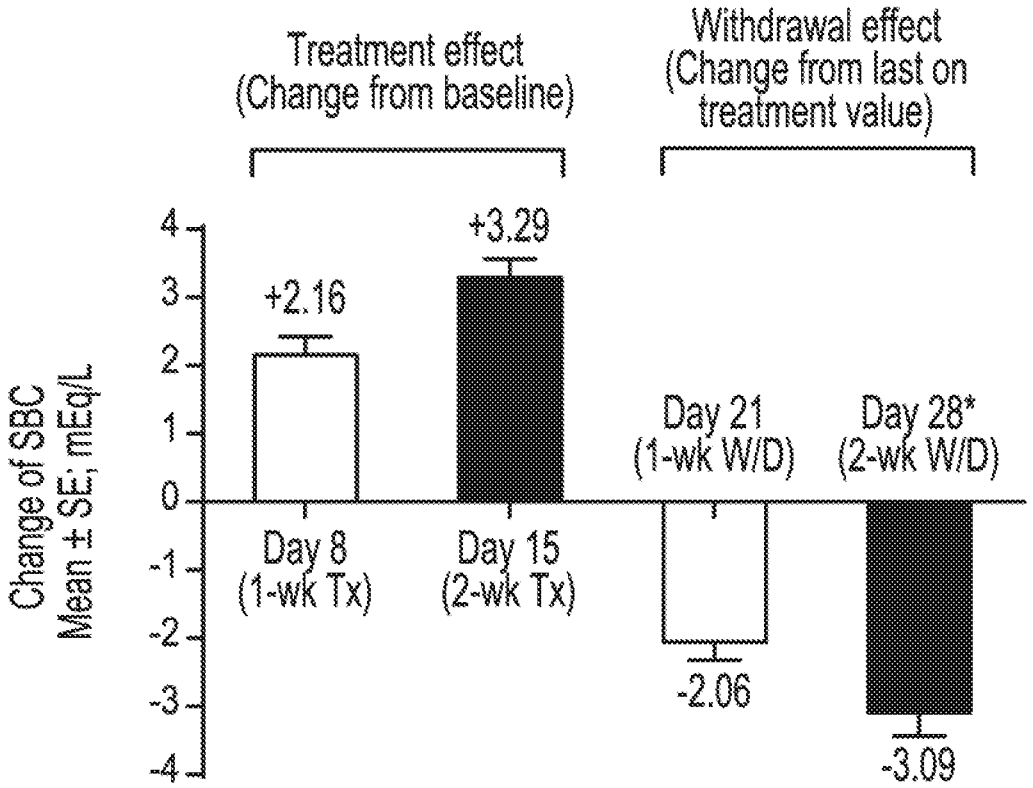

Treatment effect
(Change from baseline)
Withdrawal effect
(Change from last on
treatment value)
Change of SBC
Mean ± SE; mEq/L
4
3
2
1
0
-1
-2
-3
-4
+2.16
+3.29
Day 8
(1-wk Tx)
Day 15
(2-wk Tx)
Day 21
(1-wk W/D)
Day 28*
(2-wk W/D)
-2.06
-3.09

FIG. 9

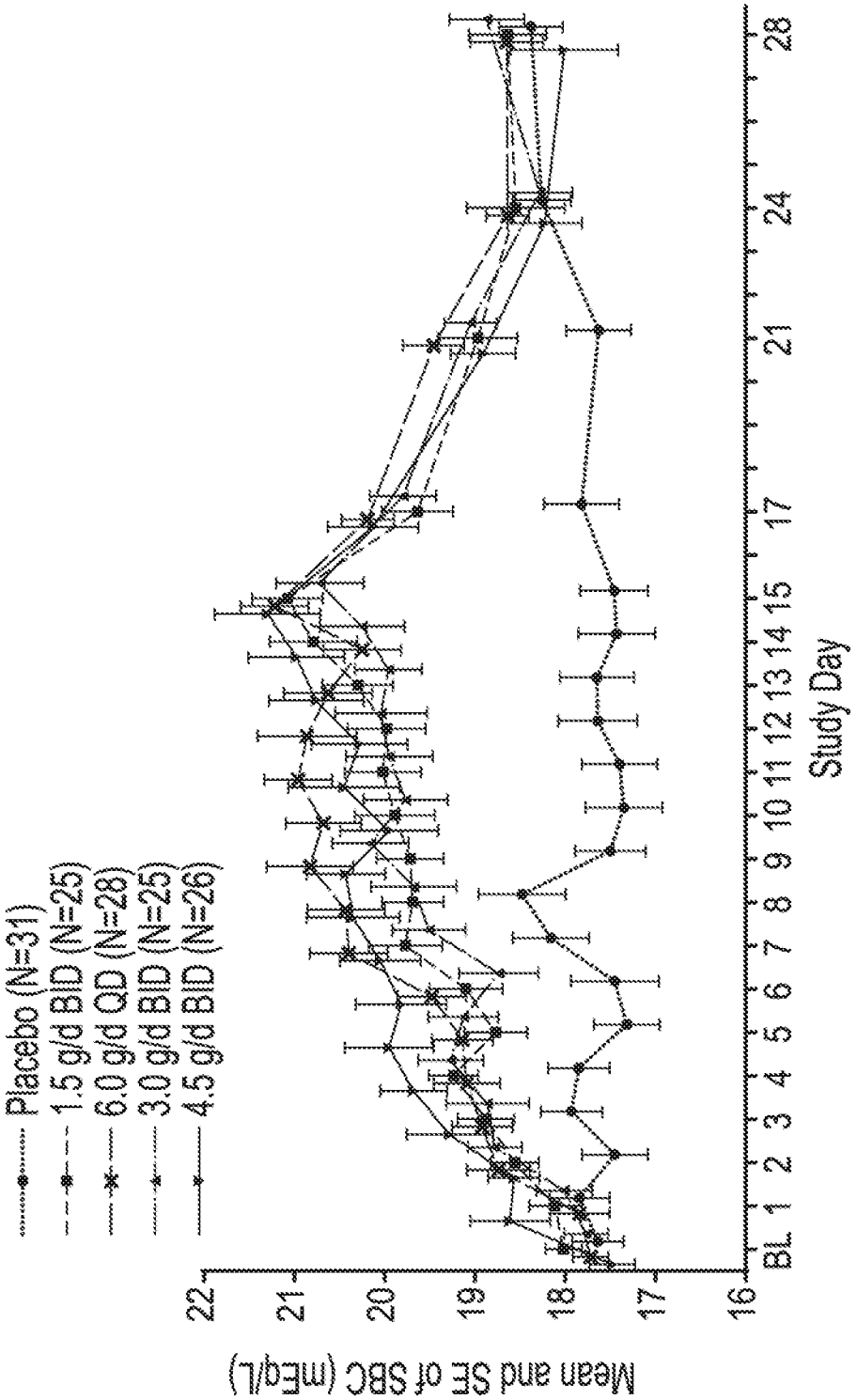

Placebo (N=31)
1.5 g/d BID (N=25)
6.0 g/d QD (N=28)
3.0 g/d BID (N=25)
4.5 g/d BID (N=26)
Mean and SE of SBC (mEq/L)
22
21
20
19
18
17
16
BL 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 17 21 24 28
Study Day

FIG. 10

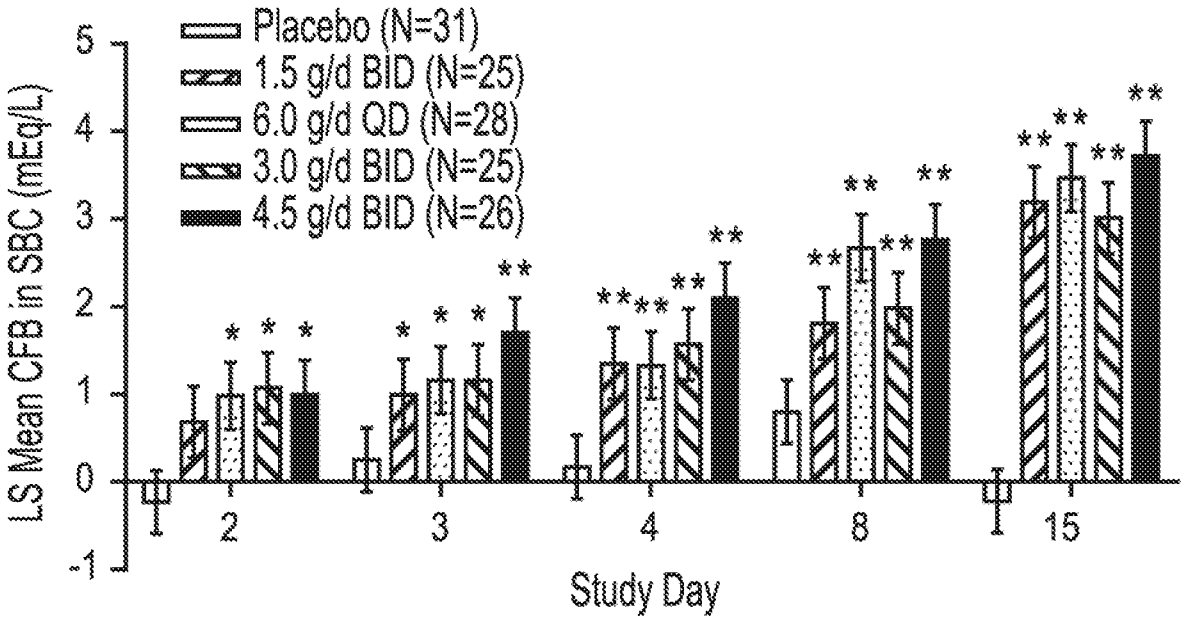

Placebo (N=31)
1.5 g/d BID (N=25)
6.0 g/d QD (N=28)
3.0 g/d BID (N=25)
4.5 g/d BID (N=26)
LS Mean CFB in SBC (mEq/L)
5
4
3
2
1
0
-1
2
3
4
8
15
Study Day

FIG. 11

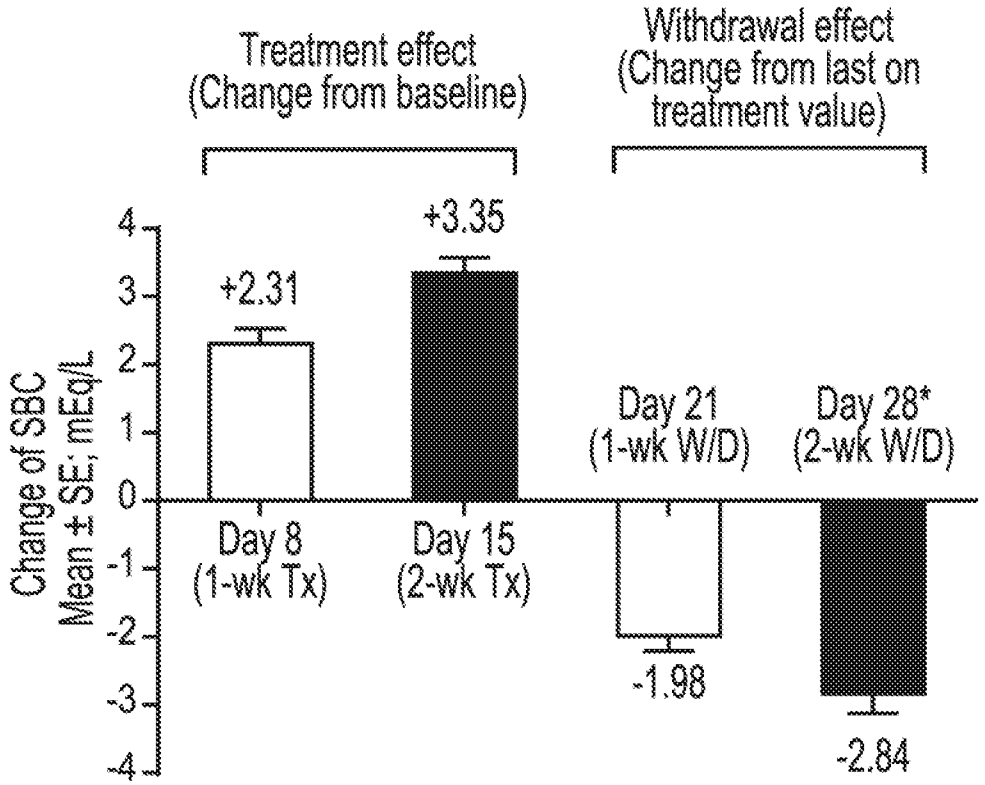

Treatment effect
(Change from baseline)
Withdrawal effect
(Change from last on
treatment value)
Change of SBC
Mean ± SE; mEq/L
4
3
2
1
0
-1
-2
-3
-4
+2.31
+3.35
-1.98
-2.84
Day 8
(1-wk Tx)
Day 15
(2-wk Tx)
Day 21
(1-wk W/D)
Day 28*
(2-wk W/D)

