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(54) **THERAPEUTIC AGENTS FOR REGULATING SERUM PHOSPHORUS**

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AGENTS THÉRAPEUTIQUES POUR LA RÉGULATION DU PHOSPHORE SÉRIQUE

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Description

TECHNICAL FIELD

[0001] The present disclosure provides a method for treating hemodialysis patients with hyperphosphatemia comprising administering a calcium sensing receptor (CaSR) agonist.

REFERENCE TO SEQUENCE LISTING

[0002] A Sequence Listing is being submitted electronically via EFS in the form of a text file, created June 8, 2012, and named "632008021 US00.txt" (87,702 bytes.

BACKGROUND

[0003] Phosphate (phosphorus) is critical for a variety of biologic and cellular processes. Phosphate along with calcium is a major component of the skeletal system, providing mineral strength to bone. Phosphate is also an integral component of nucleic acids as well as the phosphate bonds of the cellular energy molecule ATP. Phosphate functions as a buffer in bone, serum, and urine. Accordingly, physiological levels of phosphate in the blood are careful regulated by a variety of organ systems of in the body

[0004] The bulk of total body phosphate (85%) is in the bone as part of the mineralized extracellular matrix. About 300 mg of phosphate enters and exits bone tissue each day. Excessive losses or failure to add phosphate to bone leads to osteomalacia. The kidneys along with parathyroid hormone (PTH), which is secreted by the parathyroid gland, play an important role in phosphate homeostasis by controlling the excretion of phosphate, while the digestive tract and the hormone Vitamin D play yet another important role in phosphate homeostasis by controlling its absorption from the diet.

[0005] The kidneys provide the primary route of excretion for excess phosphorus absorbed from ingested food or liberated from bone. Consequently in chronic kidney disease (CKD) patients as kidney function worsens elevation in blood levels of serum phosphorus directly stimulate PTH secretion by the parathyroid glands, which can then further exacerbate the homeostasis by liberating more phosphorus from bone. Since failing kidneys can no longer adequately handle the burden of excess phosphorus, CKD patients must control their diet to reduce phosphate intake. Increases in serum phosphorus level begin early in CKD disease progression in Stage 3 and Stage 4 and can get progressively worse as kidney function declines. Stage 5 CKD patients (also referred to as end stage renal disease or ESRD) usually under go regular dialysis to remove excess toxins and metabolites, including phosphorus, and yet also require treatment with phosphate-binding agents in an attempt to bind-up dietary phosphates and thereby prevent systemic absorption as a way to lower serum phosphorus to acceptable levels. In the U.S., approximately 90% of dialysis patients are treated with a phosphate control product.

[0006] Elevated serum phosphorus has been linked to the development and progression of hyperparathyroidism, bone disease such as osteodystropy and soft tissue mineralization and is associated with an increased risk of death in hemodialysis patients (Block et al., 1998, AmJ. Kidney Dis, 31:607-617; Block et al., 2000, Am J. Kidney Dis, 35:1226-1237; Palmer et al., 2011, JAMA, 305:1119-1127). Severe hyperphosphatemia (serum phosphate level > 6.5 mg/dL (>2.10 mmol/L)) has been associated directly with increased overall and cardiovascular mortality in hemodialysis (HD) patients (Palmer et al., 2011, JAMA, 305:1119-1127), and even moderate hyperphosphatemia (3.0 to 5.0 mg/dL) is associated with increased cardiovascular risk in these patients. Currently, clinical guidelines recommend maintaining phosphate levels within normal range (3.0 to 5.0 mg/dL (0.97 to 1.61 mmol/L)). However, even moderate to severe hyperphosphatemia (phosphate, 5.01 to 6.5 mg/dL (1.62 to 2.10 mmol/L)) needs to be addressed since it is an independent mortality risk factor in HD patients, and phosphate binders therapy alone do not always reduce serum phosphorus levels sufficiently.

[0007] Hyperphosphatemia also leads to secondary hyperparathyroidism (SHPT) and elevated blood levels of PTH by: (a) lowering the levels of ionized calcium; (b) interfering with the production of 1,25(OH)2D3; and (c) by directly affecting PTH secretion. These processes lead to high-turnover bone disease and other adverse consequences of excess PTH.

[0008] Current clinical guidelines recommend maintaining phosphate levels within normal range (3.0 to 5.0 mg/dL (0.97 to 1.61 mmol/L)). It is generally accepted that control of serum phosphorus will lead to improved clinical outcomes and survival in hemodialysis patients. Approaches to lowering serum phosphorus include dialysis, dietary phosphorus restriction and oral phosphate binders.

[0009] Serum phosphate declines rapidly in the first 1-2 hours of dialysis and then a plateau is reached during which serum phosphate remains relatively constant. After dialysis, serum phosphorus concentration rises quickly in the first few hours, typically reaching a concentration approximating the pre-dialysis value 6-8 hours later (Haas et al., 1991, Nephrol Dial Transplant, 2:108-113; Sugisaki et al., 1983 Trans Am Soc Artif Intern Organs, 29:38-43). This phenomenon

has been referred to as "phosphate rebound." In some cases, phosphate rebound produces higher phosphate levels than were initially present.

[0010] The control of phosphorus often remains unsatisfactory in dialyzed patients. Accordingly, there is a continuing need for methods for treating hyperphosphatemia in hemodialysis patients. In particular, methods for reducing phosphate rebound are desired.

BRIEF SUMMARY

[0011] The invention is defined in the claims.

[0012] In one aspect, a method is disclosed for treatment of hyperphosphatemia in hemodialysis patients.

[0013] In another aspect, a method is disclosed for reducing phosphate rebound in hemodialysis patients.

[0014] A treatment method comprises administering to a patient receiving hemodialysis a compound comprising the formula X_1 - X_2 - X_3 - X_4 - X_5- X_6 - X_7 wherein X_1 is a subunit comprising a thiol-containing group; X_5 is a cationic subunit; X_6 is a non-cationic subunit; X_7 is a cationic a subunit; and at least two of X_2, X_3 and X_4 are independently a cationic subunit. The compound is administered within 3 hours, after hemodialysis or within 15 minutes, before completion of a hemodialysis session, and wherein the administration is effective to maintain a post-hemodialysis serum phosphorus level that is lower than a pre-hemodialysis serum phosphorus level for a period of 6 hours after completion of dialysis.

[0015] The compound is administered within a period beginning 15 minutes prior to completion of hemodialysis and ending 3 hours after completion of hemodialysis, and wherein said administering is effective to maintain a post-hemodialysis serum phosphorus level that is lower than a pre-hemodialysis serum phosphorus level for a period of at least 6 hours after completion of dialysis

[0016] The agonist is Ac-c(C)arrrar-NH_2 (SEQ ID NO:3).

[0017] Preferably the agonist is a pharmaceutically acceptable salt of SEQ ID NO:3.

[0018] Preferably the agonist is a hydrochloride salt of SEQ ID NO:3.

[0019] In one option the agonist is administered within about 1 hour after dialysis or within about 30 minutes after dialysis. In a preferred option the agonist is administered during the rinse back procedure at the end of dialysis.

[0020] The patient has been diagnosed with chronic kidney disease and receives a treatment as described herein.

[0021] In other options the patient is being treated with a drug that binds phosphate prior to and/or at the time of being treated as described herein.

[0022] In yet other options the patient has chronic kidney disease associated with diabetes. In still other options the patient has chronic kidney disease associated with hypertension that is being treated by dialysis and receives a treatment as described herein. In other embodiments, the patient is being treated via dialysis for secondary hyperparathyroidism or primary hyperparathyroidism and receives a treatment as described herein.

[0023] In yet another aspect, a method is disclosed the method comprising administering to a patient undergoing hemodialysis a calcium sensing receptor agonist, wherein the agonist is administered within about 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours after conclusion of hemodialysis or within about 3 hours, 2 hours, 1 hour, 45 minutes, 30 minutes, 20 minutes, 15 minutes, 10 minutes, 5 minutes before completion of hemodialysis, and wherein the administering is effective to maintain a post-hemodialysis serum phosphorus level that is lower than a pre-hemodialysis serum phosphorus level for a period of at least about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 24 hours, 48 hours, 72 hours or the time until the next hemodialysis is commenced. In a preferred embodiment, the agonist is administered during the rinse back procedure at the end of dialysis.

[0024] In one option of this aspect, the calcium sensing receptor agonist is not a compound of the form X_1 - X_2 - X_3 - X_4 - X_5- X_6 - X_7 wherein X_1 is a subunit comprising a thiol-containing group; X_5 is a cationic subunit; X_6 is a non-cationic subunit; X_7 is a cationic a subunit; and at least two of X_2, X_3 and X_4 are independently a cationic subunit.

[0025] In one option the calcium sensing receptor agonist is a calcimimetic. In other options the calcimimetic is cinacalcet hydrochloride ($C_{22}H_{22}F_3N$•HCl).

[0026] In still another aspect, a method for treating hyperphosphatemia in a patient who receives at least on a periodic basis hemodialysis is disclosed The method comprises administering to the patient an effective amount of a calcium sensing receptor (CaSR) agonist, wherein the agonist is administered within about 18 hours after conclusion of hemodialysis or less than about 3 hours before completion of hemodialysis, and wherein the administering is effective to maintain a post-hemodialysis serum phosphorus level that is lower than a pre-hemodialysis serum phosphorus level for a period of at least about 6 hours.

[0027] In one option the agonist is administered less than 30 minutes before completion of dialysis.

[0028] In one option the agonist is cinacalcet hydrochloride. In another option the agonist is a compound of the form X_1 - X_2 - X_3 - X_4 - X_5- X_6 - X_7 wherein X_1 is a subunit comprising a thiol-containing group; X_5 is a cationic subunit; X_6 is a non-cationic subunit; X_7 is a cationic a subunit; and at least two of X_2, X_3 and X_4 are independently a cationic subunit.

[0029] In one option the agonist is Ac-c(C)arrrar-NH_2 (SEQ ID NO:3) or a salt thereof.

[0030] In other aspects, a method for regulating serum phosphorus concentration in a patient receiving at least on a periodic basis hemodialysis is disclosed The method comprises administering to the patient an effective amount of a calcium sensing receptor (CaSR) agonist, wherein the agonist is administered within about 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours after conclusion of hemodialysis or less than about 3 hours, 2 hours, 1 hour, 45 minutes, 30 minutes, 20 minutes, 15 minutes, 10 minutes, 5 minutes before completion of hemodialysis. In one option the administration is effective to maintain a post-hemodialysis serum phosphorus level that is lower than a pre-hemodialysis serum phosphorus level for a period of at least about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 24 hours ,48 hours, 72 hours, or the time until the next hemodialysis session is begun. In a preferred embodiment, the agonist is administered during the rinse back procedure at the end of dialysis.

[0031] After oral administration of cinacalcet hydrochloride, Cmax is achieved in approximately 2 to 6 hours. Accordingly, in another embodiment, the method comprises administering to the patient an effective amount of cinacalcet hydrochloride, wherein the cinacalcet hydrochloride is administered within about 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours after conclusion of hemodialysis or less than about 9 hours, 8 hours, 7 hours, 6 hours, 5 hours, 4 hours, 3 hours, 2 hours, 1 hour, 45 minutes, 30 minutes, 20 minutes, 15 minutes, 10 minutes, 5 minutes before completion of hemodialysis. In one embodiment, the administration is effective to maintain a post-hemodialysis serum phosphorus level that is lower than a pre-hemodialysis serum phosphorus level for a period of at least about 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 24 hours ,48 hours, 72 hours, or the time until the next hemodialysis session is begun.