FIG. 12

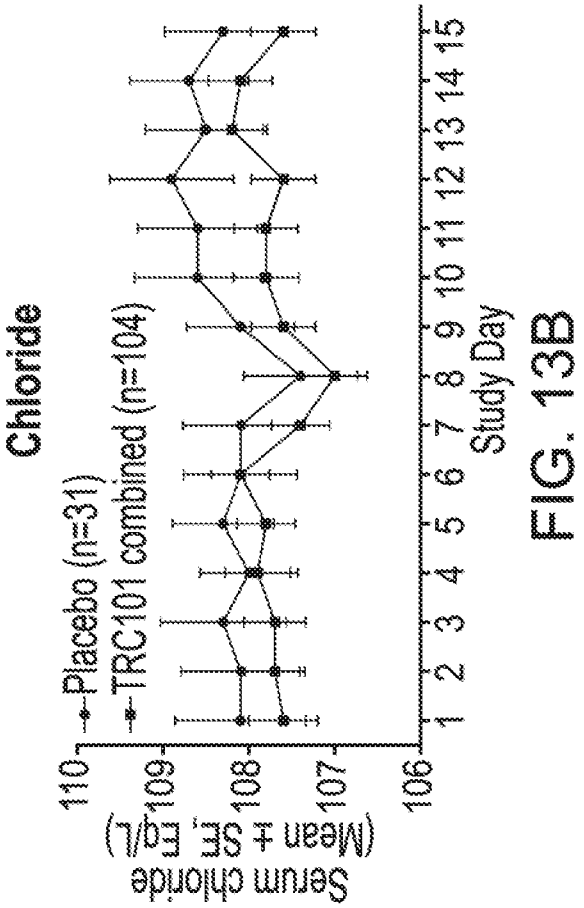


FIG. 13B

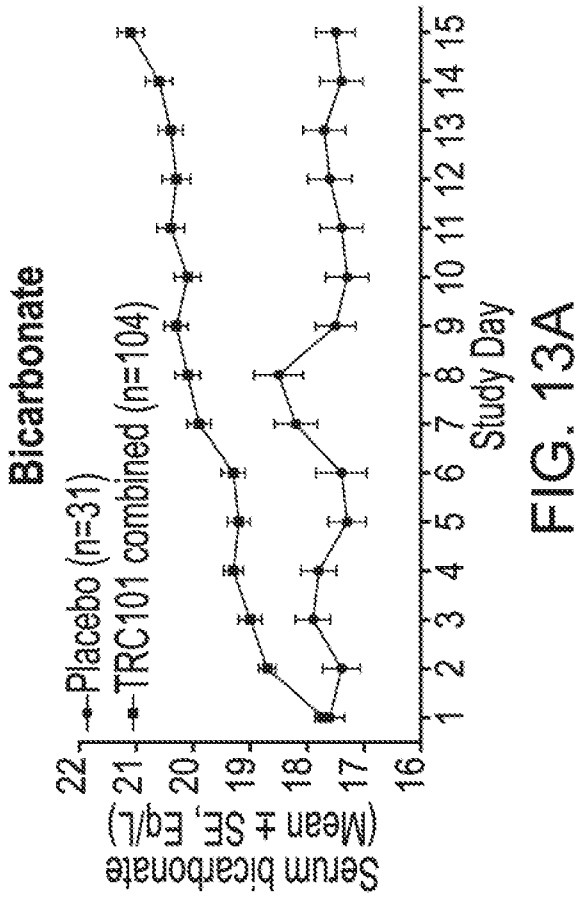


FIG. 13A

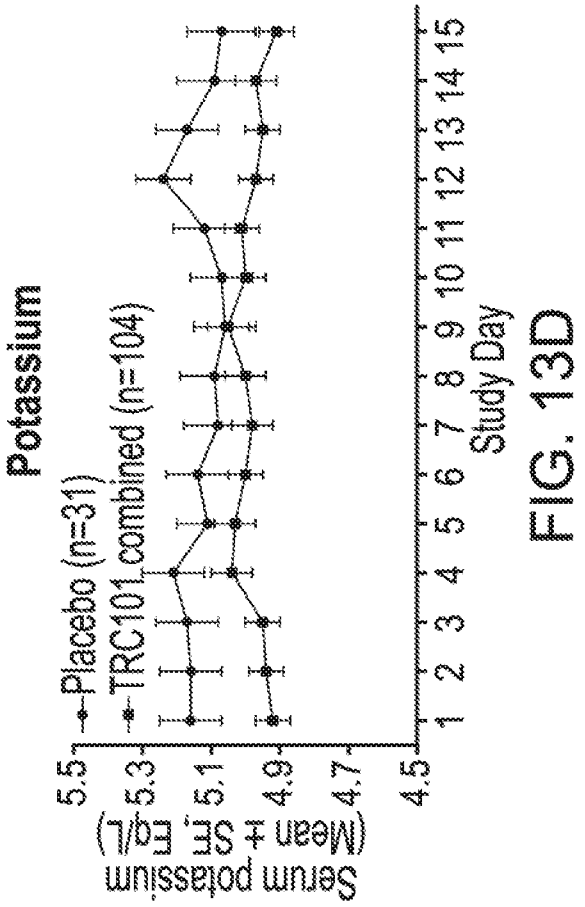


FIG. 13D

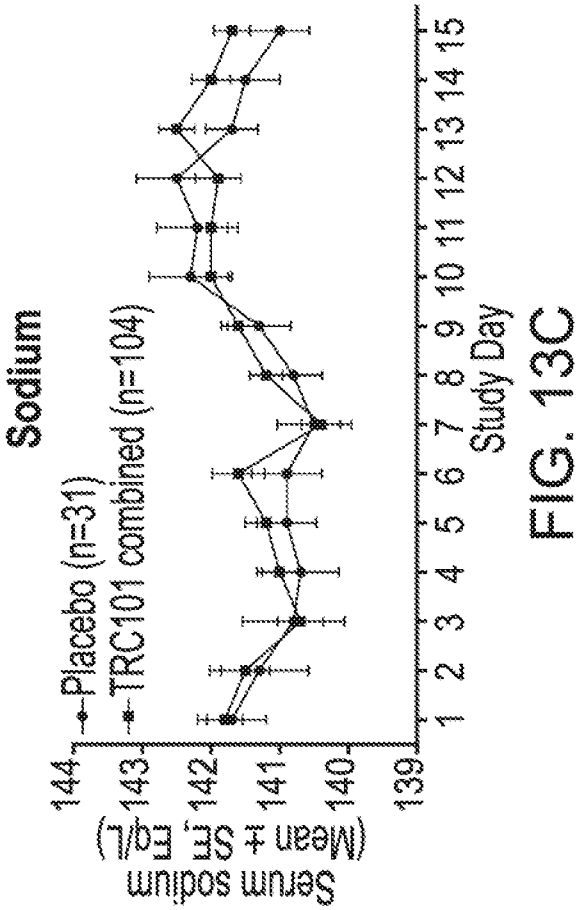


FIG. 13C

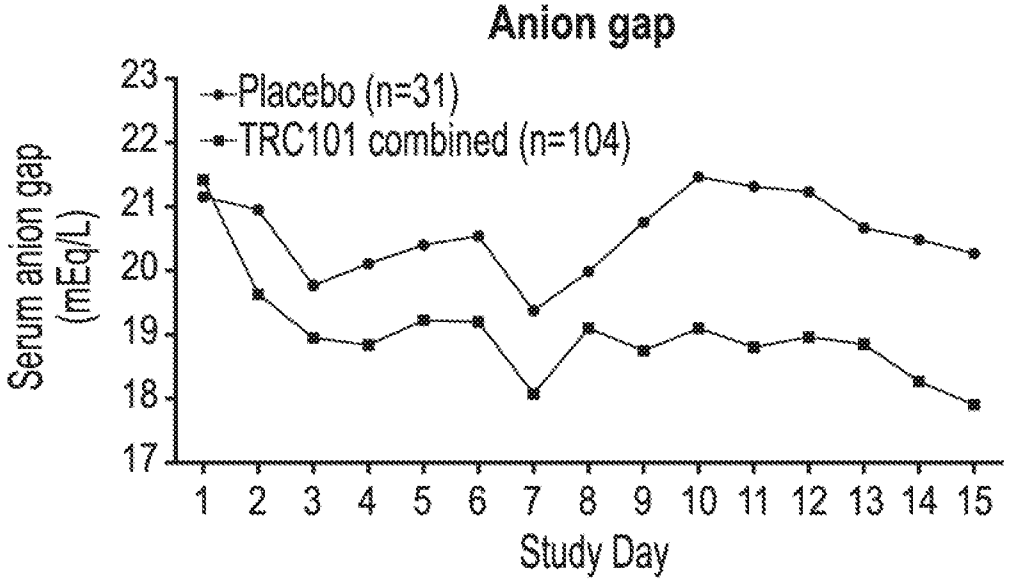
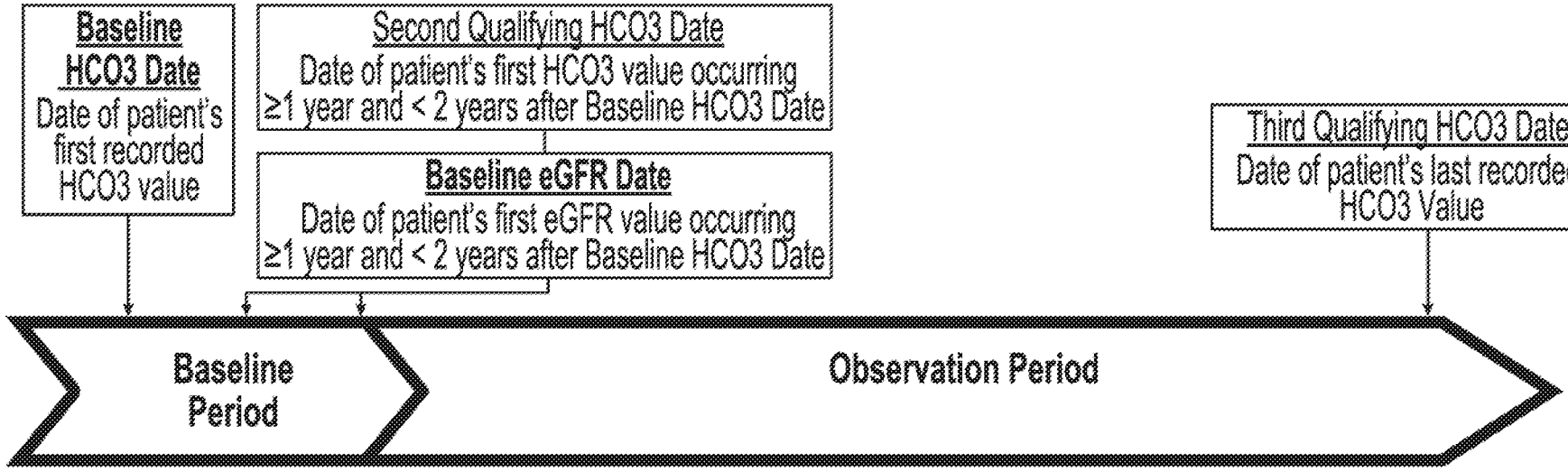

Anion gap
Placebo (n=31)
TRC101 combined (n=104)
Serum anion gap (mEq/L)
23
22
21
20
19
18
17
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Study Day

FIG. 14

Optum Dataset Analysis Diagram and Timeline



Baseline HCO3 Value
- Average of all HCO3 values occuring 30 days after Baseline HCO3 Date
- Must be 12 to 29 mEq/L
- Patients assigned to 1 of 3 strata:
  (1) 12 to 20 mEq/L
  (2) >20 to <22 mEq/L
  (3) 22 to 29 mEq/L

First Qualifying eGFR Date
Calculated from average of all serum creatinine values occurring ±30 days from Baseline HCO3 Date
Must be 15 to <45 mL/min/1.73m^2

Second Qualifying HCO3 Value
- Average of all HCO3 values occurring during the 90 days prior to Second Qualifying HCO3 Date
- Must be in same strata as Baseline HCO3 Value, while allowing for measurement variability

(1) <22 mEq/L
(2) 18 to <24 mEq/L
(3) 20 to 29 mEq/L

Baseline eGFR Value
- Calculated from average of all serum creatinine values occurring during the 90 days prior to Baseline eGFR Date
- Must be 10 to <50mL/min/1.73m^2

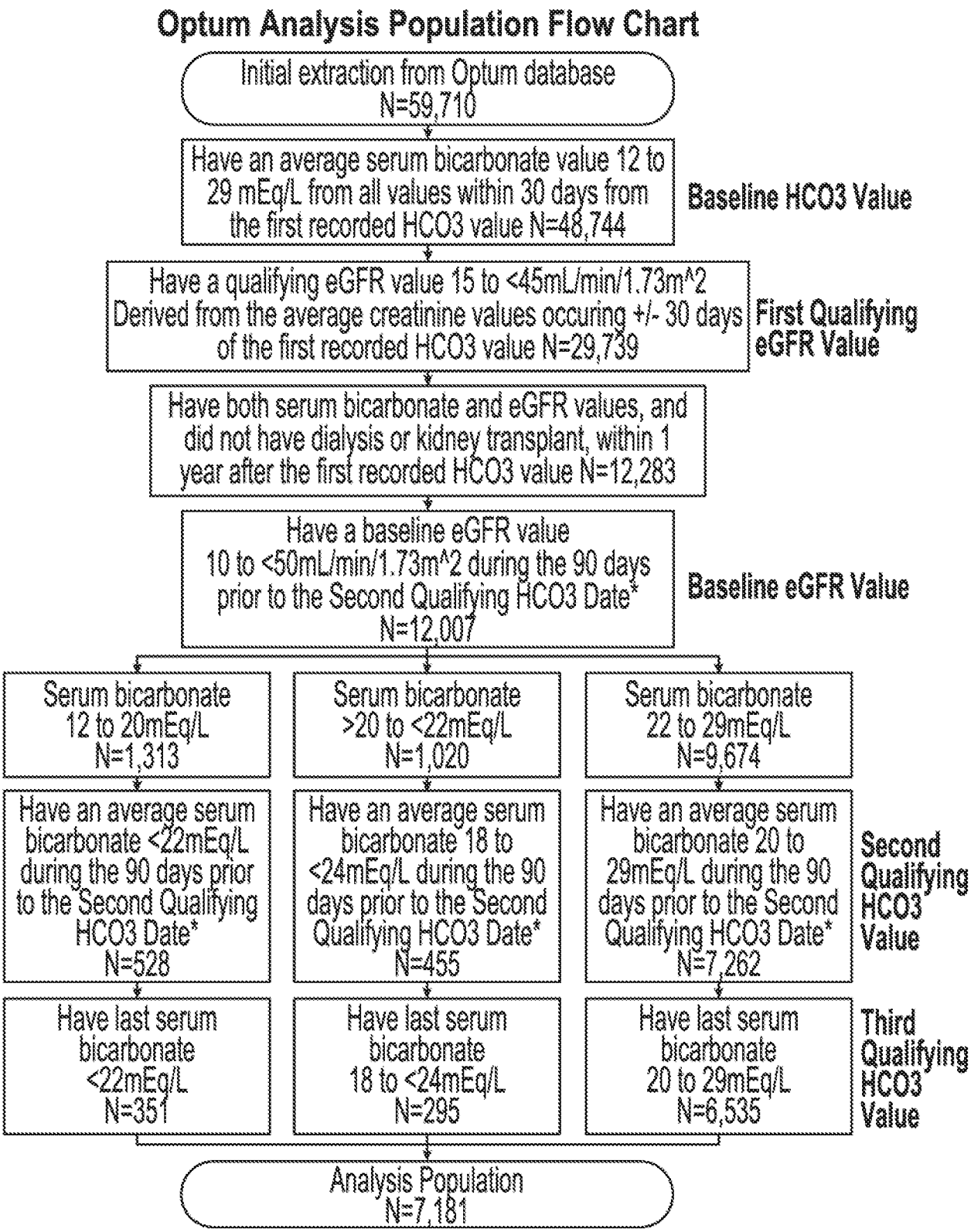
Third Qualifying HCO3 Value
- Last HCO3 value in the patient's record
- Must be in same strata as Second Qualifying HCO3 Value

(1) <22 mEq/L
(2) 18 to <24 mEq/L
(3) 20 to 29 mEq/L

Two Confirmatory eGFR Values
- To establish ≥ 40% eGFR reduction from Baseline eGFR Value
- Can occur at any time in the observation period

eGFR = estimated glomerular filtration rate; HCO3 = serum bicarbonate

FIG. 15



*Second Qualifying HCO3 Date is the date of patient's first HCO3 value occuring ≥1 year and <2 years after the first recorded HCO3 value.

Note: All HCO3 and creatinine values occuring on or after dialysis or kidney transplant were excluded.

eGFR = estimated glomerular filtration rate; HCO3 = serum bicarbonate

FIG. 16

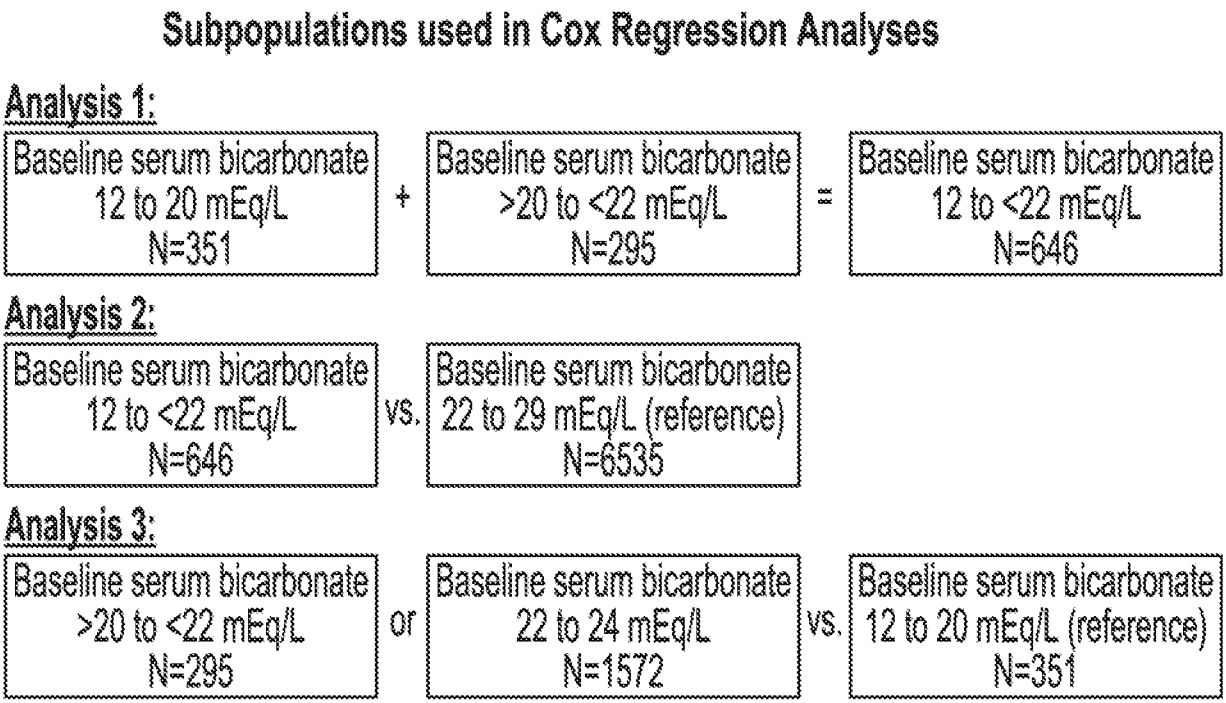
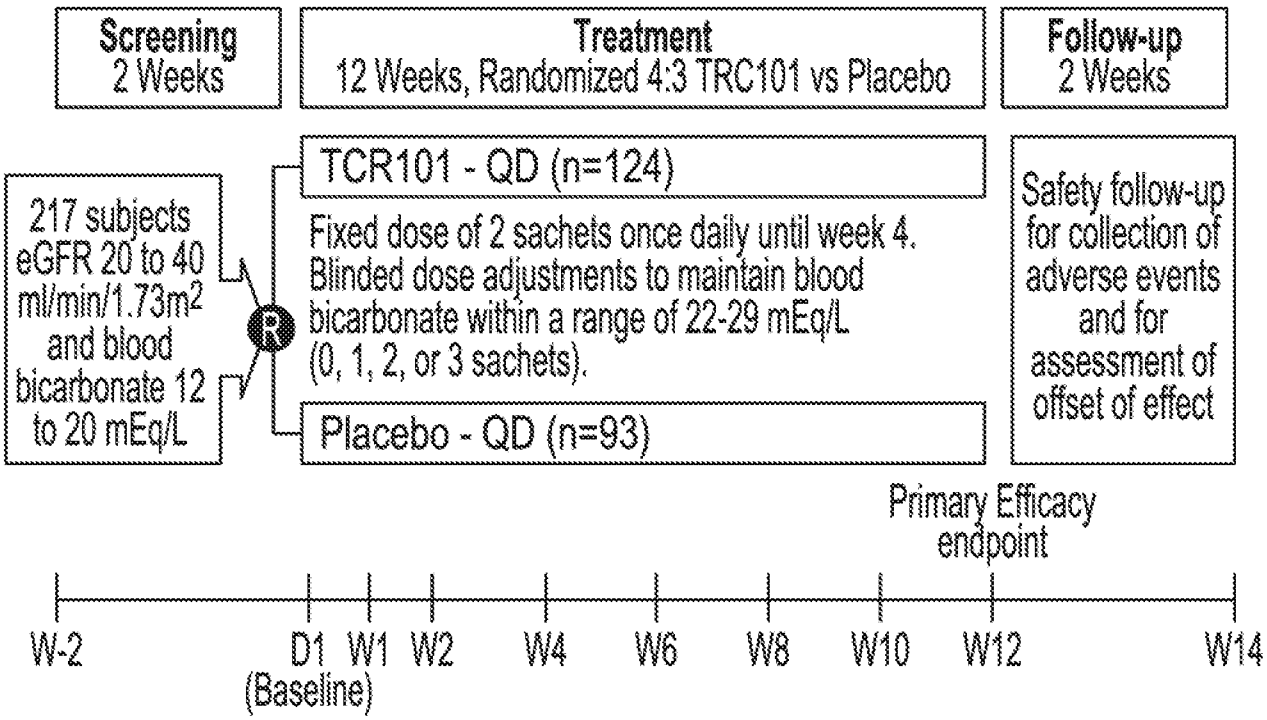

Subpopulations used in Cox Regression Analyses
Analysis 1:
Baseline serum bicarbonate 12 to 20 mEq/L N=351
+
Baseline serum bicarbonate >20 to <22 mEq/L N=295
=
Baseline serum bicarbonate 12 to <22 mEq/L N=646
Analysis 2:
Baseline serum bicarbonate 12 to <22 mEq/L N=646
vs.
Baseline serum bicarbonate 22 to 29 mEq/L (reference) N=6535
Analysis 3:
Baseline serum bicarbonate >20 to <22 mEq/L N=295
or
Baseline serum bicarbonate 22 to 24 mEq/L N=1572
vs.
Baseline serum bicarbonate 12 to 20 mEq/L (reference) N=351

FIG. 17



GFR = Estimated glomerular filtration rate, QD = Once daily

FIG. 18

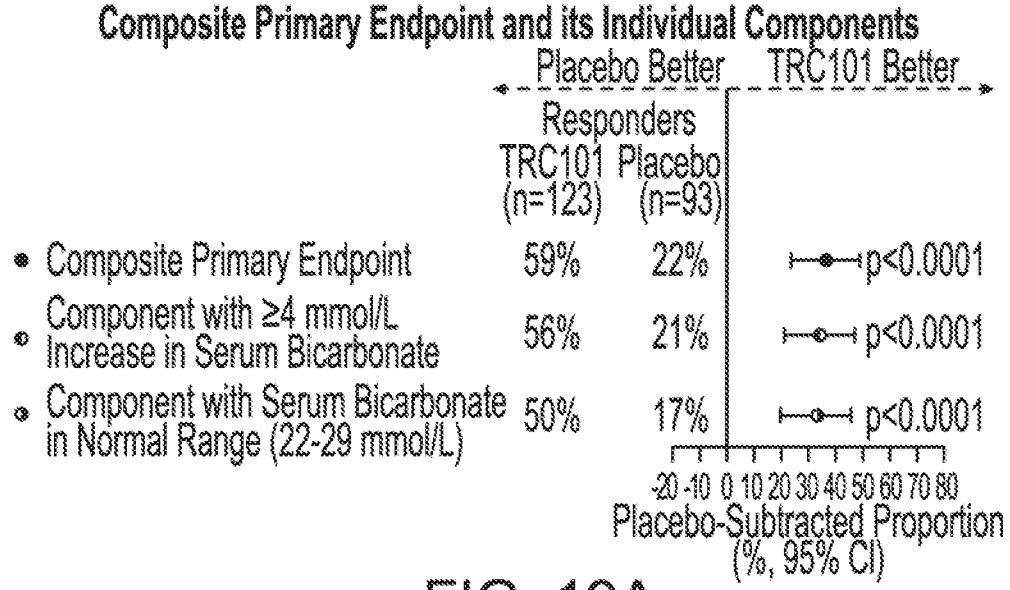


FIG. 19A

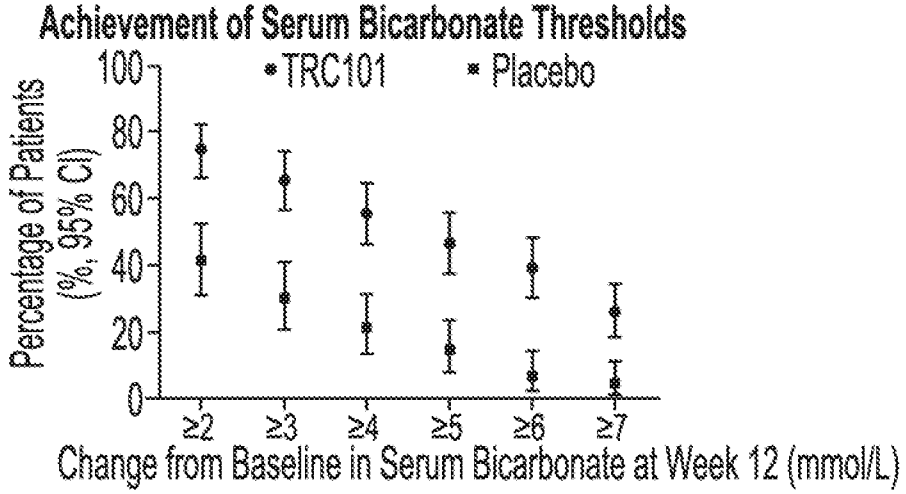


FIG. 19B

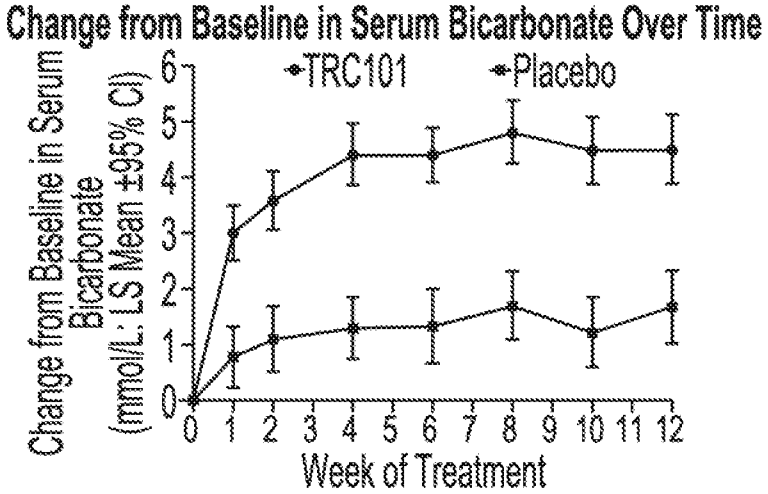


FIG. 19C

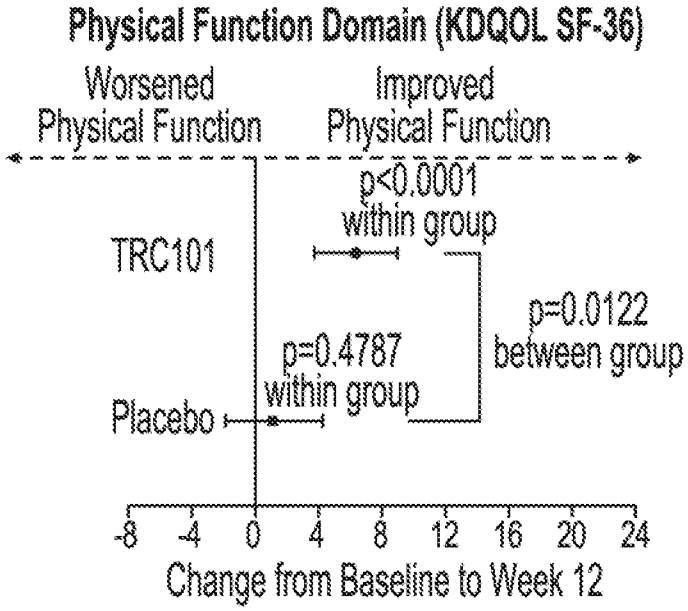


FIG. 20A

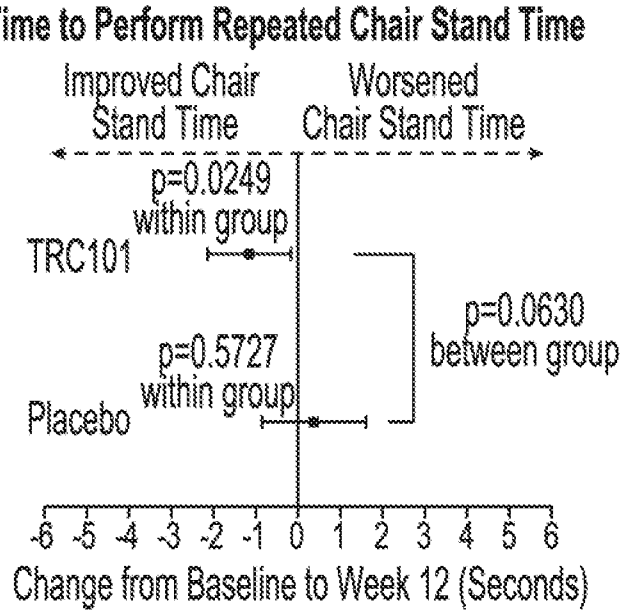


FIG. 20B

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? [Mark an X in a box on each line.]

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifiting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several blocks	☐ 1	☐ 2	☐ 3
i Walking one block	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

FIG. 21

Chair Stand Protocols

Required Equipment

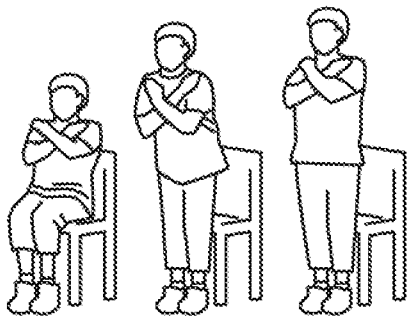
- A chair without cushions that has a straight back without arm rests. The following chair dimensions (or close to these) are recommended: seat 44.5 cm (17 1/2 inches) high and 38 cm (15 inches) deep.
- A Stopwatch.

Instructions

Instructions to the subject are shown in ***bold italic*** and should be given exactly as they are written in this script. The subject must be able to stand unassisted without the use of a cane or walker.

> ***Now let's begin the repeated chair stand evaluation. I will first describe and show the movement to you. Then I'd like you to try to do it. If you cannot do sit-stand movement, or if you feel it would be unsafe to try to do it, please tell me. Let me emphasize that I do not want you to try to do this exercise if you feel it might be unsafe. Do you have any questions before we begin?***

Single Chair Stand (Practice Test)



1. ***Do you think it would be safe for you to try to stand up from a chair without using your arms?***
2. ***This test measures the strength in your legs***
3. (Demonstrate and explain the procedure.) ***First, fold your arms across your chest and sit so that your feet are on the floor; then stand up keeping your arms folded across your chest***
4. ***Please stand up keeping your arms folded across your chest.*** (Record result).
5. If subject cannot rise without using arms, say: ***"Okay, try to stand up using your arms."*** This is the end of their test. Record result and go to the scoring page.

Repeated Chair Stand Test

1. ***Do you think it would be safe for you to try to stand up from a chair five times without using your arms?***
2. (Demonstrate and explain the procedure.) ***Please stand up straight as QUICKLY as you can five times, without stopping in between. After standing up each time, sit down and then stand up again. Keep your arms folded across your chest. I will be timing you with a stopwatch.***
3. When the subject is properly seated, say ***"Ready? Stand"***, and begin timing using a stopwatch.
4. Count out loud as the subject arises each time, up to five times.
5. Stop if subject becomes tired or short of breath during repeated chair stands.
6. Stop the stopwatch when subject has straightened up completely for the fifth time.
7. Also stop:
   - If subject uses his/her arms
   - After 1 minute, if subject has not completed five rises
   - At your discretion, if concerned for subject's safety
8. If the subject stops and appears to be fatigued before completing the five stands, confirm this by asking: ***"Can you continue?"***
9. If subject says "Yes", continue timing. If subject says "No", stop and reset the stopwatch.

FIG. 22A

Single Chair Stand **SCORING**

		YES	NO
A.	Safe to stand without help	☐	☐
B.	Results:		
	Subject stood without using arms	☐	→Go to Repeated Chair Stand Test
	Subject used arms to stand	☐	→End test: score as 0 points
	Test not completed	☐	→End test: score as 0 points
C.	If subject did not attempt test or failed, circle why:		
	Tried but unable	1	
	Subject could not stand unassisted	2	
	Not attempted, you felt unsafe	3	
	Not attempted, subject felt unsafe	4	
	Subject unable to understand instructions	5	
	Other (Specify)	6	
	Subject refused	7	

Repeated Chair Stand Test

		YES	NO
A.	Safe to stand five times	☐	☐
B.	If five stands done successfully, record time in seconds.		
	Time to complete five stands _ _._ _ seconds		
C.	If subject did not attempt test or failed, circle why:		
	Tried but unable	1	
	Subject could not stand unassisted	2	
	Not attempted, you (person administering test) felt unsafe	3	
	Not attempted, subject felt unsafe	4	
	Subject unable to understand instructions	5	
	Other (Specify)_____	6	
	Subject refused	7	

Scoring the Repeated Chair Stand Test

Subject unable to complete 5 chair stands or completes stands in >60 sec:	☐ 0 points
If chair stand time is 16.70 sec or more:	☐ 1 points
If chair stand time is 13.70 to 16.69 sec:	☐ 2 points
If chair stand time is 11.20 to 13.69 sec:	☐ 3 points
If chair stand time is 11.19 sec or less:	☐ 4 points

FIG. 22B

	Placebo (N=93)	TRC101 (N=123)
Baseline		
n	93	123
Mean (SD)	54.14 (27.073)	53.33 (23.597)
Median	55.00	50.00
Min, Max	0.0, 100.0	10.0, 100.0
Week 12/ET		
n	90	121
Mean (SD)	55.56 (25.367)	59.71 (22.139)
Median	55.00	60.00
Min, Max	0.0, 100.0	0.0, 100.0
Week 12/ET Change from Baseline[a]		
n	90	121
Mean (SD)	0.89 (15.169)	6.45 (16.259)
Median	0.00	5.00
Min, Max	-40.0, 35.0	-50.0, 60.0
Within Group CFB		
LS Mean (SE)	1.10 (1.549)	6.29 (1.334)
95% CI of LS Mean	-1.95, 4.15	3.66, 8.92
p-value	0.4787	<.0001
Between Group CFB Difference (TRC101 Treated - Placebo)		
LS Mean (SE)	NA	5.19 (2.053)
95% CI of LS Mean	NA	1.14, 9.24
p-value	NA	0.0122

CFB = change from baseline; CI = confidence interval; eGFR = estimated glomerular filtration rate; ET = Early termination; LS = least squares; Max = maximum; Min = minimum; NA = not applicable; SD = standard deviation; SE = standard error of LS mean.