[0032] In another aspect, a dosing regimen for administration of a compound for treating hyperparathyroidism in a patient undergoing hemodialysis is disclosed The dosing regimen comprises administering to the patient a calcium sensing receptor agonist, wherein the agonist is administered within about 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours after conclusion of hemodialysis or less than about 3 hours, 2 hours, 1 hour, 45 minutes, 30 minutes, 20 minutes, 15 minutes, 10 minutes, 5 minutes before completion of hemodialysis. In a preferred option the agonist is administered during the rinse back procedure at the end of dialysis. The regimen is effective to maintain a post-hemodialysis serum phosphorus level that is lower than a pre-hemodialysis serum phosphorus level for a period of at least about 6 hours.

[0033] In another aspect, a method for treating hyperphosphatemia in a subject that receives dialysis is disclosed wherein the subject is treated with a CaSR agonist compound as described herein. The treatment is effective to provide a post-dialysis serum phosphorus level that is less than a pre-dialysis serum phosphorus level for the duration of a period between dialysis sessions, i.e, the interdialytic period. In one option the post-dialysis serum phosphorus level is at least about 10%, 15%, 20% or 25% less than a pre-dialysis serum phosphorus level for the duration of the interdialytic period. The CaSR agonist compound is administered in accord with any of the treatment options described herein, for example, before completion of a dialysis session or within about 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, or 4 hours after a dialysis session.

[0034] In options of any of the aspects noted herein, the CaSR agonist can be a compound comprising the sequence carrrar (SEQ ID NO:2). In other options the CaSR agonist is a conjugate comprised of the peptide carrrar (SEQ ID NO:2), where the peptide is conjugated at its N-terminal residue to a Cys residue. In a preferred option the conjugate is Ac-c(C)arrrar-NH_2 (SEQ ID NO:3).

BRIEF DESCRIPTION OF THE DRAWINGS

[0035]

FIG. 1 is a graph showing the percent change in serum intact PTH levels following administration of SEQ ID NO:3 or placebo by intravenous injection shortly after dialysis. Placebo, closed circles; 5 mg SEQ ID NO:3, open circles; 10 mg SEQ ID NO:3, inverted open triangles; 20 mg SEQ ID NO:3, inverted closed triangles; 40 mg SEQ ID NO:3, closed squares; 60 mg SEQ ID NO:3, open squares.

FIG. 2 is a graph showing the percent change in serum phosphorus levels during the interdialytic interval (i.e., shortly after hemodialysis and the subsequent ~72 hours until the next time the subject underwent hemodialysis) following administration of SEQ ID NO:3 or placebo by injection after dialysis. Placebo, closed circles; 5 mg SEQ ID NO:3, open circles; 10 mg SEQ ID NO:3, inverted open triangles; 20 mg SEQ ID NO:3, inverted closed triangles; 40 mg SEQ ID NO:3, closed squares; 60 mg SEQ ID NO:3, open squares.

FIG. 3 is a graph showing the mean difference in serum phosphorus (mg/dL) (active v. placebo within cohort) for the 5 mg, 10 mg and 20 mg dose groups receiving SEQ ID NO: 3 (measured at discharge from the Phase 1 Unit).

[0036] The present subject matter may be understood more readily by reference to the following detailed description of the preferred embodiments and the examples included herein.

DETAILED DESCRIPTION

I. Definitions

[0037] Within this application, unless otherwise stated, definitions of the terms and illustration of the techniques of this application may be found in any of several well-known references such as: Sambrook, J., et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press (1989); Goeddel, D., ed., Gene Expression Technology, Methods in Enzymology, 185, Academic Press, San Diego, CA (1991); "Guide to Protein Purification" in Deutshcer, M.P., ed., Methods in Enzymology, Academic Press, San Diego, CA (1989); Innis, et al., PCR Protocols: A Guide to Methods and Applications, Academic Press, San Diego, CA (1990); Freshney, R.I., Culture of Animal Cells: A Manual of Basic Technique, 2nd Ed., Alan Liss, Inc. New York, NY (1987); Murray, E.J., ed., Gene Transfer and Expression Protocols, pp. 109-128, The Humana Press Inc., Clifton, NJ and Lewin, B., Genes VI, Oxford University Press, New York (1997).

[0038] As used herein, the singular form "a", "an", and "the" include plural references unless indicated otherwise. For example, "a" modulator peptide includes one of more modulator peptides.

[0039] As used herein, "amino acid" refers to natural and non-natural amino acids. The twenty naturally occurring amino acids (L-isomers) are designated by the three letter code with the prefix "L-" (except for glycine which is achiral) or by the one letter code in upper-case: alanine ("L-Ala" or "A"), arginine ("L-Arg" or "R"), asparagine ("L-Asn" or "N"), aspartic acid ("L-Asp" or "D"), cysteine ("L-Cys" or "C"), glutamine ("L-Gln" or "Q"), glutamic acid ("L-Glu" or "E"), glycine ("Gly" or "G"), histidine ("L-His" or "H"), isoleucine ("L-Ile" or "I"), leucine ("L-Leu" or "L"), lysine ("L-Lys" or "K"), methionine ("L-Met" or "M"), phenylalanine ("L-Phe" or "F"), proline ("L-Pro" or "P"), serine ("L-Ser" or "S"), threonine ("L-Thr" or "T"), tryptophan ("L-Trp" or "W"), tyrosine ("L-Tyr" or "Y") and valine ("L-Val" or "V"). L-norleucine and L-norvaline may be represented as (NLeu) and (NVal), respectively. The nineteen naturally occurring amino acids that are chiral have a corresponding D-isomer which is designated by the three letter code with the prefix "D-" or by the lower-case one letter code: alanine ("D-Ala" or "a"), arginine ("D-Arg" or "r"), asparagine ("D-Asn" or "a"), aspartic acid ("D-Asp" or "d"), cysteine ("D-Cys" or "c"), glutamine ("D-Gln" or "q"), glutamic acid ("D-Glu" or "e"), histidine ("D-His" or "h"), isoleucine ("D-Ile" or "i"), leucine ("D-Leu" or "l"), lysine ("D-Lys" or "k"), methionine ("D-Met" or "m"), phenylalanine ("D-Phe" or "f"), proline ("D-Pro" or "p"), serine ("D-Ser" or "s"), threonine ("D-Thr" or "t"), tryptophan ("D-Trp" or "w"), tyrosine ("D-Tyr" or "y") and valine ("D-Val" or "v"). D-norleucine and D-norvaline may be represented as (dNLeu) and (dNVal), respectively. Although "amino acid residue" is often used in reference to a monomeric subunit of a peptide, polypeptide or protein, and "amino acid" is often used in reference to a free molecule, usage of these terms in the art overlaps and varies. The term "amino acid" and "amino acid residue" are used interchangeably and may refer to a free molecule or a monomeric subunit of a peptide, polypeptide or protein, depending on context.

[0040] A "cationic amino acid" intends an amino acid residue that has a net positive charge at physiologic pH (7.4), as is the case, for example, in the amino acid residues where the side chain, or "R group", contains an amine functional group or other functional group that can accept a proton to become positively charged at physiologic pH, such as a guanidine or imidazole moiety. Cationic amino acid residues include arginine, lysine, histidine, 2,3-diaminopropionic acid (Dap), 2,4-diaminobutyric acid (Dab), ornithine, and homoarginine.

[0041] A "cationic subunit" intends a subunit that has a net positive charge at physiologic pH (7.4).

[0042] As used herein, "conservative amino acid substitutions" are substitutions which do not result in a significant change in the activity or tertiary structure of a selected polypeptide or protein. Such substitutions typically involve replacing a selected amino acid residue with a different amino acid residue having similar physico-chemical properties. Groupings of amino acids and amino acid residues by physico-chemical properties are known to those of skill in the art. For example, among the naturally-occurring amino acids, families of amino acid residues having similar side chains have been defined in the art, and include basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine).

[0043] As used herein, "chemical cross-linking" refers to covalent bonding of two or more molecules.

[0044] A peptide or peptide fragment is "derived from" a parent peptide or polypeptide if it has an amino acid sequence that is identical or homologous to at least a contiguous sequence of five amino acid residues, more preferably eight amino acid residues, of the parent peptide or polypeptide.

[0045] The compounds described herein may be in the form of pharmaceutically acceptable salts. Pharmaceutically acceptable salts include acid addition salts, such as hydrochloride, hydrobromide, sulfurate, nitrate, phosphorate, acetate, propionate, glycolate, pyruvate, oxalate, malate, malonate, succinate, maleate, fumarate, tartarate, citrate, benzoate, cinnamate, mandelate, methanesulfonate, ethanesulfonate, p-toluenesulfonate, salicylate and the like, and base addition salts, such as sodium, potassium, calcium, magnesium, lithium, aluminum, zinc, ammonium, ethylenediamine, arginine,

piperazine and the like.

[0046] As used herein, the term "hyperparathyroidism" refers to primary, secondary and tertiary hyperparathyroidism, unless otherwise indicated.

[0047] As used herein, an "isolated" or "purified" polypeptide or biologically active portion thereof is free of some of the cellular material when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of polypeptides in which the polypeptide is separated from some of the cellular components of the cells in which it is naturally or recombinantly produced. When the polypeptide or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture medium represents less than about 20%, more preferably less than about 10%, and most preferably less than about 5% of the volume of the polypeptide preparation. The language "substantially free of chemical precursors or other chemicals" includes preparations of polypeptides in which the polypeptide is separated from chemical precursors or other chemicals that are involved in the synthesis of the polypeptide. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of a polypeptide having less than about 30% (by dry weight) of chemical precursors or other chemicals, preferably less than about 20% chemical precursors or other chemicals, more preferably less than about 15% chemical precursors or other chemicals, still more preferably less than about 10% chemical precursors or other chemicals, and most preferably less than about 5% chemical precursors or other chemicals. In preferred embodiments, isolated polypeptides, or biologically active portions thereof, lack contaminating polypeptides from the same organism from which the domain polypeptide is derived.

[0048] A "non-cationic amino acid" intends an amino acid residue that has no charge or a net negative charge at physiologic pH (7.4), as is the case, for example, in the amino acid residues where the side chain, or "R group", is neutral (neutral polar and neutral non-polar) and acidic. Non-cationic amino acids include those residues with an R group that is a hydrocarbon alkyl or aromatic moiety (e.g., valine, alanine, leucine, isoleucine, phenylalanine); a neutral, polar R group (asparagine, cysteine, glutamine, serine, threonine, tryptophan, tyrosine); or a neutral, non-polar R group (glycine, methionine, proline, valine, isoleucine). Non-cationic amino acids with an acidic R group include asparatic acid and glutamic acid.

[0049] A "polymer" refers to a linear chain of two or more identical or non-identical subunits joined by covalent bonds.

[0050] As used herein, "peptide" and "polypeptide" refer to any polymer made up of a chain of amino acid residues linked by peptide bonds, regardless of its size. Although "protein" is often used in reference to relatively large polypeptides, and "peptide" is often used in reference to small polypeptides, usage of these terms in the art overlaps and varies. Thus, for simplicity, the term "peptide" will be used herein, although in some cases the art may refer to the same polymer as a "polypeptide." Unless otherwise indicated, the sequence for a peptide is given in the order from the amino terminus to the carboxyl terminus.

[0051] A "thiol-containing group" or "thiol-containing moiety" as used herein intends a functional group comprising a sulfur-hydrogen bond (-SH), and that is capable of reacting with another thiol under physiologic conditions to form a disulfide bond. A thiol that is capable of forming a disulfide bond with another thiol is referred to herein as a "reactive thiol." In a preferred embodiment the thiol-containing group is less than 6 atoms away from the backbone of the compound. In a more preferred embodiment, the thiol-containing group has the structure (-SH-CH_2-CH_2-C(O)-O-)-.