[a]LS mean, SE, 95% CI of LSmean, and p-values are based on the analysis of covariance model with the CFB in total score as the dependent variable; treatment (Placebo or TRC101) as a fixed effect; as well as baseline total score, baseline eGFR, and baseline serum bicarbonate as continuous covariates.

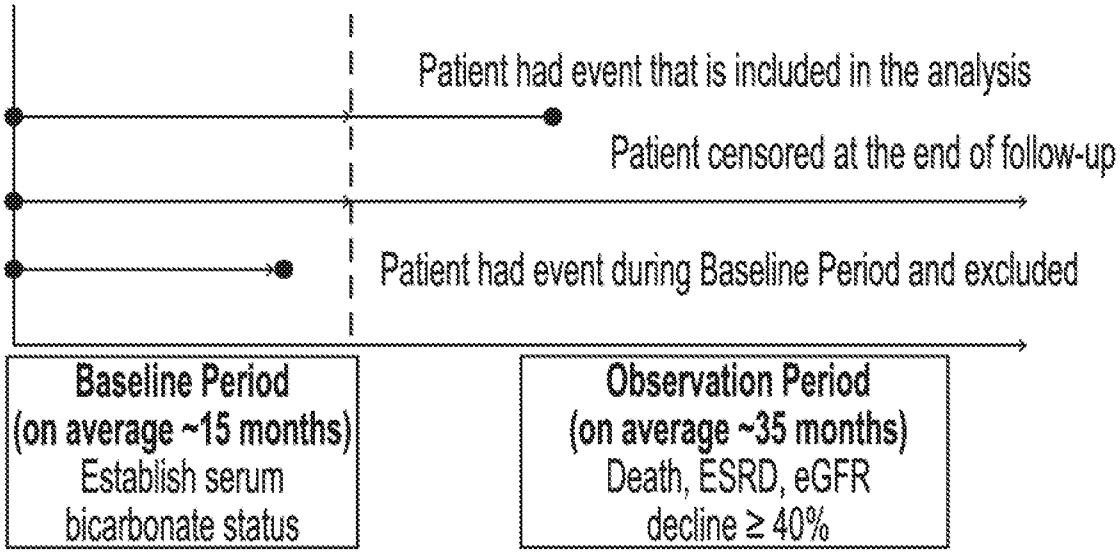
FIG. 23

	Placebo (N=82)	TRC101 (N=115)
Baseline		
n	79	111
Mean (SD)	15.47 (8.850)	17.39 (11.616)
Median	13.08	14.32
Min, Max	6.7, 50.0	7.5, 100.0
Week 12/ET		
n	79	113
Mean (SD)	16.03 (9.175)	16.54 (8.928)
Median	13.80	13.68
Min, Max	7.7, 53.8	7.8, 56.1
Week 12/ET Change from Baseline[a]		
n	76	109
Mean (SD)	0.64 (2.836)	-1.37 (8.559)
Median	0.03	-0.40
Min, Max	-6.9, 17.9	-85.0, 10.9
Within Group CFB		
LS Mean (SE)	0.35 (0.619)	-1.17 (0.515)
95% CI of LS Mean	-0.87, 1.57	-2.18, -0.15
p-value	0.5727	0.0249
Between Group CFB Difference (TRC101 Treated - Placebo)		
LS Mean (SE)	NA	-1.52 (0.810)
95% CI of LS Mean	NA	-3.11, 0.08
p-value	NA	0.0630

CFB = change from baseline; CI = confidence interval; eGFR = estimated glomerular filtration rate; ET = Early termination; LS = least squares; Max = maximum; Min = minimum; NA = not applicable; SD = standard deviation; SE = standard error of LS mean.

[a]LS mean, SE, 95% CI of LSmean, and p-values are based on the analysis of covariance model with the CFB in time of completing 5 chair stands as the dependent variable; treatment (Placebo or TRC101) as fixed effect; as well as baseline value (time to complete 5 stands), baseline eGFR, and baseline serum bicarbonate as continuous covariates.

FIG. 24



eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease

FIG. 25

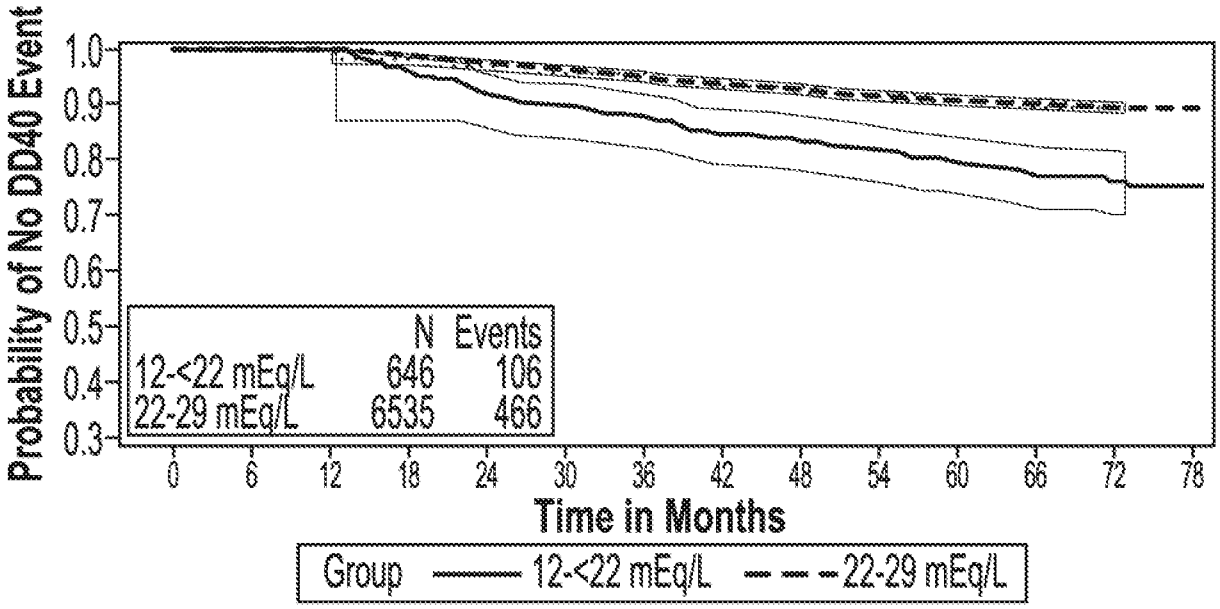

Probability of No DD40 Event
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
N Events
12-<22 mEq/L 646 106
22-29 mEq/L 6535 466
0 6 12 18 24 30 36 42 48 54 60 66 72 78
Time in Months
Group 12-<22 mEq/L 22-29 mEq/L

FIG. 26

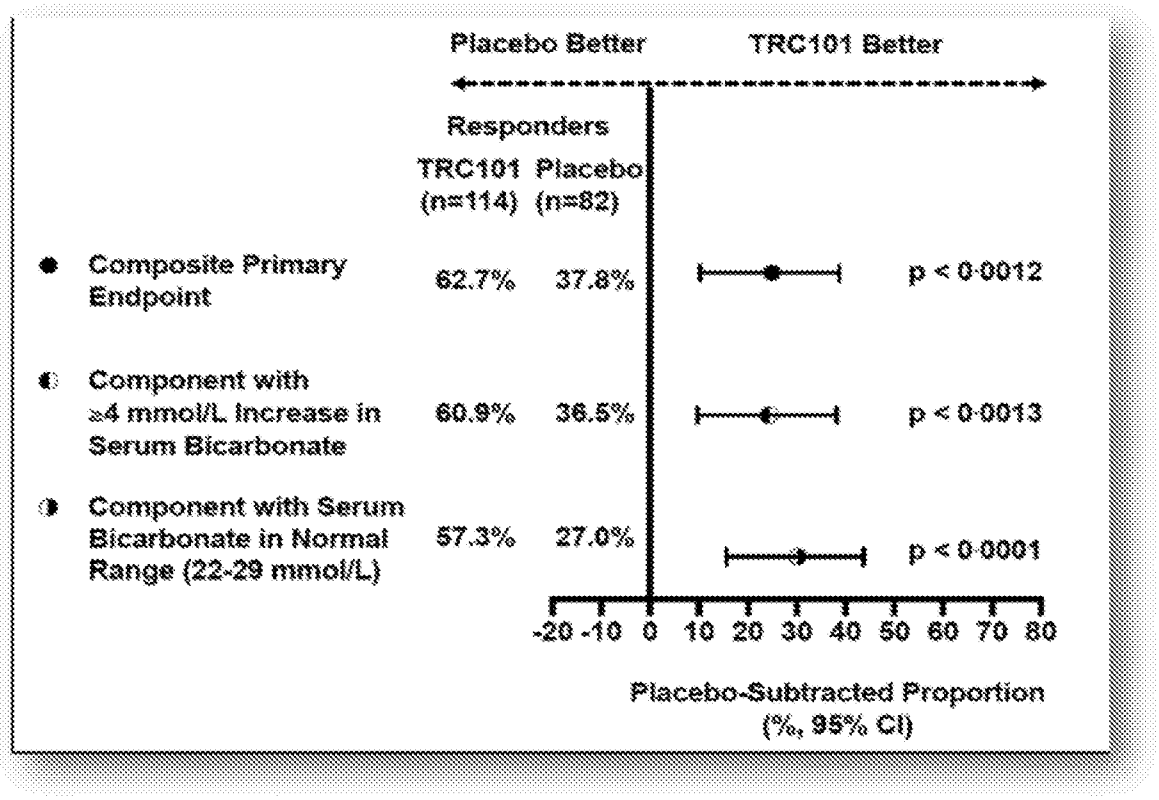
TRCA-301E: Study Results – Secondary (Efficacy) Endpoints

Endpoint (Evaluated at End of Treatment)	TRC101	Placebo	Between Group Difference (TRC101-Placebo)	p-value (TRC101 vs placebo)
Serum Bicarbonate Responders at Week 52	62.7%	37.8%	24.9%	p = 0.0015
Serum Bicarbonate Change from Baseline at Week 52, mEq/L LS Mean	4.70	2.71	1.99	p = 0.0002
KDQOL Physical Functioning Survey[1] Change from Baseline, points	+11.42	-0.71	12.13	p < 0.0001
Chair Stand Test[2] Change from Baseline, sec	-4.28	-1.42	-2.86	p < 0.0001

[1]Higher values indicate greater improvement in physical function. Week 40 value was used if Week 52 was missing.

[2] Lower values indicate less time needed (i.e., greater improvement) in physical function. Week 40 value was used if Week 52 was missing.

FIG. 27



Serum Bicarbonate Responders - Durability of Effect

FIG. 28

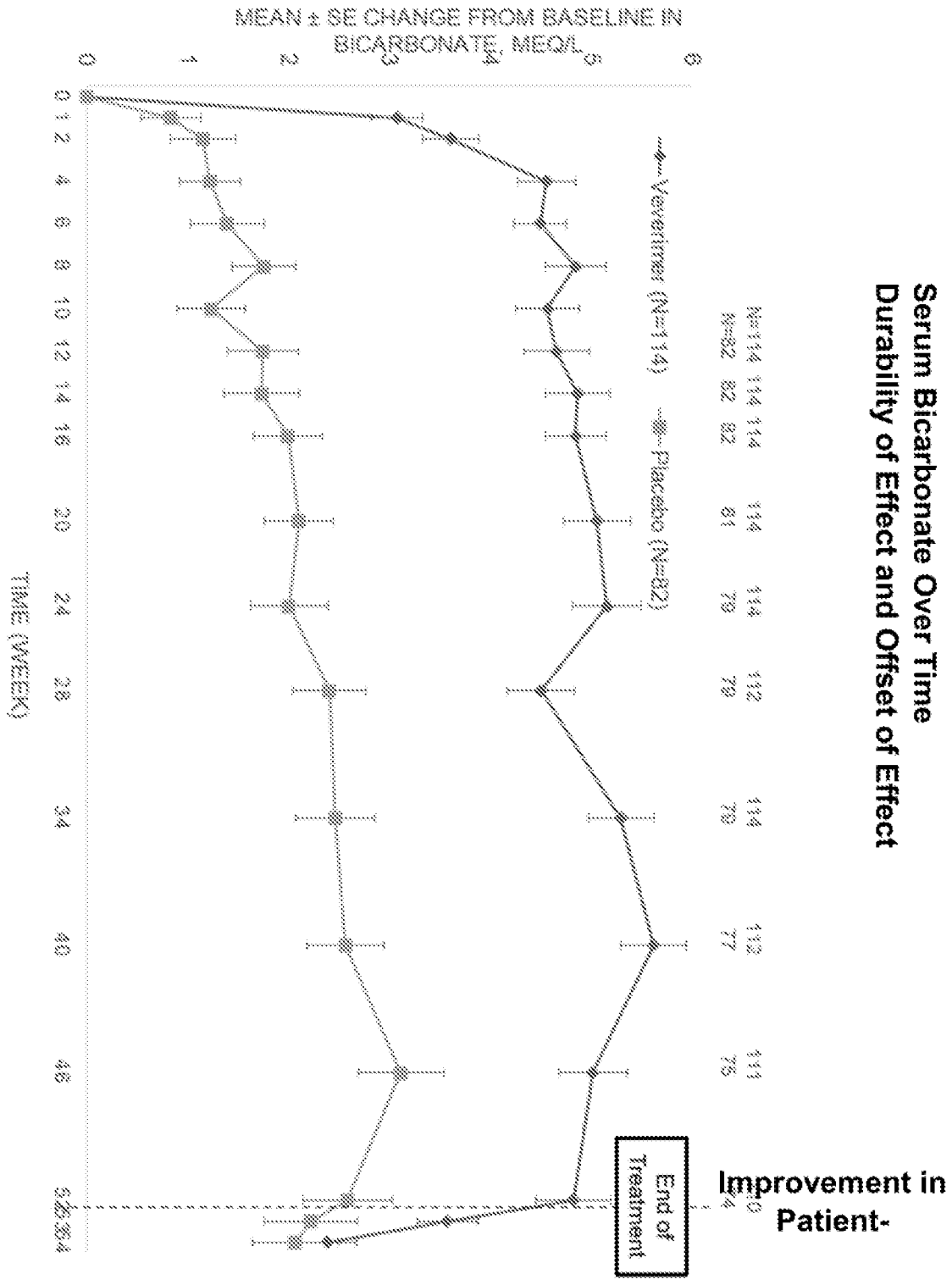
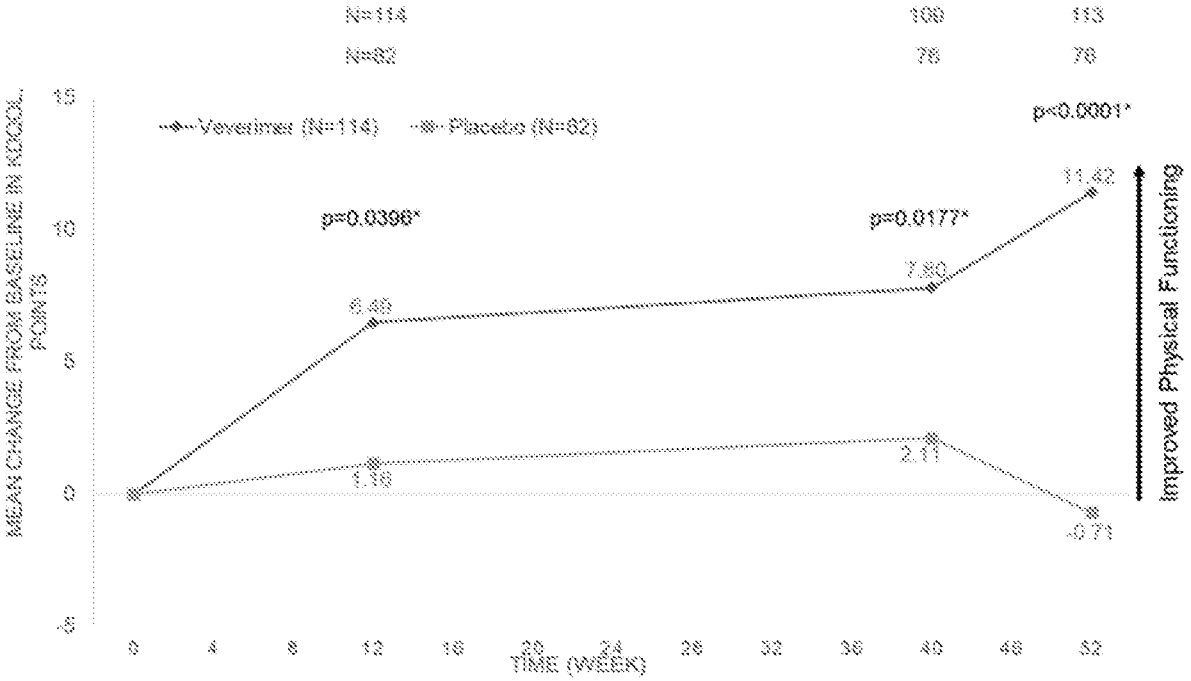