[0052] As used herein, "subject" refers to a human subject or an animal subject. Likewise, "patient" refers to a human patient or an animal patient.

[0053] A "subunit" intends a monomeric unit that is joined to more than one other monomeric unit to form a polymeric compound, where a subunit is the shortest repeating pattern of elements in the polymeric compound. Exemplary subunits are amino acids, which when linked form a polymer compound such as those referred to in the art as a peptide, a polypeptide or a protein.

[0054] As used herein, a "therapeutically effective amount" is an amount required to produce a desired therapeutic effect.

II. Methods of Treatment

[0055] In one aspect, a method for treatment of hyperphosphatemia in a subject in need thereof is provided. In other aspects, methods of modulating, regulating, and/or reducing serum phosphorus levels in a dialysis patient are provided. In other aspects, methods of improving the treatment of patients receiving at least periodic dialysis are provided. In another aspect, a method is provided for reducing and/or attenuating phosphate rebound in the subject undergoing dialysis. These aspects will now be described.

[0056] As described in Example 1, a study was conducted in support of the methods of treatment described herein, wherein subjects with end stage renal disease (ESRD) receiving hemodialysis were treated with a calcimimetic agent. The patients in the study were diagnosed with secondary hyperparathyroidism (SHPT), and required regular hemodialysis sessions. The exemplary agent selected for the study was a calcium sensing receptor agonist compound of the formula

described below, and having the sequence identified as SEQ ID NO:3. The compound was administered by intravenous injection immediately after hemodialysis at doses of 5, 10, 20, 40 or 60 mg to the patients after being randomized into treatment groups. For three days subsequent to treatment with the compound, blood concentrations of intact PTH and phosphorus were assessed. Results are shown in Figs. 1-2.

[0057] As seen in Fig. 1, following injection of SEQ ID NO:3 post dialysis, there is a rapid 60-80% decrease in the levels of intact PTH in the blood followed by a dose dependant return towards baseline over the following 48 hours. There is an associated small (10-16%) decrease in serum calcium. As seen in Fig. 2, serum phosphorus levels, which were decreased by dialysis, rose rapidly over the first 8 hours to a plateau and then increased more slowly during the remaining interdialytic interval. In placebo subjects (closed circles), mean serum phosphorus increased rapidly during the first ~36 hours post-dose after which phosphorus levels tended to plateau at 84% above baseline levels at discharge. Surprisingly, the rate of return to the plateau level of phosphorus was markedly modified by administration of SEQ ID NO:3. Doses of the agonist compound greater than about 5 mg (open circles) provided a marked attenuation or decreased in the rise of serum phosphorus after dialysis. At discharge, the mean percent increase from baseline in serum phosphorus in subjects receiving 20-60 mg of the agonist identified by SEQ ID NO:3 ranged from 23% to 60% and was at least ~24 percentage points lower than placebo.

[0058] This data shows that after completion of a hemodialysis session, serum phosphorus concentration rises quickly in the first few hours. That is, serum phosphorus rebounds following hemodialysis and returns to the pre-dialysis value within the first ~10 hours after completion of dialysis, and reaches a plateau ~80% above the post-dialysis baseline levels approximately 18 hours after completion of dialysis. Table 1 sets forth the mean baseline pre-treatment values for PTH and phosphorus in ESRD subjects shortly (within 2 hours) following hemodialysis but prior to administration ("pre-dose") with SEQ ID NO:3 or placebo by intravenous injection. The serum phosphorus levels in the ESRD subjects receiving placebo increases (rebounds) most quickly during the first 3-10 hours after completion of dialysis. Without wishing to be bound by theory, it is thought that the 80-100% rebound in serum phosphorus following dialysis could result from mobilization of phosphate from intracellular space and/or from bone or possibly by stimulation of phosphate absorption from the digestive tract in response to and perhaps induced by the removal of phosphate by dialysis.

Table1

Mean (SD)	5 mg (N=4)	10 mg (N=4)	20 mg (N=4)	40 mg (N=8)	60 mg (N=8)
iPTH (pg/mL)	450 (96)	632 (255)	1610 (1577)	911 (935)	821 (213)
Phosphorus (mg/dL)	3.15 (0.26)	3.28 (1.37)	3.92 (0.66)	3.02 (0.84)	3.74 (0.65)

[0059] It was found that if a CaSR agonist is administered to the patient within a certain time period in relation to the dialysis treatment, the phosphorus rebound can be reduced. As shown in FIG. 2, intravenous administration of a CaSR agonist (SEQ ID NO:3) at doses above 5 mg dramatically attenuated the post-dialysis rebound in serum phosphorus levels. Administration of a 10, 20, 40 or 60 mg dose of a CaSR agonist (e.g., SEQ ID NO:3) just before completion of or soon after dialysis displayed only a slight increase in phosphorus in the first 3-4 hours and dramatically attenuated or blunted the increase in serum phosphorus levels in the 4-18 hours following dialysis such that in the subsequent 18-72 hours of the post-dialytic period there was little to modest increase in serum phosphorus as measured by percent increase from post-dialysis baseline levels. Surprisingly, these data show that treatment of an ESRD patient with a CaSR agonist or a calcimimetic with the first 18 hours following dialysis dramatically attenuates or reduces the post-dialysis rebound in serum phosphorus concentration. These data reveal that much of the rebound in serum phosphorus occurs within the first 8-10 hours following dialysis and indicate, unexpectedly, that there is window during which administration of a CaSR agonist to an ESRD patient within the first 8-10 hours following dialysis can provide significant attenuation or blunting of the rebound of serum phosphorus.

[0060] Accordingly, in a first aspect, a patient receiving dialysis is treated with a CaSR agonist compound within about 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours, 4 hours after completion of the dialysis session, or about 3 hours, 2 hours, 1 hour, 45 minutes, 30 minutes, 20 minutes, 15 minutes, 10 minutes, 5 minutes before completion of the dialysis session. In a preferred option the CaSR agonist compound is administered during the rinse back procedure at the end of dialysis. As a skilled artisan understands, dialysis intends hemodialysis or peritoneal dialysis. A hemodialysis session is typically between 3-5 hours in length, and reference to a "dialysis session" or a "hemodialysis session" herein is with regard to a dialysis procedure of a duration T_D, wherein T_D can be 1 hour or more, 2 hours or more, 2.5 hours or more, 3 hours or more, 3.5 hours or more, 4 hours or more, 4.5 hours or more, 5 hours or more, or, in alternative embodiments from 1-10 hours, or 2-8 hours, or 2-6 hours, or 3-5 hours. T_D can be separated into a first portion and a second portion, where the first portion corresponds to the first half of the total time

duration T_D and the second portion corresponds to the second half of the total time duration T_D. In one embodiment, the agonist compound is administered to the dialysis patient in the second portion of the dialysis session of duration T_D. In another embodiment, T_D is separated into equal portions of three or four (thirds and quarters), and the agonist compound is administered to the dialysis patient in the latter third of the dialysis session of duration T_D or in the last quarter of the dialysis session of duration T_D. For example, in a dialysis session with a T_D of 3 hours, in one embodiment, the agonist is administered in the final hour of the dialysis session when T_D is divided into thirds, or in the final 45 minutes of the dialysis session when T_D is divided into fourths. In preferred options the agonist is administered 30 minutes, 20 minutes, 15 minutes, 10 minutes, 5 minutes or 1 minute before completion of a dialysis session of duration T_D.

[0061] In other options the agonist is administered to the hemodialysis patient immediately upon completion of a dialysis session of duration T_D, or at least within 18 hours, within 15 hours, within 10 hours, within 8 hours, within 5 hours, within 3 hours, within 2 hours, within 1 hour, within 30 minutes, within 20 minutes, within 10 minutes or within 5 minutes after completion of a dialysis session having a time duration T_D. In one option the CaSR agonist is administered to the subject less than 2 hours, less than 3 hours, less than 4 hours, less than 5 hours, less than 6 hours, less than 7 hours, less than 8 hours, less than 9 hours, less than 10 hours, less than 18 hours, or less than 20 hours after completion of the hemodialysis. In another option the compound is administered to the subject 30-60 minutes, 1-2 hours, 2-3 hours, 3-5 hours, 5-8 hours, 8-10 hours, 10-15 hours, 15-18 hours after dialysis.

[0062] In a preferred option the CaSR agonist is administered at the end of dialysis or as soon as practical after dialysis. In some options the CaSR agonist is administered during dialysis, or less than 3 hours, less than 2 hours, less than 1 hour, or less than 30 minutes, before the end of dialysis.

[0063] As shown in Fig. 3, intravenous administration of a CaSR agonist (SEQ ID NO:3) at doses of 10 mg and 20 mg or above can dramatically attenuate the post-dialysis increase or rebound in serum phosphorus level and this can translate into a mean reduction in serum phosphate of 0.5 mg/dL to 1 mg/dL or more following a single dose. It is contemplated that these effects can be further enhanced with chronic dosing of a CaSR agonist wherein the treatment is administered with each dialysis session (which typically occurs three times per week with hemodialysis) and the treatment is consistently administered during or shortly following dialysis to attenuate or blunt the post-dialysis rebound in serum phosphorus.

[0064] The patient's serum phosphorus increases by less than 10%, in the first 6 hours after dialysis.

[0065] In one option the patient has undergone or is undergoing hemodialysis and the patient's serum phosphorus increases by less than 10%, less than 20%, less than 30%, less than 40%, less than 50%, or less than 60% in the first 3 hours or 6 hours after administration of the CaSR agonist. In another option the patient has undergone or is undergoing hemodialysis and the patient's serum phosphorus increases by less than 10%, less than 20%, less than 30%, less than 40%, less than 50%, or less than 60% in the first 4 hours or 6 hours after administration of the CaSR agonist. In another option the patient has undergone or is undergoing hemodialysis and the patient's serum phosphorus increases by less than 10%, less than 20%, less than 30%, less than 40%, less than 50%, or less than 60% in the first 5 hours after administration of the CaSR agonist. In another option the patient has undergone or is undergoing hemodialysis and the patient's serum phosphorus increases by less than 10%, less than 20%, less than 30%, less than 40%, less than 50%, or less than 60% in the first 6 hours after administration of the CaSR agonist. In another option the patient has undergone or is undergoing hemodialysis and the patient's serum phosphorus increases by less than 10%, less than 20%, less than 30%, less than 40%, less than 50%, or less than 60% in the first 7 hours after administration of the CaSR agonist.

[0066] In one option the dose of CaSR agonist administered to the patient is about 10 mg to about 20 mg, about 10 mg to about 30 mg, about 20 mg to about 30 mg, about 20 mg to about 40 mg, about 30 mg to about 50 mg, about 40 mg to about 60 mg, or about 50 mg to about 80 mg. In another option the dose of the CaSR agonist administered to the patient is about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, or about 80 mg.

[0067] In one option the dose of CaSR agonist administered to the patient is between 10-20 mg, 10-30 mg, 20-30 mg, 20-40 mg, 30-50 mg, or 40-60 mg. In another option the dose of the CaSR agonist administered to the hemodialysis patient is less than 10 mg, less than 20 mg, less than 30 mg, less than 40 mg, less than 50 mg, less than 60 mg, less than 70 mg, or less than 80 mg.

[0068] In one option the patient is being treated with a phosphate binding agent. However, in another option the patient is not being treated with a phosphate binding agent.