Serum Bicarbonate Over Time
Durability of Effect and Offset of Effect
MEAN ± SE CHANGE FROM BASELINE IN BICARBONATE, MEQ/L
TIME (WEEK)
Vevelmer (N=114)
Placebo (N=82)
N=114 114 114 114 114 112 114 113 111
N=82 82 82 81 79 79 78 77 75
End of Treatment
Improvement in Patient-

FIG. 29

Reported Kidney Disease Quality of Life (KDQOL) Physical Functioning Over 1-Year

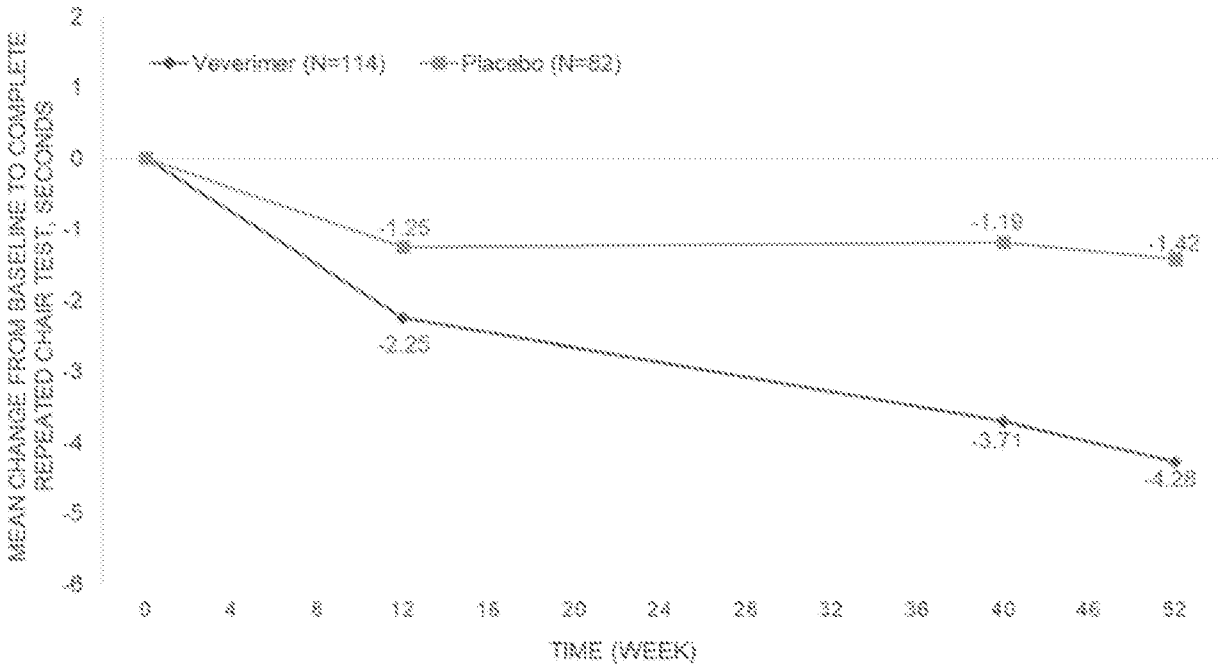


Baseline PBO = 55.73; Veverimer = 52.59
*P-value for between group difference by rank method

FIG. 30

Improvement in Measured Physical Functioning Over 1-Year

Repeated Chair Stand Test



Baseline PBO = 21.01; Veverimer = 21.65
*P-value for between group difference by rank method

FIG. 31

Adverse Events Occurring at ≥2% Difference Active vs Placebo

Event	TRC101 # Patients (%)	Placebo # Patients (%)
Hyperkalemia	16 (14.3)	9 (11.1)
Influenza	12 (10.7)	6 (7.4)
Cough	7 (6.3)	3 (3.7)
Anemia	6 (5.4)	1 (1.2)
Oropharyngeal pain	5 (4.5)	1 (1.2)
Dizziness	4 (3.6)	0 (0)
Hypoaesthesia oral	4 (3.6)	0 (0)
Ventricular extrasystoles	3 (2.7)	0 (0)
Hypoglycemia	3 (2.7)	0 (0)

FIG. 32

Adverse Events Occurring at ≥5% in Either Group

Event	TRC101 # Patients (%)	Placebo # Patients (%)
Headache	17 (15.2)	20 (24.7)
Hyperkalemia	16 (14.3)	9 (11.1)
Influenza	12 (10.7)	6 (7.4)
Flatulence	8 (7.1)	5 (6.2)
Diarrhea	7 (6.3)	5 (6.2)
Cough	7 (6.3)	3 (3.7)
Anemia	6 (5.4)	1 (1.2)
Renal impairment	5 (4.5)	7 (8.6)

FIG. 33

TRCA-301/301E: Summary of Withdrawals from the Study

Study	TRC101 (301/301E) N=124/114	Placebo (301/301E) N=93/82
TRCA-301	5 (4.0%)	4 (4.3%)
TRCA-301E	3 (6.2%)	8 (9.8%)
	8 (6.5%)	12 (12.9%)
Withdrawal Reason:		
• Death	0	4 (2/2)
• Adverse Event (other than death)	1 (1/0)	1 (1/0)
• Dialysis	1 (1/0)	1 (0/1)
• Withdrawal of Consent	3 (2/1)	4 (1/3)
• Loss to Follow-up	2 (0/2)	1 (0/1)
• Other	1 (1/0)	1 (0/1)

FIG. 34

TRCA-301 / TRCA-301E: DD50 Events

No. and % of Subjects with Event	TRC101 (N = 124)	Placebo (N = 93)
Death[a]	0	4 (4.3%)
Dialysis	1 (0.8%)	1 (1.1%)
≥50% eGFR decline	5 (4.0%)	7 (7.5%)
Death[a]/Dialysis/ ≥50% eGFR decline (DD50)	5 (4.0%)	10 (10.8%)

[a] All-cause mortality

FIG. 35

TRCA-301 / TRCA-301E: Study Results – Pre-Specified Time-to-Event Analyses

Annualized Incidence Rate[a]	TRC101	Placebo	p-value
Death[b]	0	4.7%	p = 0.0190
Death[b]/Dialysis (DD)	0.8%	5.9%	p = 0.0395
Death[b]/Dialysis/ ≥50% eGFR decline (DD50)	4.2%	12.0%	p = 0.0224

[a] Incidence rate is calculated as 100 × number of events / total person-years
[b] All-cause mortality

FIG. 36

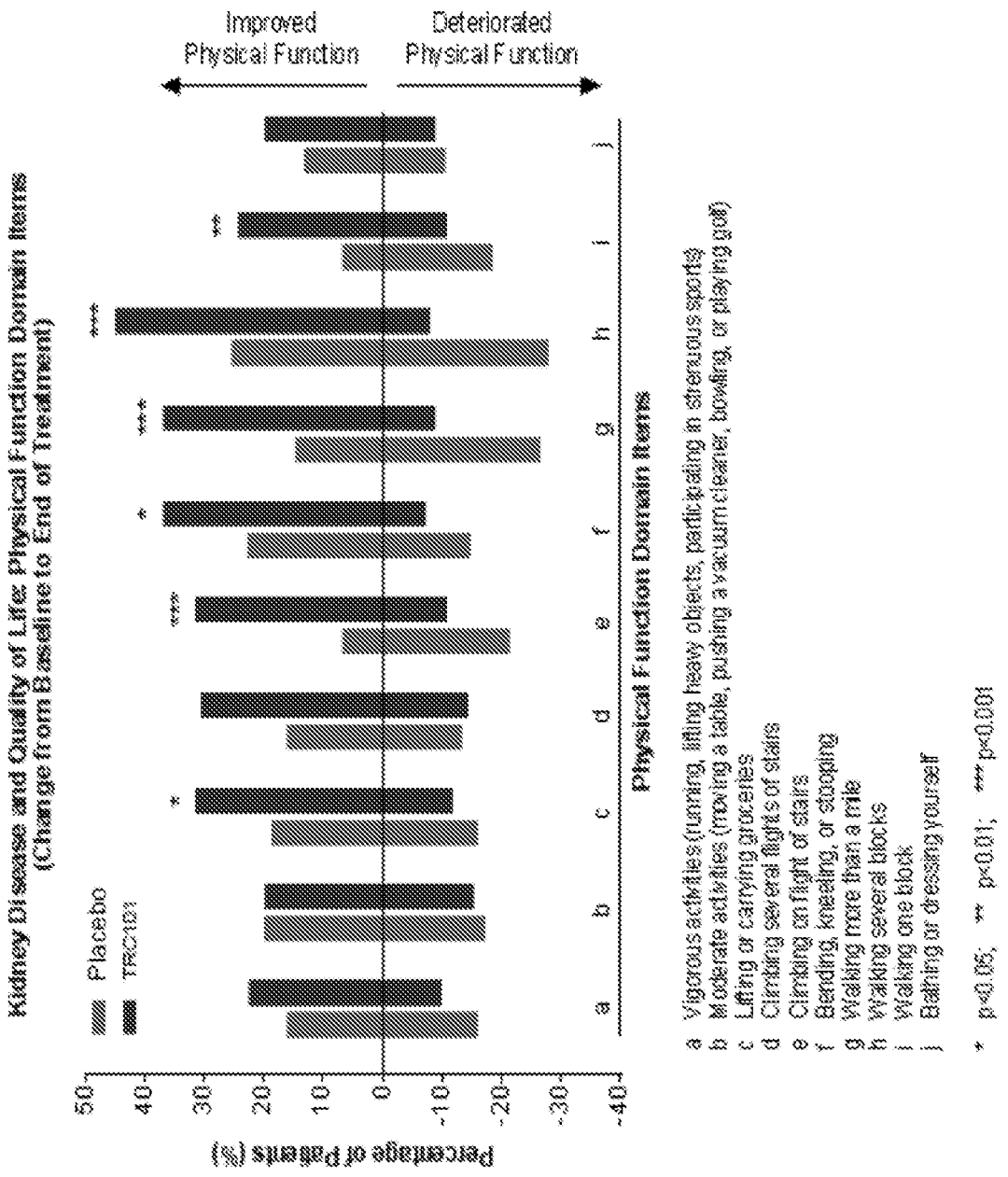

Kidney Disease and Quality of Life: Physical Function Domain Items
(Change from Baseline to End of Treatment)
Improved Physical Function
Deteriorated Physical Function
Placebo
Percentage of Patients (%)
50
40
30
20
10
0
-10
-20
-30
-40
Physical Function Domain Items
a b c d e f g h i j
a Vigorous activities (running, lifting heavy objects, participating in strenuous sports)
b Moderate activities (moving a table, pushing a vacuum cleaner, bowling, or playing golf)
c Lifting or carrying groceries
d Climbing several flights of stairs
e Climbing one flight of stairs
f Bending, kneeling, or stooping
g Walking more than a mile
h Walking several blocks
i Walking one block
j Bathing or dressing yourself
* p<0.05; ** p<0.01; *** p<0.001

FIG. 37

Baseline Characteristics of All Enrolled Participants

Parameter	Placebo N=82	Veverimer N=114
Age (years)	61·7 (11·9)	62·9 (12·1)
≥65 years	38 (46%)	58 (51%)
Sex		
Male	51 (62%)	68 (60%)
Female	31 (38%)	46 (40%)
Race		
White	79 (96%)	113 (99%)
Black or African American	3 (4%)	1 (1%)
Region		
Europe	71 (87%)	108 (95%)
USA	11 (13%)	6 (5%)
Body mass index (kg/m^2)	27·9 (3·9)	28·6 (4·0)
Systolic blood pressure (mmHg)	136·5 (9·0)	135·9 (8·9)
Selected medical history		
Hypertension	79 (96%)	110 (96%)
Diabetes mellitus	57 (70%)	70 (61%)
	48 (59%)	70 (61%)
Dyslipidaemia/hyperlipidaemia/hypercholesterolaemia	35 (43%)	56 (49%)
Left ventricular hypertrophy	28 (34%)	34 (30%)
Congestive heart failure	14 (17%)	19 (17%)
Percutaneous coronary intervention or coronary bypass graft	10 (12%)	17 (15%)
Myocardial infarction	8 (10%)	8 (7%)
Stroke	6 (7%)	7 (6%)
Atrial fibrillation or atrial flutter	6 (7%)	5 (4%)
Peripheral vascular disease	3 (4%)	1 (1%)
Peripheral vascular disease intervention/surgical arterial bypass	0	1 (1%)
Transient ischemic attack		

FIG. 38A

Chronic kidney disease etiology		
Hypertension	27 (33%)	36 (32%)
Diabetes and hypertension	23 (28%)	37 (32%)
Diabetes	18 (22%)	15 (13%)
Glomerulonephritis	7 (9%)	7 (6%)
Interstitial nephritis	3 (4%)	6 (5%)
Cystic renal disease	3 (4%)	5 (4%)
Other/unknown/urologic	1 (1%)	8 (7%)
Medication use		
Sodium bicarbonate	5 (6%)	10 (9%)
ACE inhibitors/ARBs	66 (80%)	74 (65%)
Diuretics	52 (63%)	70 (61%)
Calcium channel blockers	49 (60%)	65 (57%)
Anti-diabetic drugs	45 (55%)	62 (54%)
Beta blockers	46 (56%)	53 (46%)
Lipid modifying agents	41 (50%)	49 (43%)
Anti-thrombotic agents	41 (50%)	44 (39%)
Laboratory values		
Serum bicarbonate (mmol/L)	17·1 (1·5)	17·2 (1·4)
> 18 mmol/L	23 (28%)	37 (32%)
≤ 18 mmol/L	59 (72%)	77 (68%)
Venous blood pH	7·30 (0·09)	7·30 (0·08)
Venous blood base excess (mmol/L)	-9·3 (2·2)	-9·3 (2·2)
Estimated GFR (mL/min per 1·73m^2)	27·9 (5·4)	29·4 (6·4)
Blood urea nitrogen (mmol/L)	13·6 (4·6)	13·7 (4·8)
Serum creatinine (µmol/L)	204·3 (51·8)	193·4 (47·5)
Serum sodium (mmol/L)	139·4 (2·9)	139·9 (2·6)
Serum potassium (mmol/L)	4·9 (0·6)	4·9 (0·6)
Serum chloride (mmol/L)	107·3 (4·8)	106·9 (3·7)
Serum calcium (mmol/L)	2·3 (0·1)	2·3 (0·1)
Serum phosphate (mmol/L)	1·2 (0·2)	1·2 (0·2)
Serum magnesium (mmol/L)	0·86 (0·11)	0·87 (0·11)
Serum anion gap (mmol/L)*	20·0 (4·1)	20·8 (3·9)
Haemoglobin (g/L)	125·6 (17·4)	125·7 (17·7)
Urine albumin-to-creatinine ratio (mg/mmol)†	34·5 (23·4-50·7)	23·5 (16·6-33·6)
Physical functioning		
KDQOL-PFD total score‡	55·7 (26·2)	52·6 (22·4)
Repeated chair stand (s)§	21·0 (17·1)	21·7 (16·9)

Data are mean (SD), n (%), or geometric mean (95% CI). Baseline characteristics were measured prior to randomisation in the parent study. ACE=angiotensin converting enzyme. ARB=angiotensin II receptor blockers. GFR=glomerular filtration rate. KDQOL-PFD=Kidney Disease and Quality of Life Physical Function Domain.