[0069] In one option conventional hemodialysis treatment alone is insufficient to control the patient's serum phosphorus levels.

[0070] In one ption conventional hemodialysis treatment combined with administration of phosphate binders is insufficient to control the patient's serum phosphorus levels.

[0071] In one option conventional hemodialysis treatment combined with dietary restrictions is insufficient to control

the patient's serum phosphorus levels.

[0072] In one option conventional hemodialysis treatment combined with phosphate binders and dietary restrictions is insufficient to control the patient's serum phosphorus levels.

[0073] In one option the patient is also taking vitamin D or a vitamin D analog.

[0074] Other causes of hyperphosphatemia include increased exogenous phosphorus load or absorption resulting from phosphorus-rich cow's milk in premature neonates, intravenous phosphorus supplements, white phosphorus burns, PO^3_4-containing enemas or acute phosphorus poisoning. Hyperphosphatemia may result from increased endogenous loads due to tumor lysis syndrome, rhabdomyolysis, bowel infarction, malignant hyperthermia, heat stroke, acid-base disorders, organic acidosis, lactic acidosis, ketoacidosis, respiratory acidosis, or chronic respiratory alkalosis. Hyperphosphatemia may be caused by reduced urinary excretion resulting from renal failure, hypoparathyroidism, pseudohypoparathyroidism, Vitamin D intoxication, growth hormone, insulin-like growth factor-1, glucocorticoid withdrawal, Mg^{2+} deficiency, tumoral calcinosis, diphosphonate therapy or hypophosphatasia. It is understood that methods of administration disclosed herein may be useful for treatment of subjects diagnosed with hyperphosphatemia resulting from any one or more of the above causes.

[0075] Methods for treatment as disclosed herein are useful to treat a variety of patient populations. For example, a method is provided for treating hemodialysis patients with concomitant hyperphosphatemia, for treating patients for whom conventional hemodialysis treatment alone is insufficient to control serum phosphate levels. In an alternative aspect, a method is provided for treating hemodialysis patients who are on a phosphorus restricted diet. Also provided is a method for treating hemodialysis patients who are being administered phosphate binders and/or who are taking vitamin D and experiencing a concomitant increase in serum phosphorus.

[0076] In any of the aspects described herein, any one or more of the CaSR agonists is contemplated to be individually excepted or removed from the scope of compounds disclosed herein to be administered. In certain options the peptides identified by any one or more of SEQ ID NOs: 162-182, individually or in any combination, are excluded from the methods.

[0077] For example, in one aspect, a method for treating a dialysis patient with, for example, SHPT or CKD or ESRD, is provided, wherein a CaSR agonist is administered within about 18 hours after conclusion of dialysis (preferably hemodialysis), or within about 6 hours, 4 hours, 3, hours, 2 hours, 1 hour, 30 minutes, 20 minutes, 10 minutes, or 9, 8, 7, 6, 5, 4, 3, 2, or 1 minute after conclusion of dialysis (preferably hemodialysis). Administration of the CaSR in this fashion is effective to maintain a post-dialysis serum phosphorus level that is lower than a pre-dialysis serum phosphorus level for a period of at least 6 hours, more preferably for a period of 24 hours, still more preferably for a period of 36, 48, 60 or 72 hours. In one option the post-dialysis serum phosphorus level remains lower than a pre-dialysis serum phosphorus level of the patient for the duration of the between dialysis sessions (also referred to as an interdialytic period). In one option of this method, the CaSR agonist is not a compound of the form X_1 - X_2 - X_3 - X_4 - X_5 - X_6 - X_7, wherein the X subunits are as defined herein.

[0078] In another aspect, a method for treating hyperphosphatemia in a subject that receives dialysis is provided, wherein the subject is treated with a CaSR agonist compound as described herein. The treatment is effective to provide a post-dialysis serum phosphorus level that is less than a pre-dialysis serum phosphorus level for the duration of the interdialytic period. In one option the post-dialysis serum phosphorus level is at least about 10% or 25% less than a pre-dialysis serum phosphorus level for the duration of the interdialytic period. The CaSR agonist compound is administered in accord with any of the treatments described herein, for example, before completion of a dialysis session or within about 2, 4, 6, 10, or 18 hours after a dialysis session.

III. Calcium Sensing Receptor Agonist Compounds and Compositions

[0079] The methods described herein comprise administration of a CaSR agonist to a subject. Such agonists are described in U.S. Patent Nos. 6,011,068 and 6,031,003 and U.S. Patent Publication Nos. 2011/0028394 and 2009/0023652.

[0080] It has been unexpectedly found that administration of these compounds to subjects suffering from CKD and in need of dialysis results in an inhibition or reduction of the accumulation of serum phosphorus after dialysis.

[0081] In one option the method comprises administering a CaSR agonist to the patient. In one option the CaSR agonist is a calcimimetic. In another option the CaSR agonist is an allosteric agonist. In another option the CaSR agonist is cinacalcet hydrochloride. In another option the CaSR agonist is a compound comprising the formula:

$$X_1 - X_2 - X_3 - X_4 - X_5 - X_6 - X_7$$

wherein X_1 is a subunit comprising a thiol-containing group; X_5 is a cationic subunit; X_6 is a non-cationic subunit; X_7 is a cationic a subunit; and at least two of X_2, X_3 and X_4 are independently a cationic subunit.

[0082] In one option the CaSR agonist is a compound comprising the sequence carrrar (SEQ ID NO:2). In another option the CaSR agonist is a conjugate

comprised of the peptide carrrar (SEQ ID NO:2), where the peptide is conjugated at its N-terminal residue to a Cys residue. In a preferred option the conjugate is Ac-c(C)arrrar-NH_2 (SEQ ID NO:3). Although the invention may be described in terms of certain preferred embodiments, such as SEQ ID NO:3, it will be within the understanding of one of skill in the art that the disclosure also applies to other CaSR agonists, including the compounds and conjugates described in U.S. Patent Nos. 6,011,068 and 6,031,003 and U.S. Patent Publication Nos. 2011/0028394 and 2009/0023652. Likewise, although the invention may be described in terms of certain preferred options such as hemodialysis (claimed), it will be within the
understanding of one of skill in the art that the disclosure also applies to other forms of dialysis, such as peritoneal dialysis, and other approaches, such as quotidian hemodialysis.

[0083] In one option the CaSR agonist is administered as a composition of the CaSR agonist compound and a pharmaceutically acceptable excipient. The excipient in some options is a buffer or saline, such that the composition is in solution form when administered to the patient. In one option the agonist compound is provided as a lyophilized product that is reconstituted into a solution or suspension for administration in accord with the methods described herein. In one option the lyophilized product is a salt form of the agonist product, such as cinacalet hydrochloride or a hydrochloride salt form of a peptide of the form SEQ ID NO:3.

Peptide Compounds and Structure-Activity Relationships

[0084] Several compounds were synthesized for testing their effects on decreasing serum phosphorus and on hyperphosphatemia. These compounds are listed in Table 2 below. In Table 1, and throughout the specification, residues provided in capital letters are L-amino acids, while lower case letters indicate D-amino acids. "Ac" indicates an acetyl capping group, "NH_2" indicates an amide capping group, "Ac-bAla" is an acetylated beta-alanine, "GSH" indicates reduced glutathione, "GS" indicates oxidized glutathione, "PEG" refers to polyethylene glycol, "PEG2" and "PEG5" refer to polyethylene glycol moieties of 2kDa and 5kDa, respectively, and "Mpa" refers to mercaptopropionic acid. A group bracketed by parentheses indicates that group or moiety is attached to the side-chain of the preceding subunit or amino acid residue.

Table 2

SEQ ID NO	Compound Structure
SEQ ID NO:1	XXXXXXX
SEQ ID NO:2	carrrar
SEQ ID NO:3	Ac-c(C)arrrar-NH_2
SEQ ID NO:4	Ac-crrrr-NH_2
SEQ ID NO:5	Ac-crrrrr-NH_2
SEQ ID NO:6	Ac-crrrrrr-NH_2
SEQ ID NO:7	Ac-crrrrrrr-NH_2
SEQ ID NO:8	Ac-carrrrr-NH_2
SEQ ID NO:9	Ac-crarrrr-NH_2
SEQ ID NO:10	Ac-crrarrr-NH_2
SEQ ID NO:11	Ac-crrrarr-NH_2
SEQ ID NO:12	Ac-crrrrar-NH_2
SEQ ID NO:13	Ac-crrrrra-NH_2
SEQ ID NO:14	Ac-crrarra-NH_2
SEQ ID NO:15	Ac-cararrr-NH_2
SEQ ID NO:16	Ac-carrarr-NH_2
SEQ ID NO:17	Ac-crraarr-NH_2
SEQ ID NO:18	Ac-crararr-NH_2
SEQ ID NO:19	Ac-carrrra-NH_2

(continued)

SEQ ID NO	Compound Structure
SEQ ID NO:20	Ac-crarrra-NH_2
SEQ ID NO:21	Ac-crrraar-NH_2
SEQ ID NO:22	Ac-caarrrr-NH_2
SEQ ID NO:23	Ac-crarrar-NH_2
SEQ ID NO:24	Ac-craarrr-NH_2
SEQ ID NO:25	Ac-crrarar-NH_2
SEQ ID NO:26	Ac-carrrar-NH_2
SEQ ID NO:27	Ac-c(C)arrrar-NH_2
SEQ ID NO:28	Ac-c(C)rrarar-NH_2
SEQ ID NO:29	Ac-arrrar-NH_2
SEQ ID NO:30	Ac-bAla-crrrrrr-NH_2
SEQ ID NO:31	Mpa-rrrrrr-NH_2
SEQ ID NO:32	Ac-dHcy-rrrrrr-NH_2
SEX ID NO:33	Ac-dPen-rrrrrr-NH_2
SEQ ID NO:34	Ac-C(C)arrrar-NH_2
SEQ ID NO:35	Ac-c(C)Arrrar-NH_2
SEQ ID NO:36	Ac-c(C)aRrrar-NH_2
SEQ ID NO:37	Ac-c(C)arRrar-NH_2
SEQ ID NO:38	Ac-c(C)arrRar-NH_2
SEQ ID NO:39	Ac-c(C)arrrAr-NH_2
SEQ ID NO:40	Ac-c(C)arrraR-NH_2
SEQ ID NO:41	Ac-crrrrrrrr-NH_2
SEQ ID NO:42	Ac-cGrrrGr-NH_2
SEQ ID NO:43	Ac-cArrrAr-NH_2
SEQ ID NO:44	Ac-CaRrRaR-NH_2
SEQ ID NO:45	CHDAPIGYD
SEQ ID NO:46	CPDYHDAGI
SEQ ID NO:47	Ac-CYGRKKRRQRRR-NH_2
(SEQ ID NO:45) (SEQ ID NO:47)	CHDAPIGYD | Ac-CYGRKKRRQRRR-NH_2
SEQ ID NO:46 SEQ ID NO:47	CPDYHDAGI | Ac-CYGRKKRRQRRR-NH_2
SEQ ID NO:48	Ac-YGRKKRRQRRR-NH_2
SEQ ID NO:49	Ac-caraarrr-NH_2

(continued)

SEQ ID NO	Compound Structure
SEQ ID NO:50	Ac-cygrkkrrqrrr-NH_2
SEQ ID NO:51	H_2N-crrrrrr-NH_2
SEQ ID NO:51 | SEQ ID NO:51	H_2N-crrrrrr-NH_2 | H_2N-crrrrrr-NH_2
SEQ ID NO:52	Ac-carrrar-NH_2
SEQ ID NO:52 | SEQ ID NO:52	Ac-carrrar-NH_2 | Ac-carrrar-NH_2
SEQ ID NO:53	Ac-c(GS)rrrrrr-NH_2
SEQ ID NO:54	GS-crrrrrr
SEQ ID NO:55	Ac-c(Ac-C)arrrar-NH_2
SEQ ID NO:56	Ac-c(Mpa)arrrar-NH_2
SEQ ID NO:57	Ac-c(PEG2-C)arrrar-NH_2
SEQ ID NO:58	Ac-c(PEG5-C)rrrrrr-NH_2
SEQ ID NO:59	Ac-c(PEG2-C)rrrrrr-NH_2
SEQ ID NO:60	c(C)arrrar-NH_2
SEQ ID NO:61	Ac-bAla-c(C)arrrar-NH_2
SEQ ID NO:62	bAla-c(C)arrrar
SEQ ID NO:63	Ac-cGrrrGr
SEQ ID NO:64	Ac-cArrrAr
SEQ ID NO:65	Ac-cvrrrvr-NH_2
SEQ ID NO:66	Ac-cvrrrvr
SEQ ID NO:67	Ac-Crrrrrr-NH_2
SEQ ID NO:68	Ac-carrrer-NH_2
SEQ ID NO:69	Ac-cerrrar-NH_2
SEQ ID NO:70	Ac-carrrak-NH_2
SEQ ID NO:71	Ac-qrrrar- NH_2
SEQ ID NO:72	Ac-cakrrar-NH_2
SEQ ID NO:73	Ac-carkrar-NH_2
SEQ ID NO:74	Ac-carrrar-OH
SEQ ID NO:75	Ac-CARRRAR-NH_2
SEQ ID NO:76	Ac-caarrrrrr-NH_2
SEQ ID NO:77	Ac-caaarrrrrr-NH_2
SEQ ID NO:78	Ac-carararar-NH_2
SEQ ID NO:79	Ac-carrrarar-NH_2

(continued)

SEQ ID NO	Compound Structure
SEQ ID NO:80	crrrrrr-NH_2
SEQ ID NO:32	Ac-dHcy rrrrrr-NH_2
SEQ ID NO:81	Ac-c(Benzoyl)rrrrrr-NH_2
SEQ ID NO:82	Ac-c(acetyl)rrrrrr-NH_2
SEQ ID NO:83	Ac-carrrfr-NH_2
SEQ ID NO:84	Ac-carrrir-NH_2
SEQ ID NO:85	Ac-carrrlr-NH_2
SEQ ID NO:68	Ac-carrrer-NH_2
(SEQ ID NO:87	Ac-carrrvr-NH_2
SEQ ID NO:88	Ac-carrrpr-NH_2
SEQ ID NO:89	Ac-carrrhr-NH_2
SEQ ID NO:90	Ac-carrrqr-NH_2
SEQ ID NO:91	Ac-carrrtr-NH_2
SEQ ID NO:92	Ac-carrrsr-NH_2
SEQ ID NO:93	Ac-carrrGr-NH_2
SEQ ID NO:94	Ac-cerrrar-NH_2
SEQ ID NO:95	Ac-cGrrrar-NH_2
SEQ ID NO:96	Ac-cirrrar-NH_2
SEQ ID NO:97	Ac-cprrrar-NH_2
SEQ ID NO:98	Ac-clrrrar-NH_2
SEQ ID NO:99	Ac-cqrrrar-NH_2
SEQ ID NO:100	Ac-ctrrrar-NH_2
SEQ ID NO:101	Ac-cvrrrar-NH_2
SEQ ID NO:102	Ac-csrrrar-NH_2
SEQ ID NO:103	Ac-chrrrar-NH_2
SEQ ID NO:104	Ac-cfrrrar-NH_2
SEQ ID NO:105	Ac-crrGrar-NH_2
SEQ ID NO:106	Ac-crrprar-NH_2
SEQ ID NO:107	Ac-crrerar-NH_2
SEQ ID NO:108	Ac-crrtrar-NH_2
SEQ ID NO:109	Ac-crrhrar-NH_2
SEQ ID NO:110	Ac-crrfrar-NH_2
SEQ ID NO:111	Ac-crrsrar-NH_2
SEQ ID NO:112	Ac-crrqrar-NH_2
SEQ ID NO:113	Ac-crrvrar-NH_2
SEQ ID NO:114	Ac-crrlrar-NH_2
SEQ ID NO:115	Ac-crrirar-NH_2
SEQ ID NO:116	Ac-crr-Sar-rar-NH_2

(continued)

SEQ ID NO	Compound Structure
SEQ ID NO:117	Ac-carrr-Sar-r-NH_2
SEQ ID NO:118	Ac-c-Nma-rrr-Nma-r-NH_2
SEQ ID NO:119	Ac-crrar-Nma-r-NH_2
SEQ ID NO:120	Ac-c-Aib-rrr-Aib-r-NH_2
SEQ ID NO:121	Ac-crr-Nma-rar-NH_2
SEQ ID NO:122	Ac-carrr-Nma-r-NH_2
SEQ ID NO:123	Ac-c-Aib-rrrar-NH_2
SEQ ID NO:124	Ac-carrr-Aib-r-NH_2
SEQ ID NO:125	Ac-c-Sar-rrr-Sar-r-NH_2
SEQ ID NO:126	Ac-crrar-Sar-r-NH_2
SEQ ID NO:127	Ac-c-Nma-rrrar-NH_2
SEQ ID NO:128	Ac-c-Sar-rrrar-NH_2
SEQ ID NO:129	Ac-carrr-Nle-r-NH_2
SEQ ID NO:130	Ac-c-dNle-rrr-dNle-r-N H_2
SEQ ID NO:131	Ac-carrr-dNva-r-NH_2
SEQ ID NO:132	Ac-c-dNva-rrr-dNva-r-NH_2
SEQ ID NO:133	Ac-crrar-dNle-r-NH_2
SEQ ID NO:134	Ac-c-dNle-rrrar-NH_2
SEQ ID NO:135	Ac-crrar-dNva-r-NH_2
SEQ ID NO:136	Ac-c-dNva-rrrar-NH_2
SEQ ID NO:137	Ac-crr-dNva-rar-NH_2
SEQ ID NO:138	Ac-crr-dNle-rar-NH_2
SEQ ID NO:139	Ac-c(dHcy)arrrar-NH_2
SEQ ID NO:140	Ac-c(Mpa)arrrar-NH_2
SEQ ID NO:141	Ac-c(Ac-C)arrrar-NH_2
SEQ ID NO:142	Ac-c(c)arrrar-NH_2
SEQ ID NO:143***	Ac-c(C-PEG20)rrrrrr-NH_2
SEQ ID NO:144****	Ac-c(C-PEG40)rrrrrr-NH_2
SEQ ID NO:145	CEEEEEE
SEQ ID NO:145 | SEQ ID NO:6	CEEEEEE | Ac-crrrrrr-NH_2
SEQ ID NO:145 | SEQ ID NO:26	CEEEEEE | Ac-carrrar-NH_2

(continued)

SEQ ID NO	Compound Structure
SEQ ID NO:25 | SEQ ID NO:25	Ac-crrarar-NH_2 | Ac-crrarar-NH_2
SEQ ID NO:26 | SEQ ID NO:26	Ac-carrrar-NH_2 | Ac-carrrar-NH_2
SEQ ID NO:146	Ac-crrrraa-NH_2
SEQ ID NO:147	Ac-cakkkak-NH_2
SEQ ID NO:148	Ac-cararar-NH_2
SEQ ID NO:149	Ac-crrarGr-NH_2
SEQ ID NO:150	Ac-crrarqr-NH_2
SQ ID NO:151	Ac-crrarhr-NH_2
SEQ ID NO:152	Ac-crrarir-NH_2
SEQ ID NO:153	Ac-ca(DAP)rrar-NH_2
SEQ ID NO:154	Ac-ca(dHar)(dHar)(dHar)ar-NH_2
SEQ ID NO:162	HDAPIGYD
SEQ ID NO:163	CHDAPIGYD
SEQ ID NO:164	YGRKKRRQRRR
SEQ ID NO:165	CYGRKKRRQRRR
SEQ ID NO:166	CSFNSYELGSL
SEQ ID NO:167	CPDYHDAGI
SEQ ID NO:168	CEAVSLKPT
SEQ ID NO:169	ESVSLKPT
SEQ ID NO:170	CRFARKGALRQKNV
SEQ ID NO:171	YGRKKR
SEQ ID NO:172	CYGRKKR
SEQ ID NO:173	YGRRARRRARR
SEQ ID NO:174	CYGRRARRRARR
SEQ ID NO:175	CRRR
SEQ ID NO:176	CRRRR
SEQ ID NO:177	CRRRRRRR
SEQ ID NO:178	CRRRRRRRR
SEQ ID NO:179	CRRRRRRRRR
SEQ ID NO:180	CRRRRRRRRRR
SEQ ID NO:181	CRRRRRRRRRRR

(continued)

SEQ ID NO	Compound Structure
SEQ ID NO:182	CRRRRRRRRRRR
*Bolded font showing in parenthesis indicates respective thiol-containing conjugating groups. GS = oxidized glutathione; dHcy = D-homocysteine; Mpa = Mercaptopropionic acid; PEG = polyethylene glycol.	

[0085] These compounds include (i) Ac-crrrr-NH_2 (SEQ ID NO:4), (ii) Ac-crrrrr-NH_2 (SEQ ID NO:5), (iii) Ac-crrrrrr-NH_2 (SEQ ID NO:6), and (iv) Ac-crrrrrrr-NH_2 (SEQ ID NO:7). In previous studies, the compounds identified as SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:7 were each administered by a 30-minute IV infusion to 1 K1 C model animals and effected a reduction in plasma PTH levels as a percent of the predosing (baseline) level. All four compounds dosed at 3 mg/kg produced a significant drop in plasma PTH, but differences in the potency and duration of PTH reduction suggest a relationship between the net positive charge and PTH-lowering activity. For example, the compound Ac-crrrrrr-NH_2 (SEQ ID NO:6) with six cationic (arginine) subunits had increased efficacy as well as the duration of action compared to the compounds Ac-crrrr-NH_2 (SEQ ID NO:4) and Ac-crrrrr-NH_2 (SEQ ID NO:5), containing four and five cationic (arginine) subunits, respectively. Surprisingly, the compound Accrrrrrr-NH_2 (SEQ ID NO:6) with six cationic (arginine) subunits had increased duration of action compared to the compound Ac-crrrrrrr-NH_2 (SEQ ID NO:7) with seven cationic (arginine) residues, suggesting that activity or potency of the compounds does not correlate merely with increasing cationic charge of the compound. That is, the compound Ac-crrrrrrr-NH_2 (SEQ ID NO:7) with seven cationic subunits (arginine residues) produced a similar initial drop in PTH as the compounds with fewer cationic residues, but over the 24 hours following dosing was less efficacious than Ac-crrrrrr-NH_2 (SEQ ID NO:6) and Ac-crrrrr-NH_2 (SEQ ID NO:5). These latter two compounds produced a mean PTH reduction of ~40% and 60% at the 24 hour time point, respectively. It should be noted that the compounds in this study were administered at the same mg/kg dose but, due to differences in molecular weight, a different number of moles of each compound was actually dosed. Therefore, Ac-crrrrrr-NH_2 (SEQ ID NO:6) was significantly more potent than Ac-crrrr-NH_2 (SEQ ID NO:4) and Ac-crrrrr-NH_2 (SEQ ID NO:5) on a per mole basis.