*Serum anion gap was calculated as Na + K - (Cl + HCO_3^-)

†Values are from a spot urine collection, geometric mean (95% CI) was reported.

‡Placebo, n=82; Veverimer, n=114

§Placebo, n=81; Veverimer, n=114

FIG. 38B

Safety Summary

	Placebo (N=81)	Veverimer (N=112)
Deaths — no. (%)	2 (2)	0
Serious Adverse Events — no. (%)	4 (5)	2 (2)
Adverse Events Related to Study Drug	12 (15)	11 (10)
Premature Discontinuation of Study Drug Treatment Due to Adverse Event — no. (%)	1 (1)	0
Dialysis — no. (%)	1 (1)	0
Adverse Events ≥ 5% in Either Treatment Arm[b]		
	Placebo (N=81)	**Veverimer (N=112)**
Adverse Event — no. (%) of patients		
Any	65 (80)	91 (81)
Headache	20 (25)	17 (15)
Hyperkalemia	9 (11)	16 (14)
Influenza	6 (7)	12 (11)
Flatulence	5 (6)	8 (7)
Diarrhea	5 (6)	7 (6)
Cough	3 (4)	7 (6)
Anemia	1 (1)	6 (5)
Renal impairment	7 (9)	5 (4)

[a]This population excluded 3 patients (2 veverimer, 1 placebo) enrolled in the 40-week extension on a dose hold. Their serum bicarbonate levels remained in the normal range throughout the remainder of the study; therefore, they did not receive study drug during the extension study.

[b]There was no significant difference between groups in the incidence of any common adverse event. Adverse events occurring during the first 12 weeks of treatment (parent study) have been previously reported. [6]

FIG. 39

Dose Titration Algorithm

continued

Serum Bicarbonate (mmol/L)	Interactive Response Technology System Algorithm
<12[a]	*At Week 12 Visit*: **Do not enroll patient in Study TRCA-301E** *During Treatment Period*: Evaluate for new acute acidotic process, contact Medical Monitor. Maintain dose(s) of study drug and oral alkali, if applicable, pending discussion with Medical Monitor.
12 to <22	Increase the study drug dose by 1 packet/day (maximum dose is 3 packets/day). Only increase the dose if **NO** dose changes have been made during the previous 14 days. Retest serum bicarbonate at next scheduled visit. Maintain oral alkali dose, if applicable, until next scheduled visit.
22 to <27	Maintain study drug dose until next scheduled visit. If applicable, discontinue oral alkali supplement until the next scheduled visit. If bicarbonate remains ≥22 mmol/L, do not re-instate oral alkali. If bicarbonate is <22 mmol/L at the next scheduled visit, increase study drug dose by one packet and retest bicarbonate at the next scheduled visit. If a patient who was taking oral alkali at the Week 12 Visit had their oral alkali discontinued, AND they are receiving the maximum dose of study drug (i.e., 3 packets) AND their blood bicarbonate value is <22 mmol/L, re-instate the same oral alkali supplement patient was taking at the Week 12 Visit at the same dose taken at the Week 12 Visit.[b] If the Investigator judges that re-starting alkali treatment poses a safety risk, the risk should be documented. In this situation, alkali will not be re-started.

FIG. 40A

27 to 30	Maintain study drug dose until next scheduled visit.[b] Invite patient for a visit in approximately 1 to 2 weeks to retest serum bicarbonate. If applicable, discontinue oral alkali supplement until the next scheduled visit. If bicarbonate remains ≥22 mmol/L, do not re-instate oral alkali. If bicarbonate is <22 mmol/L at the next scheduled visit, increase study drug dose by one packet and retest bicarbonate at the next scheduled visit. If a patient who was taking oral alkali at the Week 12 Visit had their oral alkali discontinued, AND they are receiving the maximum dose of study drug (i.e., 3 packets) AND their blood bicarbonate value is <22 mmol/L, re-instate the same oral alkali supplement patient was taking at the Week 12 Visit at the same dose taken at the Week 12 Visit.[c] If the Investigator judges that re-starting alkali treatment poses a safety risk, the risk should be documented. In this situation, alkali will not be re-started.
>30[a]	Interrupt (hold) study drug. Invite patient for a visit in approximately 1 week to retest serum bicarbonate. If serum bicarbonate at that visit is ≤30 mmol/L, restart study drug at a lower dose (1 packet/day less than before dose interruption) except for patients on 1 packet/day prior to dose interruption, who will restart study drug at 1 packet/day dose. If serum bicarbonate at that visit is >30 mmol/L, continue to hold the dose and retest again in approximately 1 week. Discontinue oral alkali supplement, if applicable.

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

b The dose was down-titrated if bicarbonate was 27-30 mmol/L prior to implementation of protocol amendment 2 (dated 31 May 2018) at a study site.

c The Week 12 dose is defined as the average daily dose prescribed during Week 12.

FIG. 40B

Restricted Concomitant Medications

Drug or Drug Class	Restriction
Investigational medications	Not allowed
Potassium binders	Use allowed with dose separation of ≥4 h from the study drug dose
Other polymeric binder drugs	Use allowed with dose separation of ≥4 h from the study drug dose
Sodium bicarbonate, potassium citrate, sodium citrate or other alkali therapy	No initiation of new alkali therapy or alkali dose increases beyond the Week 12 Visit dose.
Non-ophthalmic carbonic anhydrase inhibitors	Keep dose stable, if possible
Antacids, H2-blockers, proton pump inhibitors, calcium supplements	Keep dose stable, if possible
RAAS inhibitors	Keep dose stable, if possible, but dose changes necessary for the management of comorbidities or acute events (e.g., hyperkalemia/worsening hyperkalemia) not prohibited
Diuretics	Keep dose stable, if possible, but dose changes necessary for the management of comorbidities or acute events (e.g., heart failure, acute kidney injury) not prohibited

"Stable dose" is defined as no starting or stopping of these medications and no change in dose. For diuretics, dose changes of up to ± 50% relative to the Week 12 dose is considered "stable".

FIG. 41

Baseline Characteristics of Patients Randomised in Parent Study who Did and Did Not Enroll in the Extension Study

	Patients from Parent Study Who Did Not Participate in the Extension Study (n=12)	Patients from Parent Study Who Did Participate in the Extension Study (n=196)
Age (years)	69	62
Male Sex (%)	75	61
Baseline Serum Bicarbonate (mmol/L)	18·0	17·2
Baseline eGFR (mL/min/1·73m^2)	26	29
Urine Albumin-to-Creatinine Ratio (mg/mmol)	22·8	27·6

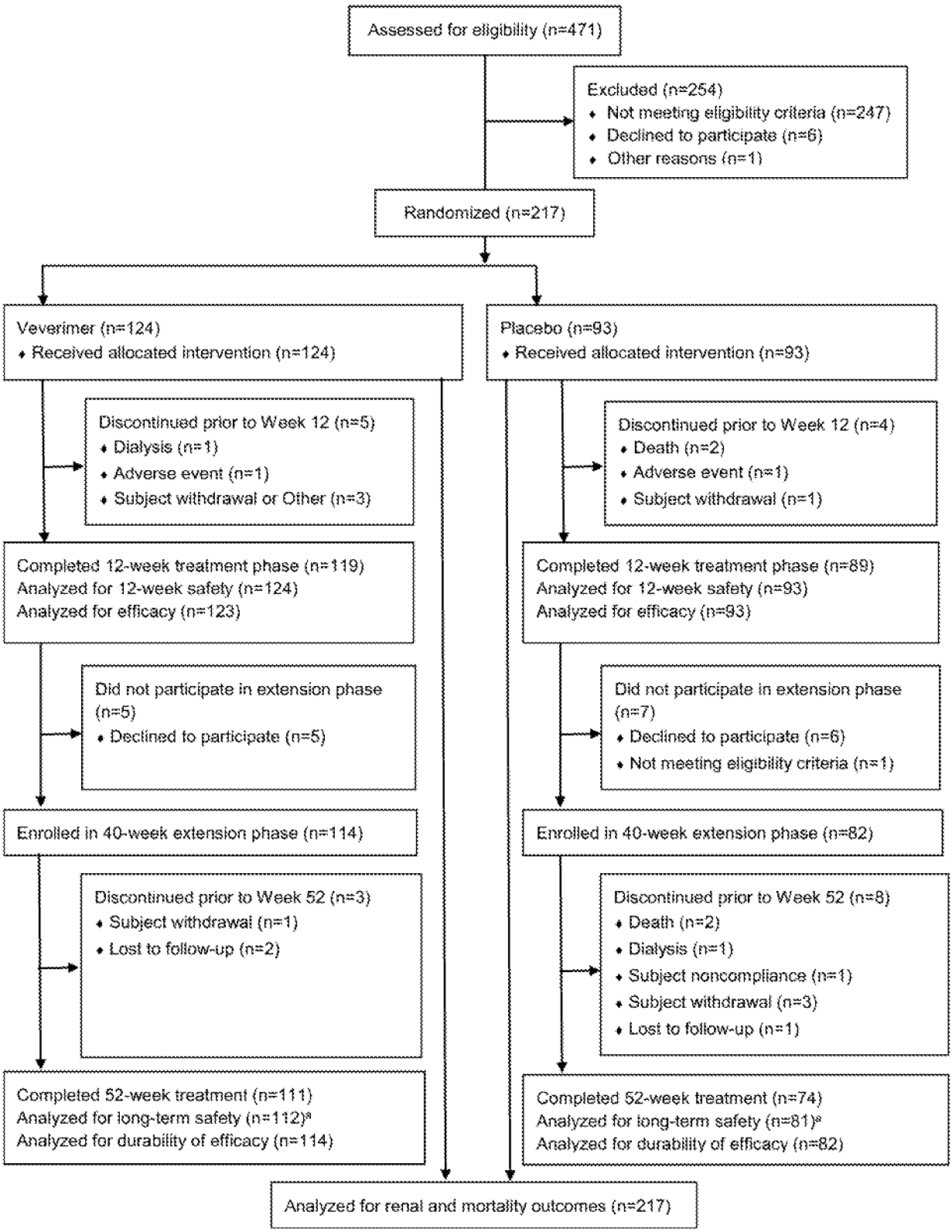
FIG. 42

Outcome Events in the 52-Week Treatment Period

Outcome Event (N [%])	Placebo (N=93)	Veverimer (N=124)
Death	4 (4)	0
Renal Replacement Therapy	1 (1)	1 (1)
Confirmed ≥50% Decline in eGFR	7 (8)	5 (4)

Reasons for death were as follows: acute coronary syndrome in one patient, community-acquired pneumonia in one patient, uremia in one patient (who refused dialysis), and congestive heart failure, worsening kidney function, hyponatremia, and pneumonia in one patient. No patients were transplanted.

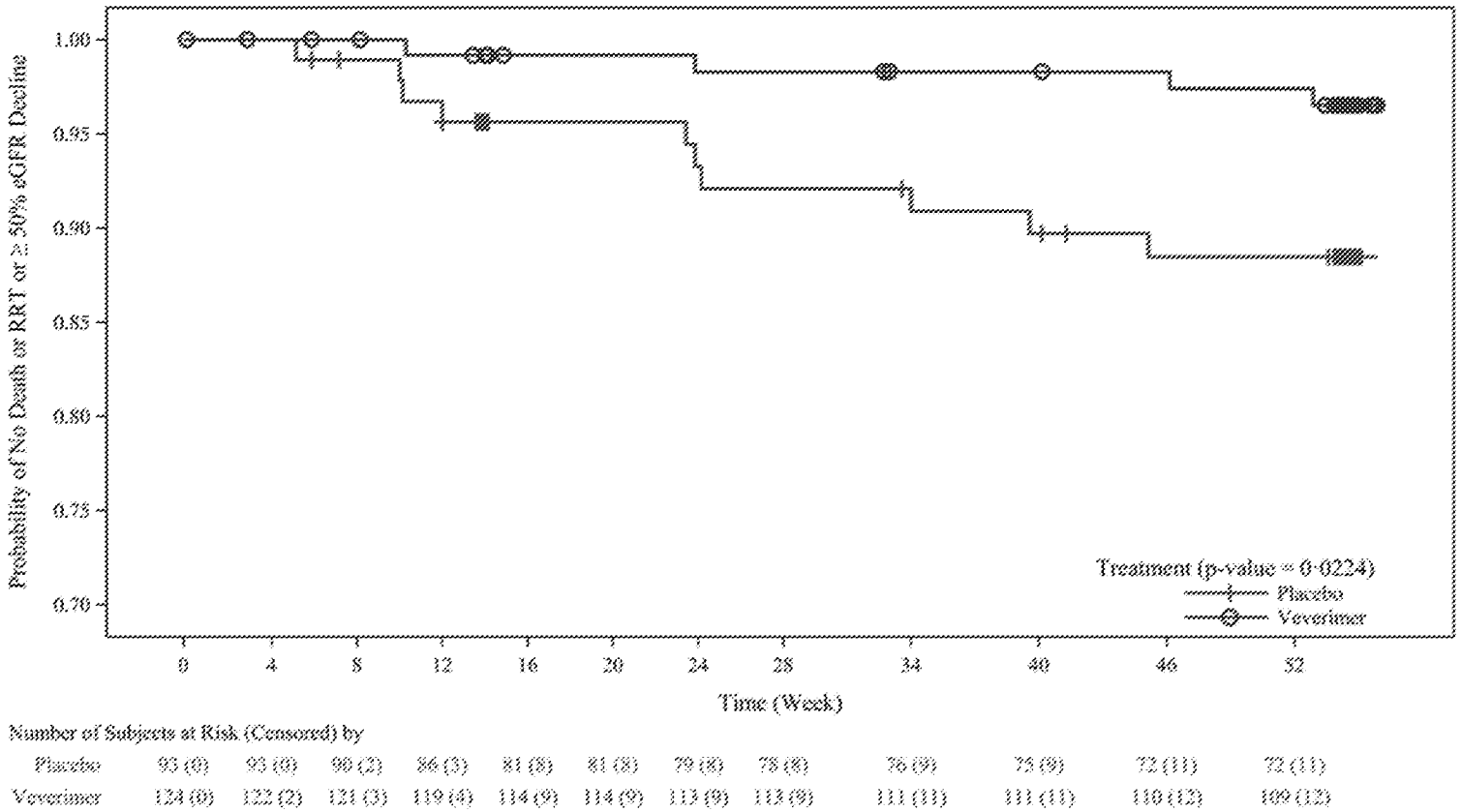
FIG. 43



a Three patients (2 veverimer, 1 placebo) enrolled in the 40-week extension on a dose hold. Their serum bicarbonate levels remained in the normal range throughout the remainder of the study; therefore, they did not receive study drug during the extension study.