[0086] Further studies were done to explore the structure-activity relationship of the compounds. The compound Ac-crrrrrr-NH_2 (SEQ ID NO:6) was modified by sequential replacement of an arginine residue with an alanine residue at each of the subunit positions X_2-X_7. The compounds were characterized in an in vitro human calcium-sensing receptor (CaSR) assay, wherein HEK 293 cells that express the human calcium-sensing receptor were used to measure activity of exemplary compounds.

[0087] The compounds Ac-crrrrrr-NH_2 (SEQ ID NO:6), Ac-carrrrr-NH_2 (SEQ ID NO:8) and Ac-crrarrr-NH_2 (SEQ ID NO:10) were quite potent, as evidenced by the decrease in percent PTH to below the detection limit or essentially zero as measured in vivo after a single IV administration in normal rats. Substitution of the cationic (arginine) residue at positions 2, 3, 4 or 7 of Ac-crrrrrr-NH_2 (SEQ ID NO:6) resulted in an approximately twofold loss in in vitro potency. The substitution at position 5 to produce the compound Accrrrarr-NH_2 (SEQ ID NO:11) produced a 5-10 fold reduction in in vitro potency, although the in vivo percent PTH AUC reduction of 45% could be sufficiently active for clinical therapy. Surprisingly, the substitution of the cationic arginine residue at position 6 with the uncharged (alanine) residue actually improved potency. The data illustrate that cationic and uncharged residues at different positions are not all equal and there are changes in activity as a result of change in the compound structure.

[0088] To further evaluate the effect of change in activity as a function of change in compound structure, another series of analogs of Ac-crrrrrr-NH_2 (SEQ ID NO:6) was generated containing double amino acid substitutions, where two cationic (arginine) residues were replaced by uncharged (alanine) residues, and tested for potency. Unexpectedly, this suggests that position of charges as well as total cationic charge can influence potency of the compounds for reduction of PTH. The data suggest that the cationic residues of SEQ ID NO:6 are essential at positions 5 and 7 but is not required at position 6, for PTH-lowering activity.

[0089] Further structure-activity relationship studies were conducted using the in vitro cell assay in HEK 293 cells that express the human calcium-sensing receptor. The ability of the peptides Ac-carrrar-NH_2 (SEQ ID NO:26) and Ac-arrrar-NH_2 (SEQ ID NO:29) to activate the human CaSR was ascertained by the measuring accumulation of inositol monophosphate (IP_1), which is reflective of IP_3 production. Absence of the N-terminal D-cysteine residue from SEQ ID NO:29 dramatically reduced the ability of the compound to activate the CaSR as compared to SEQ ID NO:26. That is, elimination of the N-terminal cysteine residue significantly reduced the potency of the compound, as the peptides Ac-carrrar-NH (SEQ ID NO:26) and Ac-arrrar-NH_2 (SEQ ID NO:29) differ only by the presence or absence of the N-terminal D-cysteine.

[0090] The contribution of the thiol-containing group in the X_1 subunit of the compound (e.g., in certain embodiments where the compound is a peptide on the N-terminal residue), was also investigated in an in vivo study. The PTH-lowering activity of the peptides identified as SEQ ID NO:26 (Ac-carrrar-NH_2) and as SEQ ID NO:29 (Ac-arrrarNH_2) was evaluated

in vivo. A 0.5 mg/kg dose of the peptide Ac-carrrar-NH_2 (SEQ ID NO:26) decreased PTH blood concentration to a non-detectable level for up to 4 hours after dosing. In contrast, the peptide lacking an N-terminal residue with a thiol-containing group, Ac-arrrar-NH_2 (SEQ ID NO:29), did not reduce PTH concentration, even at a substantially higher dose (i.e., 9 mg/kg).

[0091] The structure-activity relationship of the thiol-containing group in the X_1 subunit of the compound was further analyzed by preparing compounds with differing X_1 subunits. The compounds, were tested in vivo in normal rats for activity to reduce PTH. The data illustrated that the thiol-containing X_1 subunit can be varied. Compounds with the following in the N-terminal residue were tested - D-cysteine (cys), D-penicillamine (dPen), d-homocysteine (dHcy) and mercaptopropionic acid (Mpa). In addition, a natural or non-natural amino acid, such as beta alanine, can be conjugated to the N-terminal thiol-containing residue. The data illustrated that cationic compounds such as Ac-crrrrrrNH_2 (SEQ ID NO:6) containing different thiol-containing groups in the X_1 subunit effectively reduce PTH in vivo. Substituting the N-terminal cysteine residue with methionine, which does not contain a thiol group, resulted in a compound with very poor in vivo PTH-lowering activity.

[0092] Based on the studies described above, compounds of the contiguous sequence of subunits X_1 - X_2 - X_3 - X_4 - X_5 - X_6 - X_7, where X_1 is a subunit comprising a thiol-containing group, have activity to decrease parathyroid hormone levels. In one embodiment, the thiol-containing group on the X_1 subunit is selected from the group consisting of thiol-containing amino acid residues and organic thiol-containing moieties. In another embodiment, the thiol-containing group is capable of reacting with another thiol group under physiologic pH and temperature. In certain options where the thiol-containing residue is an amino acid residue, the X_1 subunit can be any one of cysteine, glutathione, mercapto-propionic acid, n-acetylated cysteine and PEGylated cysteine. In options where the thiol-containing group is on a non-amino acid residue subunit, such an organic small molecule with a thiol-containing group, the X_1 subunit can be a thiol-alkyl, or thioacyl moieties such as 3-mercaptopropyl or 3-mercaptopropionyl residues. In one option the thiol is not homocysteine.

[0093] Additional structure activity studies were conducted, to further evaluate the effect of properties of each subunit in the compound on its therapeutic activity. A series of compounds having an L-amino acid residue substituted for a D-amino acid residue were prepared based on the PTH-lowering scaffold Ac-c(C)arrrar-NH_2 (SEQ ID NO:3). The compounds were administered to subjects and plasma PTH levels were assessed prior to dosing and 1, 2, 3 and 4 hours after dosing.

[0094] The exemplary compounds shown in Table 1 may be chemically modified at both the N-terminus and the C-terminus, as indicated by the Ac and NH_2 designations. The sequence of seven subunits carrrar (SEQ ID NO:3), wherein all subunits were D-amino acid residues, was modified by replacing one subunit at a time with an L-amino acid. The X_1 subunit was a D-Cys residue (or L-Cys residue in SEQ ID NO:34) conjugated via a disulfide linkage to an L-Cys residue, as indicated by the parenthetical designation (C). Previous studies have shown that chirality of Arg and Ala affect activity of the compounds. In one option a compound of the sequence X_1 - X_2 - X_3 - X_4 - X_5-X_6 - X_7 is contemplated, where at least the subunits identified as X_4 and X_7 are D-amino acid residue subunits. In another optiion the subunits identified as X_4, X_5, X_6 and X_7 are D-amino acid residue subunits. In a preferred option the subunits identified as X_3, X_4, X_5, X_6 and X_7 are D-amino acid residue subunits. In most preferred options the subunits identified as X_2, X_3, X_4, X_5, X_6 and X_7 are D-amino acid residue subunits, and all of the subunits X_1, X_2, X_3, X_4, X_5, X_6 and X_7 are D-amino acid residue subunits.

[0095] In other studies, it also was found that substitution of a peptide having all L-amino acids with all D-amino acids did not reduce the in vitro activity of the peptides tested; in fact, peptides composed entirely of D-amino acids appeared to enhance the potency for activation of the CaSR. It was also shown that some of the cationic (arginine) residues, at specific positions relative to the cysteine residue, could be substituted with uncharged (alanine) residues with minimal effect on the activity toward the CaSR.

[0096] To further characterize the relationship between structure and activity against the CaSR, a variety of cationic peptides with different numbers (4 to 8) of arginine residues (all of which contained an N-terminal cysteine) were tested using the HEK-293 in vitro cell assay. A direct correlation was found between the number of cationic subunits and the potency of the compound, where potency is evidenced by ability to activate the CaSR. Reducing the number of cationic (e.g., arginine) subunits from 5 to 4 resulted in the largest shift in potency (>10-fold) suggesting that there may be an activity inflection point between compounds having these net charges, that a cationic subunit at subunit X_5 is preferred for activity. Accordingly, the compounds of the structure X_1 - X_2 - X_3 - X_4 - X_5 - X_6 - X_7 are contemplated, wherein X_5 is a cationic subunit. In certain options the X_1 is a subunit comprises a thiol group that is capable of reacting with another thiol group under physiologic conditions (a "reactive thiol", intending a thiol that reacts with another thiol (e.g., cysteine with cysteine) under physiologic conditions of pH 7.4 and body temperature).

[0097] Unexpectedly, Ac-crrrrrr-NH_2 (SEQ ID NO:6) with six cationic residues, when evaluated in vivo, exhibited greater and more prolonged activity than Ac-crrrrrrrr-NH_2 (SEQ ID NO:41), which has eight cationic residues. This is in contrast to the observation that SEQ ID NO:41 was more potent at activating the CaSR in this in vitro cell assay. Without wishing to be bound by theory, it is thought that the superior performance of Ac-crrrrrr-NH_2 (SEQ ID NO:6) in vivo may stem from better pharmacokinetic properties of Ac-crrrrrr-NH_2 (SEQ ID NO:6), because Ac-crrrrrrrr-NH_2 (SEQ ID NO:41) is

expected to be taken up into cells by virtue of its cell-penetrating characteristic, and thus removed from proximity to the active portion of the CaSR.

[0098] To further explore the structure-activity relationship of Ac-crrrrrr-NH_2 (SEQ ID NO:6), some of the cationic (arginine) residues were replaced with uncharged (alanine) residues. It was found that replacing the cationic (arginine) residues at subunit positions X_2 and X_4 resulted in a compound (SEQ ID NO:15) that had significantly reduced potency in vitro in activating the CaSR. By contrast, replacing the cationic (arginine) residues at subunit positions X_2 and X_6 resulted in a compound (SEQ ID NO:26) that retained much of the potency seen with Ac-crrrrrr-NH_2 (SEQ ID NO:6). These results suggest that the position of charged residues in the compound contributes to potency and, in some options may outweigh the contribution of total positive charge of the peptide. It also appears that cationic (arginine) residues at certain positions, such as subunit position X_5, contribute disproportionately to potency.

[0099] It was found that the presence of an N-terminal cysteine markedly enhances the potency of the peptides for activating the CaSR. The CaSR is a 7-transmembrane G-protein-coupled receptor with a large extracellular domain that functions as a homodimeric receptor. There are 18 cysteine residues in the extracellular domain, some of which have been shown by polymorphism or mutational analysis to be important for receptor activity. Of particular note are cysteines 129 and 131 of the Loop 2 region of the extracellular domain. Cysteines 129 and 131 are thought to form an intermolecular disulfide bridge between the two monomers of the receptor complex, which is in a closed or inhibited configuration. Mutation of cysteine 129 activates the CaSR, as do a number of other mutations including a full deletion of the Loop2 region. The enhanced potency provided by the N-terminal cysteine residue in the described compounds could result from a specific interaction with one or more of the cysteine residues in the extracellular domain of the CaSR.

[0100] To further evaluate the effect of chirality of amino acid substitutions on in vitro CaSR activity, a series of analogs of Ac-crrrrrr-NH_2 (SEQ ID NO:6) were generated containing L-amino acid or achiral amino acid (glycine) substitutions at various positions and tested for potency against the CaSR. Tested analogs included Ac-cGrrrGr-NH_2 (SEQ ID NO:42), (ii) Ac-cArrrAr-NH_2 (SEQ ID NO:43), and (iii) Ac-CaRrRaR-NH_2 (SEQ ID NO:44). All of the foregoing analogs had significantly lower potency than Ac-crrrrrr-NH_2 (SEQ ID NO:6), ranging from a 10-fold difference for SEQ ID NO:44 (the most potent of the three analogs) and a more than 2000-fold difference for SEQ ID NO:43 (the least potent of the three analogs). Ac-carrrar-NH_2 (SEQ ID NO:26), in which cationic D-amino acid residues (D-arginine residues) at positions 2 and 6 of SEQ ID NO:6 were replaced by uncharged D-amino acid residues (D-arginine residues), the change in activity was much less (~3 fold difference). Thus, surprisingly, it was found that interrupting the all D-amino acid residue of Ac-crrrrrr-NH_2 (SEQ ID NO:6) with two or more L-amino acid residues resulted in a significant reduction in potency. Also surprising was that potency was decreased more than 80-fold when the interrupting residue was an uncharged achiral amino acid residue (glycine residue) compared to when it was an uncharged L-amino acid residue (L-alanine residue).

[0101] Also surprising was that replacing the two uncharged D-amino acid residues (D-alanine residues) of Ac-carrrar-NH_2 (SEQ ID NO:26) with their L- counterparts (SEQ ID NO:43), resulted in a greater than 600-fold decrease in potency, while replacing them with an uncharged achiral amino acid residue (glycine residue) (SEQ ID NO:42) resulted in less than an 8-fold reduction in potency; and that replacing three cationic D-amino acid residues (D-arginine residues) of Ac-carrrar-NH_2 (SEQ ID NO:26) with their L-counterparts (SEQ ID NO:44), resulted in less than a 4-fold difference in potency.

[0102] In another study of the structure activity relationship, the contribution of non-cationic amino acids to the potency of the peptides was evaluated by preparing a series of peptides with various D-amino acid residues or glycine or with sterically-hindered non-natural amino acids, substituted at various positions in the peptide Ac-carrrar-NH_2 (SEQ ID NO:26) and in the peptide Ac-crrarar-NH_2 (SEQ ID NO:153). The peptides were administered as an IV bolus to normal Sprague Dawley rats at a dose of 0.5 mg/kg. An intravenous (IV) bolus of saline was used as a control. Plasma PTH levels were assessed prior to dosing and 1, 2, 3 and 4 hours after dosing. The results indicate that: 1) a small amino acid such as alanine, glycine or serine is preferred at position 6 in the Ac-carrrar-NH_2 peptide (SEQ ID NO:26), and 2) the alanine in position 2 in Ac-carrrar-NH_2 (SEQ ID NO:26) is much more permissive to substitutions and can be substituted with hydrophobic (e.g. D-Val, D-Leu), aromatic (e.g. D-Phe), or polar (e.g. D-Ser, D-Gln) natural amino acids as well as non-natural bulky hydrophobic amino acids (e.g. dNle, dNva) but not acidic ones, and that 3) the alanine residue in position 4 of the Ac-crrarar-NH_2 (SEQ ID NO:25) peptide is also very permissive to substitutions and can accommodate most types of natural amino acids (as well as non-natural bulky hydrophobic amino acids (e.g. dNle, dNva) but is not permissive to amino acids that affect secondary conformation, namely glycine or proline or amino acids with acidic side chain.

[0103] The activity of a variety of peptides and conjugates was tested for their effects on the human CaSR. These studies were conducted by measuring IP_1 production in HEK293 cells that express the human CaSR. The results are presented in Table 3 below.

Table 3

Compound Name	Structure	EC_{50} (•M)
(SEQ ID NO:45) (SEQ ID NO:47)	CHDAPIGYD | Ac-CYGRKKRRQRRR-NH_2	21
(SEQ ID NO:46) (SEQ ID NO:47)	CPDYHDAGI | Ac-CYGRKKRRQRRR-NH_2	21
(SEQ ID NO:47)	Ac-CYGRKKRRQRRR-NH_2	4.5
(SEQ ID NO:48)	Ac-YGRKKRRQRRR-NH_2	16
(SEQ ID NO:41)	Ac-crrrrrrrr-NH_2	0.3
(SEQ ID NO:6)	Ac-crrrrrr-NH_2	0.5
(SEQ ID NO:15)	Ac-cararrr-NH_2	13
(SEQ ID NO:26)	Ac-carrrar-NH_2	1.6
(SEQ ID NO:4)	Ac-crrrr-NH_2	16
(SEQ ID NO:5)	Ac-crrrrr-NH_2	2.5
(SEQ ID NO:7)	Ac-crrrrrrr-NH_2	0.6
(SEQ ID NO:49)	Ac-caraarrr-NH_2	1000
(SEQ ID NO:8)	Ac-carrrrr-NH_2	1.1
(SEQ ID NO:9)	Ac-crarrrr-NH_2	1
(SEQ ID NO:10)	Ac-crrarrr-NH_2	1.1
(SEQ ID NO:50)	Ac-cygrkkrrqrrr-NH_2	2
(SEQ ID NO:51)	H_2N-crrrrrr-NH_2 | H_2N-crrrrrr-NH_2	0.44
(SEQ ID NO:3)	Ac-c(C)arrrar-NH_2	10
(SEQ ID NO:52)	Ac-carrrar-NH_2 | Ac-carrrar-NH_2	0.7
(SEQ ID NO:30)	Ac-bAla-crrrrrr-NH_2	1
(SEQ ID NO:53)	Ac-c(GS)rrrrrr-NH_2	7.8
(SEQ ID NO:54)	GS-crrrrrr	-
(SEQ ID NO:55)	Ac-c(Ac-C)arrrar-NH_2	21
(SEQ ID NO:56)	Ac-c(Mpa)arrrar-NH_2	21
(SEQ ID NO:57)	Ac-c(PEG2-C)arrrar-NH_2	2.3
(SEQ ID NO:58)	Ac-c(PEG5-C)rrrrrr-NH_2	0.58
(SEQ ID NO:59)	Ac-c(PEG2-C)rrrrrr-NH_2	0.02
(SEQ ID NO:34)	Ac-C(C)arrrar-NH_2	2.5
(SEQ ID NO:60)	c(C)arrrar-NH_2	3.1
(SEQ ID NO:61)	Ac-bAla-c(C)arrrar-NH_2	2.6
(SEQ ID NO:62)	bAla-c(C)arrrar	-

(continued)

Compound Name	Structure	EC_{50} (•M)
(SEQ ID NO:42)	Ac-cGrrrGr-NH_2	12
(SEQ ID NO:63)	Ac-cGrrrGr	-
(SEQ ID NO:64)	Ac-cArrrAr	-
(SEQ ID NO:43)	Ac-cArrrAr-NH_2	>1000
(SEQ ID NO:44)	Ac-CaRrRaR-NH_2	5.6
(SEQ ID NO:65)	Ac-cvrrrvr-NH_2	35
(SEQ ID NO:66)	Ac-cvrrrvr	-
(SEQ ID NO:67)	Ac-Crrrrrr-NH_2	6.2
(SEQ ID NO:68)	Ac-carrrer-NH_2	62
(SEQ ID NO:69)	Ac-cerrrar-NH_2	31
(SEQ ID NO:72)	Ac-cakrrar-NH_2	35
(SEQ ID NO:73)	Ac-carkrar-NH_2	31
(SEQ ID NO:74)	Ac-carrrar-OH	31
(SEQ ID NO:11)	Ac-crrrarr-NH_2	5.9
(SEQ ID NO:12)	Ac-crrrrar-NH_2	0.45
(SEQ ID NO:13)	Ac-crrrrra-NH_2	1.1
(SEQ ID NO:75)	Ac-CARRRAR-NH_2	58
(SEQ ID NO:76)	Ac-caarrrrrr-NH_2	4.5
(SEQ ID NO:77)	Ac-caaarrrrrr-NH_2	4.6
(SEQ ID NO:78)	Ac-carararar-NH_2	5.3
(SEQ ID NO:29)	Ac-arrrar-NH_2	>1000
(SEQ ID NO:79)	Ac-carrrarar-NH_2	13
(SEQ ID NO:80)	crrrrrr-NH_2	1.1
(SEQ ID NO:32)	Ac-dHcy rrrrrr-NH_2	2
(SEQ ID NO:81)	Ac-c(Benzoyl)rrrrrr-NH_2	3.6
(SEQ ID NO:82)	Ac-c(acetyl)rrrrrr-NH_2	4.1

[0104] The compounds disclosed herein typically comprise one or more thiol moieties, preferably one or more reactive thiol moieties. Subunits that have a thiol group include non-amino acid compounds having a thiol group and amino acids with a thiol group. The thiol group of the thiol-containing subunit may be in a conjugated form (e.g., via a disulfide bond to a conjugating group) or in an unconjugated form (i.e., as a reduced thiol). In a preferred embodiment, when the thiol group is in either an unconjugated form or a conjugated form, it is capable of forming a disulfide bond with a thiol-containing group. The thiol-containing residue may be located at any position along the peptide chain, including the amino terminus, the carboxy terminus, or some other position. In a preferred option the thiol-containing residue or subunit may be located at the amino terminus. In other options the thiol-containing residue or subunit may be located at the carboxy terminus or within the peptide sequence.

[0105] Some representative examples of thiol-containing residues include, without limitation, cysteine, mercaptopropionic acid, homo-cysteine, and penicillamine. When the thiol-containing residue contains a chiral center, it may be present in the L- or D-configuration. In a preferred option the thiol-containing residue is cysteine.

[0106] In some options the cross-linkage between the thiol containing subunit at the X_1 position in the compound and the thiol-containing conjugating group may be cleavable and/or exchangeable with other thiol-containing conjugating groups such as cysteine (e.g., by reduction of the disulfide linkage) in vivo to yield a biologically active form of the compound. In this way, the conjugate may function as a pro-drug of the compound. A conjugating group also may be

used to modify the physicochemical, pharmacokinetic and/or pharmacodynamic properties of the described compounds (e.g., conjugation via a disulfide linkage to a large PEGylated moiety to enhance the pharmacokinetics).

[0107] In some options the compound is a peptide comprised of the amino acid sequence (X_{aa1})-(X_{aa2})-(X_{aa3})-(X_{aa4})-(X_{aa5})-(X_{aa6})-(X_{aa7}) (SEQ ID NO:155), wherein (X_{aa1}) is a thiol-containing amino acid residue, (X_{aa2}) is a non-cationic amino acid residue, (X_{aa3}) is any amino acid residue, (X_{aa4}) is any amino acid residue, (X_{aa5}) is a cationic amino acid residue, (X_{aa6}) is a non-cationic residue, and (X_{aa7}) is any amino acid residue. The peptide may be modified at the N-terminus, the C-terminus, or both. In a preferred option the peptide is modified at both the N-terminus and C-terminus by acetylation and amidation, respectively.

[0108] In some options a peptide comprises the amino acid sequence (D-Cys)-(X_{aa2})-(X_{aa3})-(X_{aa4})-(X_{aa5})-(X_{aa6})-(X_{aa7}) (SEQ ID NO:156), wherein (X_{aa2}) is a non-cationic amino acid residue, (X_{aa3}) is any amino acid residue, (X_{aa4}) is any amino acid residue, (X_{aa5}) is selected from the group consisting of D-Arg, L-Arg, D-Lys and L-Lys, (X_{aa6}) is a non-cationic residue, and (X_{aa7}) is any amino acid residue. The peptide may have an N-terminal cap, a C-terminal cap, or both. In a preferred option the peptide has both
an N-terminal cap and a C-terminal cap.