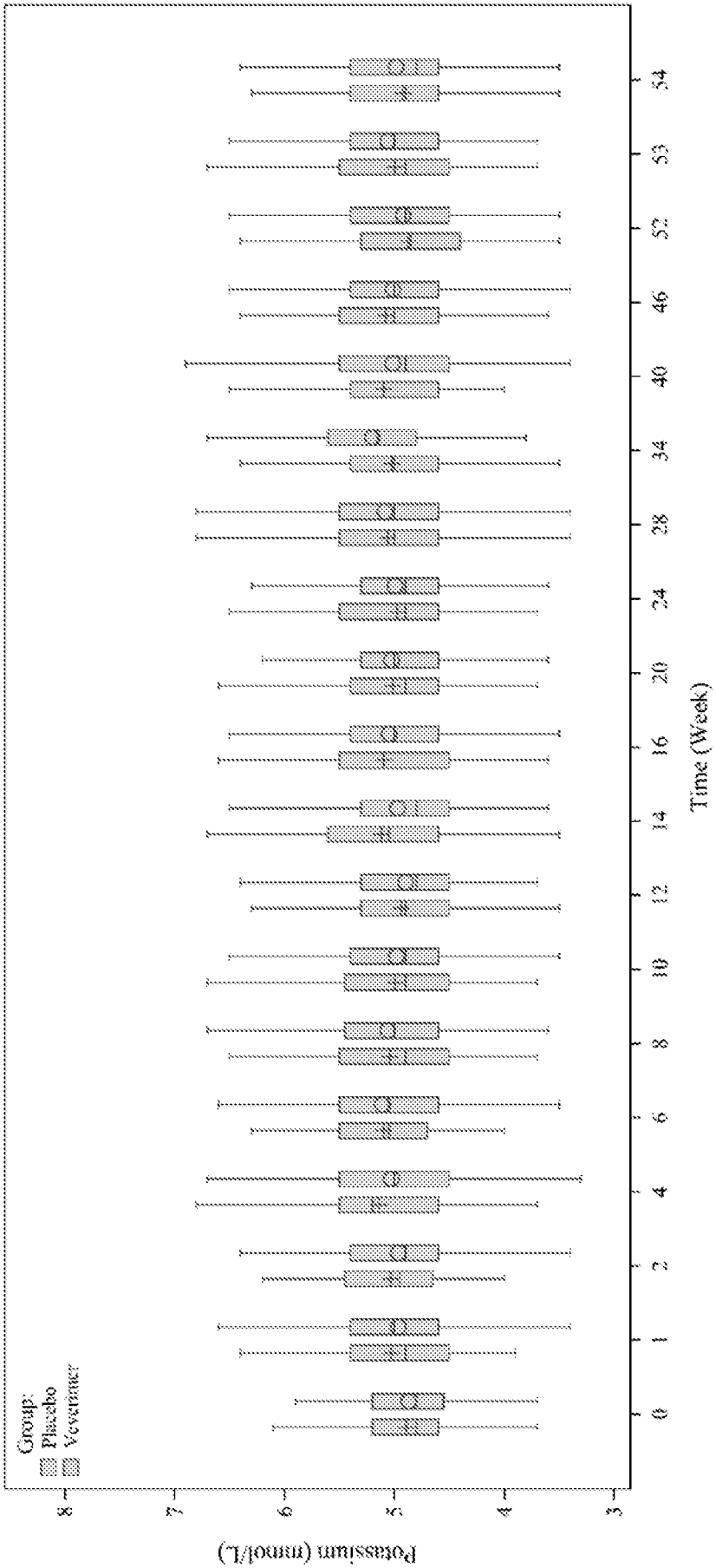
FIG. 44

Kaplan-Meier Plot of Time to First Occurrence of Death, Renal Replacement Therapy or ≥50% Decline in eGFR



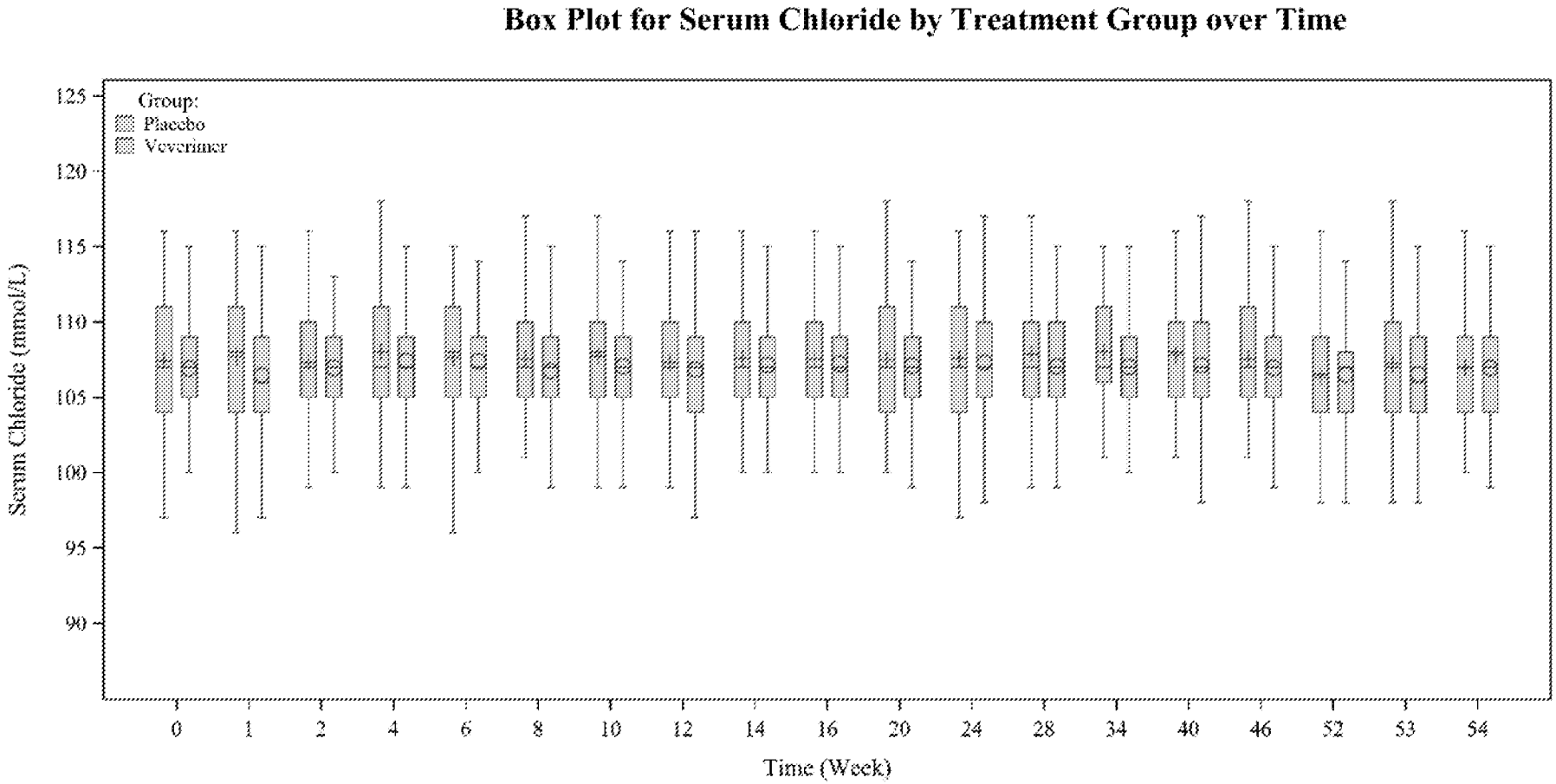
The p-value is based on a log-rank test that compares two survival distributions for the treatment effect (also see Supplement Table S4). In post-hoc analyses, the difference between treatment groups remained significant after adjustment for Screening eGFR (p=0·0358), baseline spot urine albumin-to-creatinine ratio (p=0·0428) and baseline diabetes status (p=0·0293). eGFR = estimated glomerular filtration rate; RRT = renal replacement therapy (i.e., dialysis or kidney transplantation).

FIG. 45



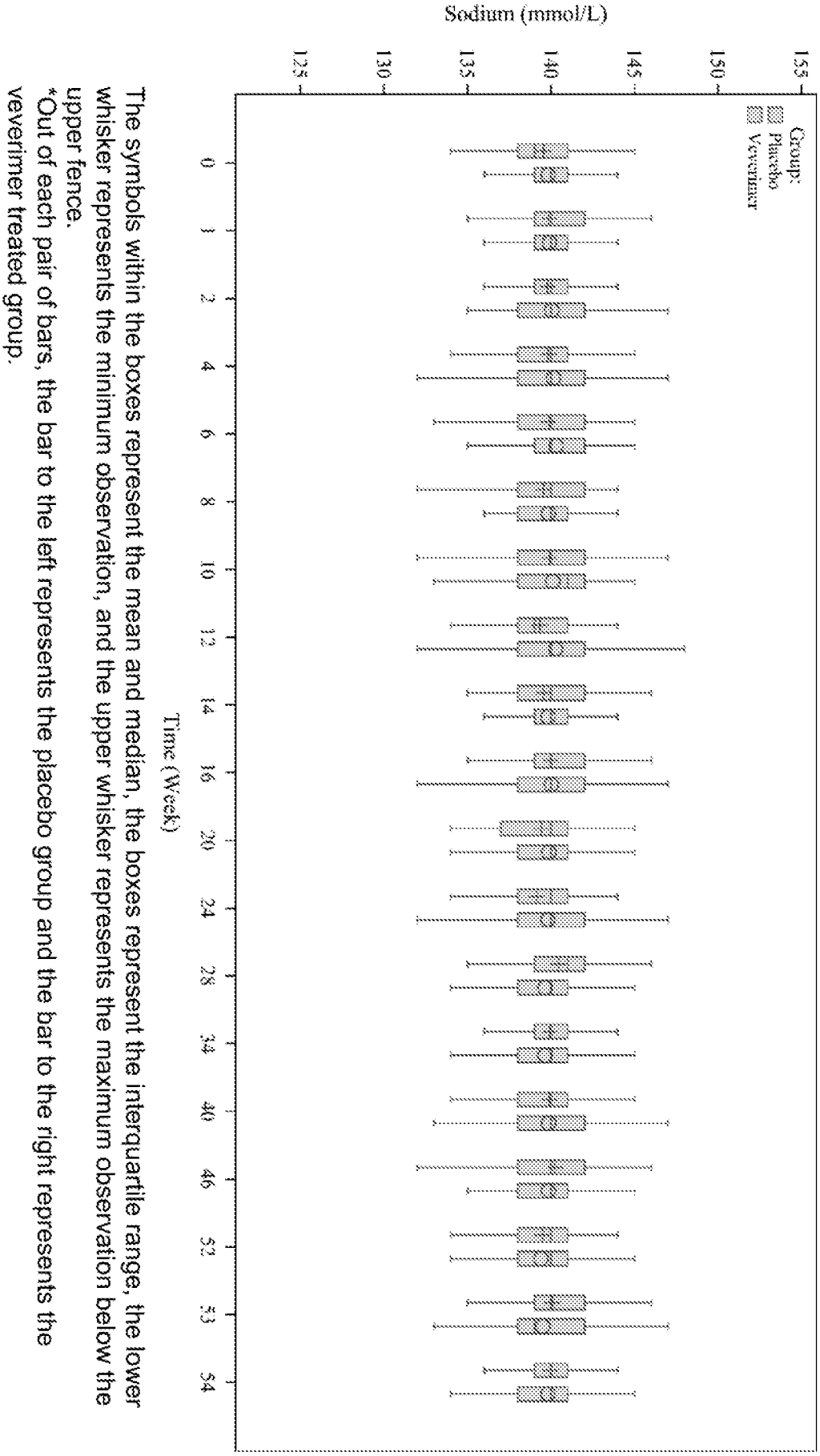
The symbols within the boxes represent the mean and median, the boxes represent the interquartile range, the lower whisker represents the minimum observation, and the upper whisker represents the maximum observation below the upper fence
*Out of each pair of bars, the bar to the left represents the placebo group and the bar to the right represents the vevorimer treated group.

FIG. 46



The symbols within the boxes represent the mean and median, the boxes represent the interquartile range, the lower whisker represents the minimum observation, and the upper whisker represents the maximum observation below the upper fence.
*Out of each pair of bars, the bar to the left represents the placebo group and the bar to the right represents the veverimer treated group.

FIG. 47



The symbols within the boxes represent the mean and median, the boxes represent the interquartile range, the lower whisker represents the minimum observation, and the upper whisker represents the maximum observation below the upper fence.
*Out of each pair of bars, the bar to the left represents the placebo group and the bar to the right represents the veverimer treated group.

FIG. 48

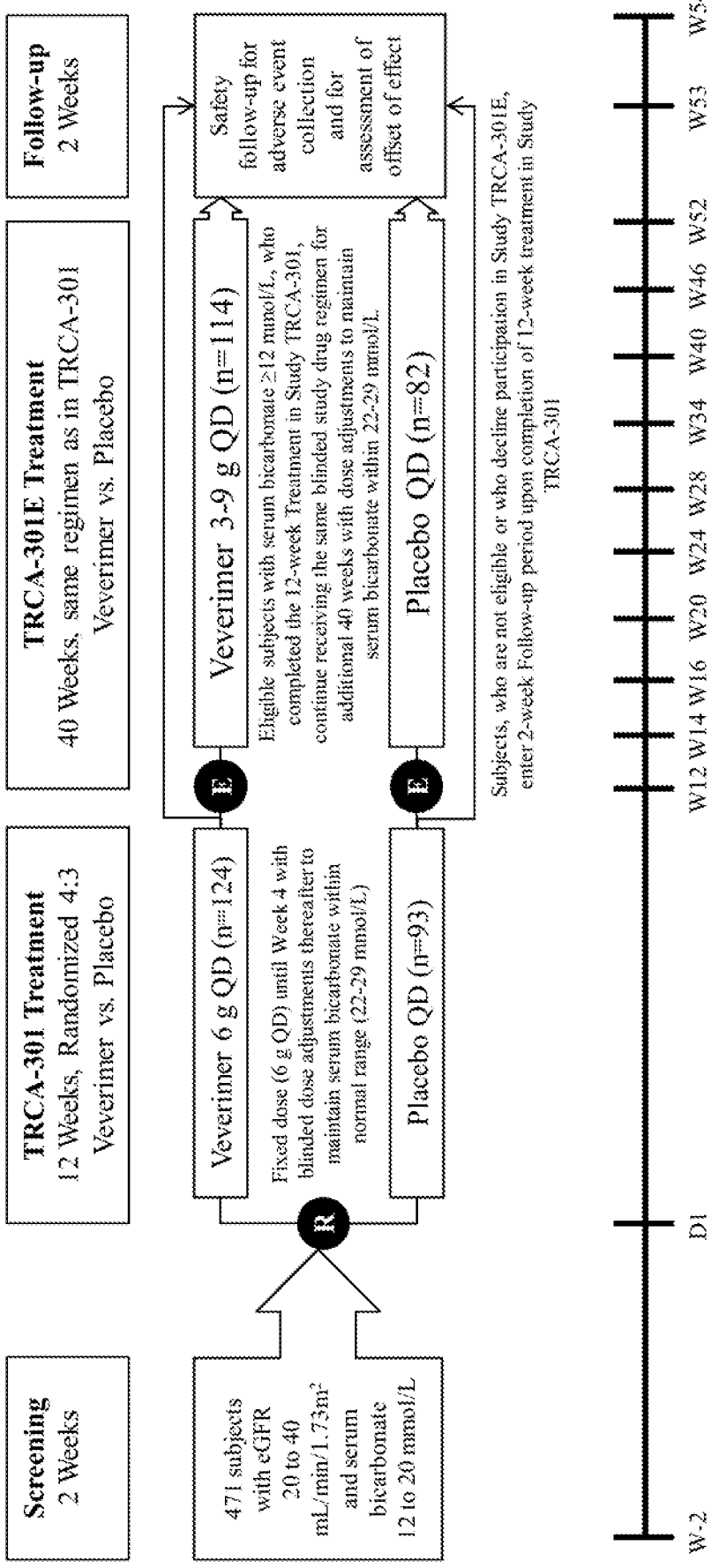
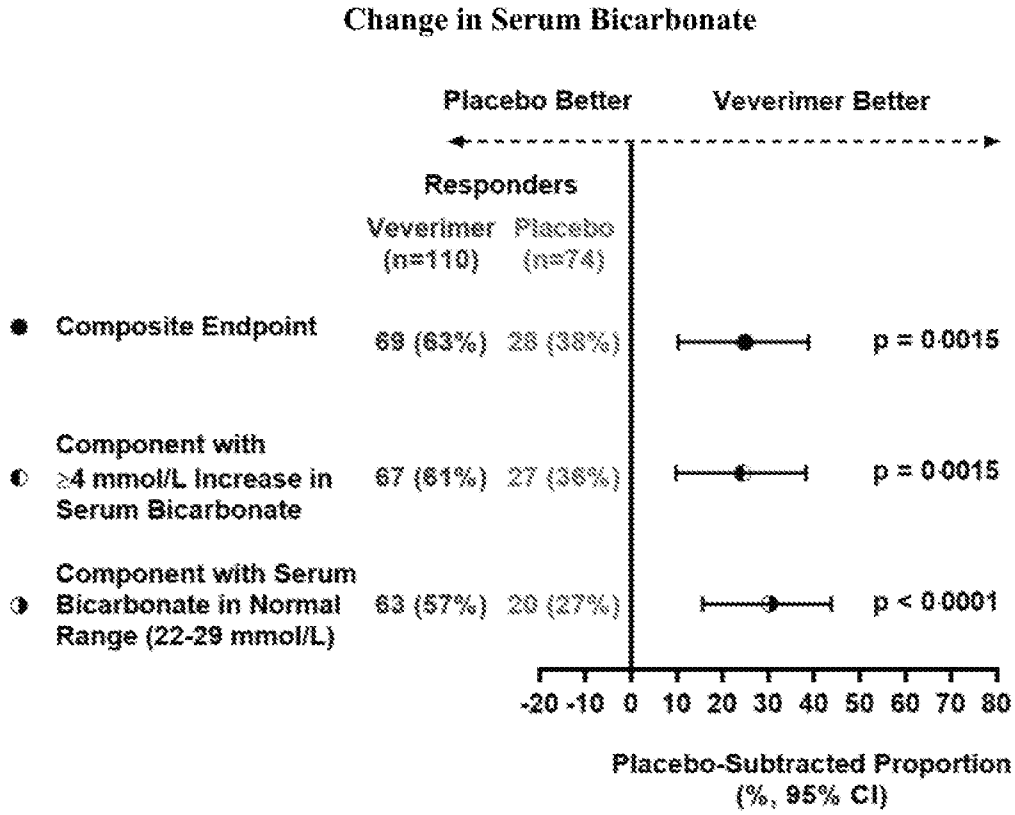


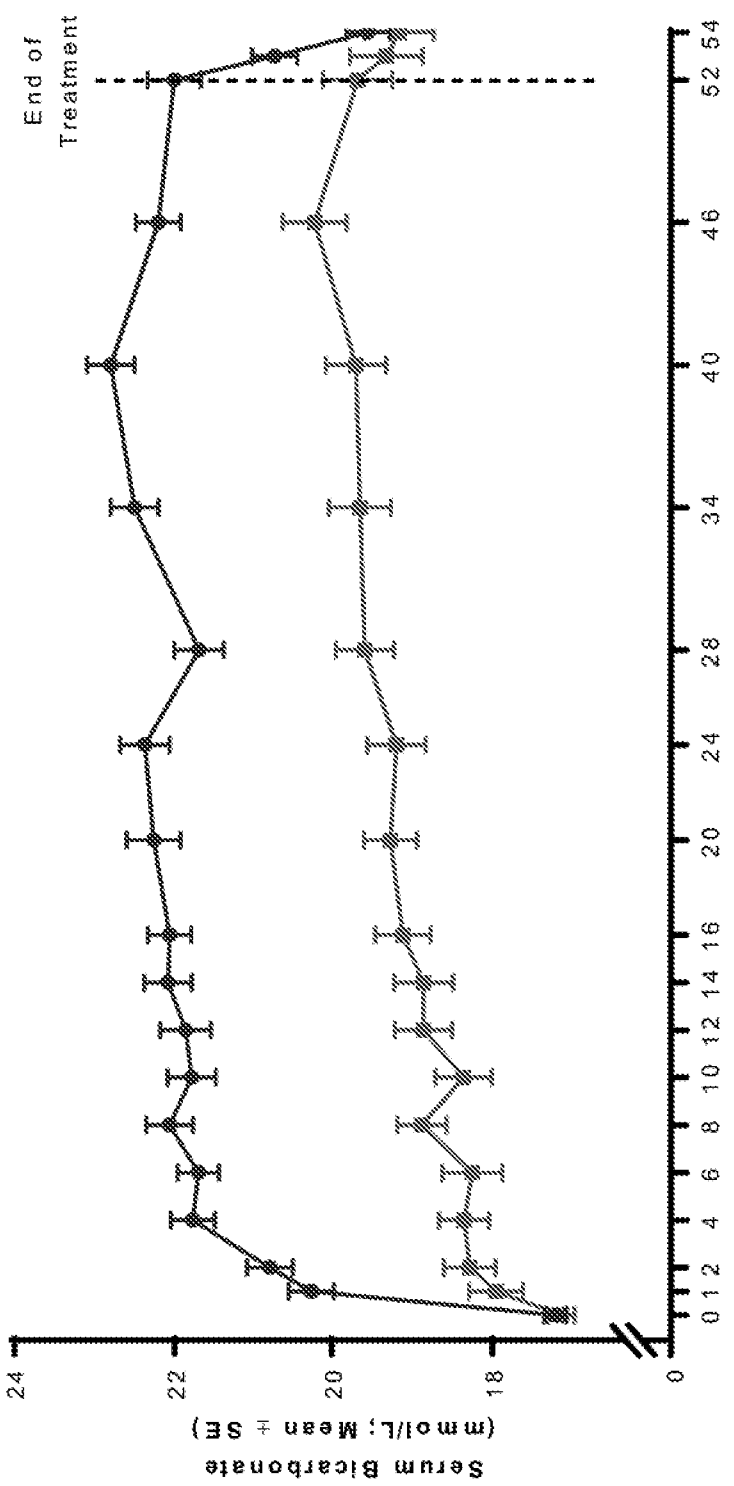
FIG. 49

Overall study design, including screening, treatment, and follow-up. D=day; eGFR=estimated glomerular filtration rate; E=enrollment; n=number of patients in each treatment group; QD=once daily; R=randomization; W=week.



The first secondary endpoint, durability of bicarbonate response, defined by the placebo-subtracted proportion of patients achieving a ≥4 mmol/L increase from baseline in serum bicarbonate or a serum bicarbonate in the normal range (22-29 mmol/L) at the end of treatment (Week 52), is depicted as the top line. The two lower lines depict each component of the endpoint. The individual endpoint component analyses were pre-specified but were not adjusted for multiple comparisons. P-values are for the difference in proportions between veverimer and placebo groups (Fisher's exact test).

FIG. 50



Week	0	1	2	4	6	8	10	12	14	16	20	24	28	34	40	46	52	53	54
Veverimer (N)	114	113	114	114	114	114	114	114	114	114	114	114	112	114	112	111	110	110	111
Placebo (N)	82	82	82	82	82	82	82	82	82	82	81	79	79	79	77	75	74	74	74

The baseline serum bicarbonate (Treatment Week 0), the mean of the Screening 1, Screening 2, and Baseline Day 1 values, was 17·2 mmol/L in the veverimer group and 17·1 mmol/L in the placebo group. Values depicted are the mean (±SE).

FIG. 51

Change from Baseline in Laboratory Parameters and Blood Pressure after 52 Weeks of Treatment

	Placebo (n=81)	Veverimer (n=112)
Blood urea nitrogen (mmol/L)		
n	72	109
Mean (SD)	1·46 (3·87)	1·14 (4·59)
Serum creatinine (µmol/L)		
n	72	109
Mean (SD)	25·46 (61·31)	21·92 (52·21)
Serum sodium (mmol/L)		
n	72	109
Mean (SD)	-0·2 (3·1)	-0·4 (2·8)
Serum potassium (mmol/L)		
n	68	101
Mean (SD)	-0·03 (0·66)	0·02 (0·68)
Serum chloride (mmol/L)		
n	72	109
Mean (SD)	-1·0 (4·2)	-0·4 (3·7)
Serum calcium (mmol/L)		
n	72	109
Mean (SD)	-0·02 (0·15)	-0·06 (0·14)
Serum phosphate (mmol/L)		
n	72	107
Mean (SD)	0·06 (0·22)	0·05 (0·25)
Serum magnesium (mmol/L)		
n	72	109
Mean (SD)	0·06 (0·13)	0·05 (0·10)
Serum anion gap (mmol/L)		
n	68	100
Mean (SD)	-1·73 (4·68)	-4·83 (4·78)
Estimated glomerular filtration rate (mL/min/1.73m^2)		
n	72	109
Mean (SD)	-1·5 (10·7)	-2·0 (6·4)

FIG. 52A

Venous blood pH		
n	73	108
Mean (SD)	0·001 (0·129)	0·031 (0·107)
Venous blood base excess (mmol/L)		
n	73	108
Mean (SD)	2·5 (4·8)	5·3 (4·7)
Total cholesterol (mmol/L)		
n	73	109
Mean (SD)	-0·20 (1·10)	0·03 (1·24)
Low-density lipoprotein cholesterol (mmol/L)		
n	70	106
Mean (SD)	-0·17 (0·84)	0·07 (1·04)
High-density lipoprotein cholesterol (mmol/L)		
n	73	109
Mean (SD)	0·02 (0·37)	-0·02 (0·34)
Hemoglobin (g/L)		
n	70	107
Mean (SD)	1·1 (15·5)	2·1 (16·8)
Systolic blood pressure (mmHg)		
n	73	109
Mean (SD)	-2·0 (7·1)	-2·0 (7·6)
Diastolic blood pressure (mmHg)		
n	73	109
Mean (SD)	-2·9 (5·8)	-2·6 (8·0)
Urine urea nitrogen (from 24-hour urine collection; mmol/L)		
n	72	109
Mean (SD)	-8·53 (85·95)	0·64 (88·99)

FIG. 52B

Kidney Disease and Quality of Life, Short-Form 36, Question 3 (Physical Function Domain)

	3. The following items are about activities you might do during a typical day. Does your health now limit you in the activities? If so, how much? [Mark an ☒ in a box on each line.]	**Yes, limited a lot ▼**	**Yes, limited a little ▼**	**No, not limited at all ▼**
a	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐	☐	☐
c	Lifting or carrying groceries	☐	☐	☐
d	Climbing several flights of stairs	☐	☐	☐
e	Climbing one flight of stairs	☐	☐	☐
f	Bending, kneeling, or stooping	☐	☐	☐
g	Walking more than a mile	☐	☐	☐
h	Walking several blocks	☐	☐	☐
i	Walking one block	☐	☐	☐
j	Bathing or dressing yourself	☐	☐	☐

Score Conversion

- Yes, limited a lot = 0
- Yes, limited a little = 50
- No, not limited at all = 100

Total score = sum of all 10, divided by 10

FIG. 53

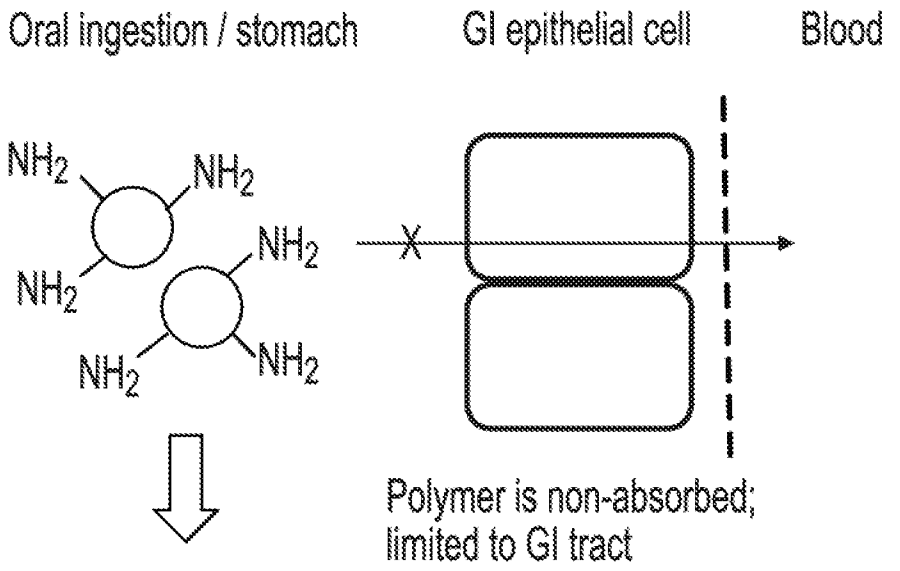


FIG. 1A

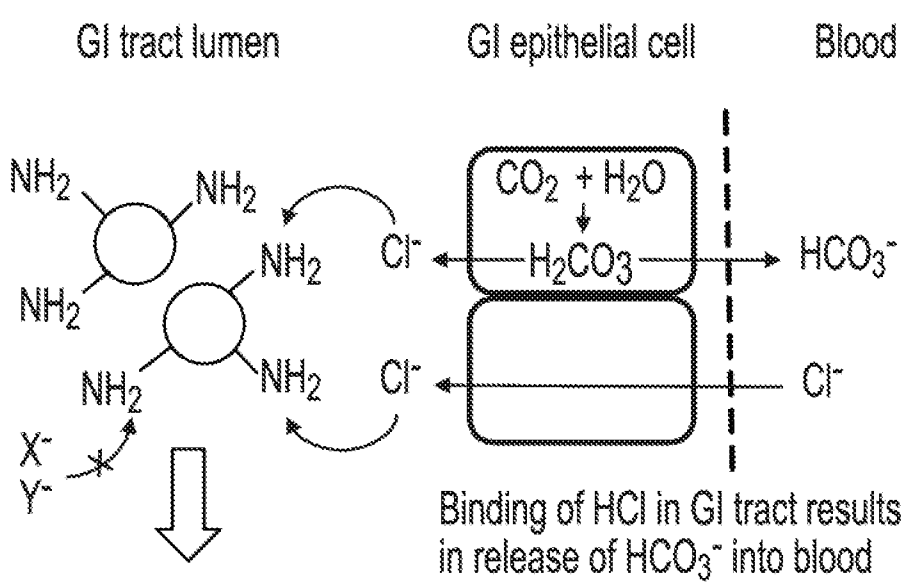


FIG. 1B

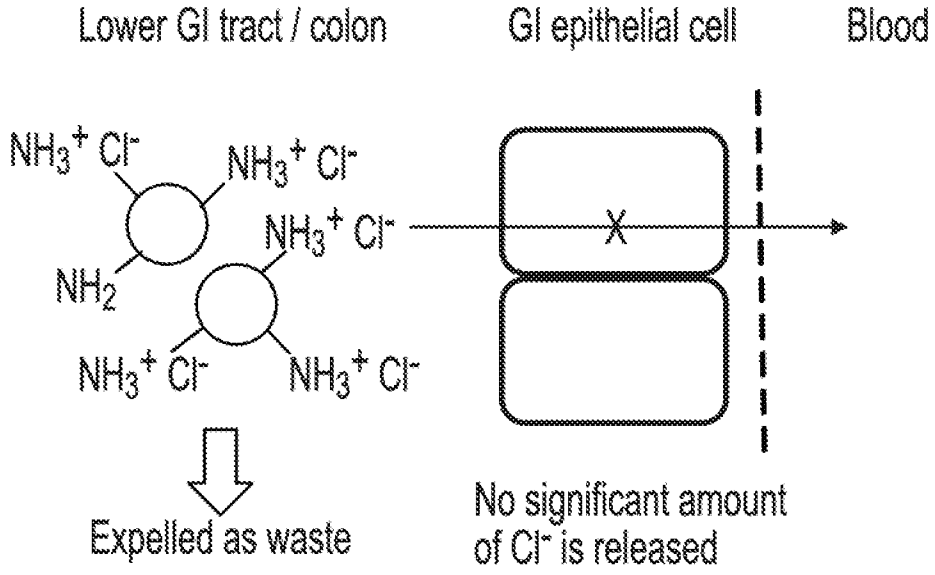


FIG. 1C