[0109] In some options a peptide comprises the amino acid sequence (D-Cys)-(X_{aa2})-(X_{aa3})-(X_{aa4})-(X_{aa5})-(X_{aa6})-(X_{aa7}) (SEQ ID NO:157), wherein (X_{aa2}), (X_{aa3}) and (X_{aa4}) are, independently, any amino acid residue (but in a preferred option are, independently, selected from the group consisting of D-Ala, D-Val, D-Leu, D-NorVal, and D-NorLeu), (X_{aa5}) and (X_{aa7}) are, independently, any cationic amino acid residue (but in a preferred option are, independently, selected from the group consisting of D-Arg, L-Arg, D-Lys and L-Lys), (X_{aa6}) is a non-cationic amino acid residue (in a preferred embodiment, selected from the group consisting of D-Ala, D-Val, D-Leu, D-NorVal and D-NorLeu). The peptide may have an N-terminal cap, a C-terminal cap, or both. In a preferred option the peptide has both an N-terminal cap and a C-terminal cap.

[0110] In some options a peptide comprises the amino acid sequence (D-Cys)-(X_{aa2})-(X_{aa3})-(X_{aa4})-(X_{aa5})-(X_{aa6})-(X_{aa7}) (SEQ ID NO:158), wherein (X_{aa2}) is a non-cationic amino acid residue, (X_{aa3}) is any amino acid residue, (X_{aa4}) is any amino acid residue, (X_{aa5}) is selected from the group consisting of D-Arg, L-Arg, D-Lys and L-Lys, (X_{aa6}) is a non-cationic residue, and (X_{aa7}) is any amino acid residue. The peptide may have an N-terminal cap, a C-terminal cap, or both. In a preferred option the peptide has both an N-terminal cap and a C-terminal cap.

[0111] In some options a peptide comprises the amino acid sequence (D-Cys)-(D-Ala)-(X_{aa3})-(X_{aa4})-(D-Arg)-(D-Ala)-(X_{aa7}) (SEQ ID NO:159), wherein (X_{aa3}) is any cationic amino acid residue, (X_{aa4}) is any cationic amino acid residue, and (X_{aa7}) is any cationic amino acid residue. The peptide may have an N-terminal cap, a C-terminal cap, or both. In a preferred option the peptide has both an N-terminal cap and a C-terminal cap.

[0112] In some options a peptide comprises the amino acid sequence (D-Cys)-(X_{aa2})-(X_{aa3})-(D-Ala)-(D-Arg)-(D-Ala)-(X_{aa7}) (SEQ ID NO:160), wherein (X_{aa2}), (X_{aa3}) and (X_{aa7}) are, independently, any cationic amino acid residue. The peptide may have an N-terminal cap, a C-terminal cap, or both. In a preferred option the peptide has both an N-terminal cap and a C-terminal cap.

[0113] Another option is a calcimimetic peptide, comprising a sequence of amino acids linked by peptide bonds, wherein the sequence comprises 5 to 10 amino acid residues, and wherein the sequence comprises an amino terminus, a carboxy terminus, at least one thiol-containing residue, and from 3 to 9 positively charged residues. In one embodiment, the at least one thiol-containing residue is a cysteine residue. In another aspect, the cysteine residue is positioned at the amino terminus of the peptide. In certain options the cysteine residue is an L-Cys residue, a D-Cys residue, or an L-or D-homoCys residue. In other options the amino acid residues of the peptide are D-amino acids or L-amino acids.

[0114] Also encompassed within the scope of the disclosure are peptidomimetic molecules that comprise approximately seven subunits, wherein at least one subunit contains a thiol moiety, preferably a reactive thiol moiety, and other subunits are a plurality of non-cationic subunits, and from 1 to 4 positively charged subunits. Such peptidomimetic molecules may comprise non-peptide bonds between two or more of the subunits. The various features of the compounds discussed above apply generally to the peptidomimetic molecule. For example, as discussed above, the subunits used to construct the molecules can be naturally-occurring amino acids, or residues with non-natural side chains, the termini of the modules can be capped or non-capped in the manner discussed above. Similarly, the amino acid residues of the molecule can be L- or D-amino acid residues. Also as discussed above, the thiol-containing residues can be in a reduced or oxidized form with any of the thiol-containing moieties discussed above.

[0115] Many peptidomimetic frameworks and methods for their synthesis have been developed (Babine, R. E.; Bender, S. L., Chem. Rev., 97:1359, 1997; Hanessian, S.; et al., Tetrahedron, 53:12789, 1997; Fletcher, M. D.; Cambell, M. C., Chem. Rev., 98:763, 1998); Peptidomimetics Protocols; Kazmierski W.M., Ed.; Methods in Molecular Medicine Series, Vol. 23; Humana Press, Inc.; Totowa, N.J. (1999).

CONJUGATES

[0116] In some options the compound is chemically cross-linked to a thiol-containing conjugating group via a disulfide

bond between the thiol of the compound and a thiol from the conjugating group. The thiol-containing conjugating group can be a small molecule, such as cysteine, or a macromolecule, such as a polypeptide containing a cysteine residue. Examples of suitable thiol-containing conjugating groups include cysteine, glutathione, thioalkyl, moieties such as thiobenzyl, mercaptopropionic acid, N-acetylated cysteine, cysteamide, N-acetylcysteamide, homocysteine, penicillamine and poly (ethylene glycol) (PEG) modified (referred to as "PEGylated") thiols such as PEGylated cysteine or a duplication of the compound (ie., to form a homodimer linked by a disulfide linkage). In a preferred option the thiol-containing conjugating group is cysteine. Other cysteine homologs are also contemplated for use as thiol-containing conjugating groups, either alone or comprised in a larger conjugating group. Similarly, stereoisomers of cysteine, homocysteine, and cysteamide are suitable for use as thiol-containing moieties. Conjugating groups can be used to improve chemical stability and therefore shelf-life of a pharmaceutical product. In certain embodiments the thiol-containing conjugating group and the peptide are the same (i.e., the conjugate is a dimer), which unexpectedly showed very good chemical stability compared to heterologous conjugating group such as cysteine. Without being bound by theory, presumably when the thiol-containing conjugating group and the peptide are the same, then any disproportionation (e.g., scrambling of the conjugating group) will reconstitute the original dimer compound. In contrast, disproportionation of a compound with a heterologous conjugating group such as cysteine can lead to formation of homo-dimers of the peptide plus cystine (cysteine - cysteine homodimer) plus residual parent compound. A homo-dimer of the peptide (i.e., conjugating group and the peptide are the same) would be converted to a cysteine conjugated form of the peptide in vivo due to the high concentration of reduced cysteine in systemic circulation.

[0117] In some options the teachings include a disulfide conjugate of a thiol-containing conjugating group and a peptide comprising the amino acid sequence (X_{aa1})-(X_{aa2})-(X_{aa3})-(X_{aa4})-(X_{aa5})-(X_{aa6})-(X_{aa7}) (SEQ ID NO:155), wherein (X_{aa1}) is an amino acid residue with a thiol-containing moiety, (X_{aa2}) is a non-cationic amino acid residue, (X_{aa3}) is any amino acid residue, (X_{aa4}) is any amino acid residue, (X_{aa5}) is a cationic amino acid residue, (X_{aa6}) is a non-cationic residue, and (X_{aa7}) is any amino acid residue. The peptide may have an N-terminal cap, a C-terminal cap, or both. In a preferred option the peptide has both an N-terminal cap and a C-terminal cap. In a preferred embodiment, the thiol-containing conjugating group is selected from the group consisting of D-Cys, L-Cys, a peptide containing D-Cys, and a peptide containing L-Cys. When the thiol-containing conjugate group is an amino acid or a peptide, it may have an N-terminal cap, a C-terminal cap, or both. In a preferred option the thiol-containing conjugate group has both an N-terminal cap and a C-terminal cap. In some options the thiol-containing conjugating group is itself a peptide comprising the amino acid sequence of SEQ ID NO:155. In some options the thiol-containing conjugating group and the peptide are the same (i.e., the conjugate is a dimer).

[0118] In some options the teachings include a conjugate of a thiol-containing conjugating group and a peptide comprising the amino acid sequence (D-Cys)-(X_{aa2})-(X_{aa3})-(X_{aa4})-(X_{aa5})-(X_{aa6})-(X_{aa7}) (SEQ ID NO:156), wherein (X_{aa2}) is a non-cationic amino acid residue, (X_{aa3}) is any amino acid residue, (X_{aa4}) is any amino acid residue, (X_{aa5}) is selected from the group consisting of D-Arg, L-Arg, D-Lys and L-Lys, (X_{aa6}) is a non-cationic residue, and (X_{aa7}) is any amino acid residue. The peptide may have an N-terminal cap, a C-terminal cap, or both. In a preferred option the peptide has both an N-terminal cap and a C-terminal cap. In a preferred option the thiol-containing conjugating group is selected from the group consisting of D-Cys, L-Cys, a peptide containing D-Cys, and a peptide containing L-Cys. When the thiol-containing conjugate group is an amino acid or a peptide, it may have an N-terminal cap, a C-terminal cap, or both. In a preferred embodiment, the thiol-containing conjugate group has both an N-terminal cap and a C-terminal cap. In some options the thiol-containing conjugating group is itself a peptide comprising the amino acid sequence of SEQ ID NO:156. In some options the thiol-containing conjugating group and the peptid are the same (i.e., the conjugate is a dimer).

[0119] In some options the teachings include a conjugate of a thiol-containing conjugating group and a peptide comprising the amino acid sequence (L-Cys)-(X_{aa2})-(X_{aa3})-(X_{aa4})-(X_{aa5})-(X_{aa6})-(X_{aa7}) (SEQ ID NO:183), wherein (X_{aa2}) is a non-cationic amino acid residue, (X_{aa3}) is any amino acid residue, (X_{aa4}) is any amino acid residue, (X_{aa5}) is selected from the group consisting of D-Arg, L-Arg, D-Lys and L-Lys, (X_{aa6}) is a non-cationic residue, and (X_{aa7}) is any amino acid residue. The peptide may have an N-terminal cap, a C-terminal cap, or both. In a preferred option the peptide has both an N-terminal cap and a C-terminal cap. In a preferred option the thiol-containing conjugating group is selected from the group consisting of D-Cys, L-Cys, a peptide containing D-Cys, and a peptide containing L-Cys. When the thiol-containing conjugate group is an amino acid or a peptide, it may have an N-terminal cap, a C-terminal cap, or both. In a preferred option the thiol-containing conjugate group has both an N-terminal cap and a C-terminal cap. In some options the thiol-containing conjugating group is itself a peptide comprising the amino acid sequence of SEQ ID NO:183. In some options the thiol-containing conjugating group and the peptide are the same (i.e., the conjugate is a dimer).

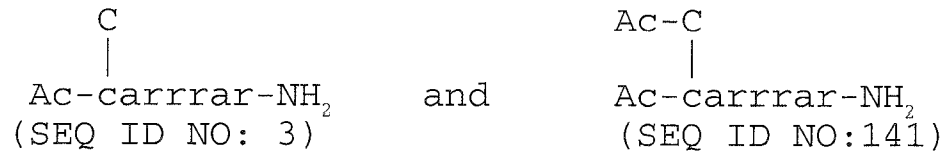
[0120] In some options the teachings include a conjugate of a thiol-containing conjugating group and a peptide comprising the amino acid sequence (D-Cys)-(D-Ala)-(X_{aa3})-(X_{aa4})-(D-Arg)-(D-Ala)-(X_{aa7}) (SEQ ID NO:161), wherein (X_{aa3}) is any amino acid residue, (X_{aa4}) is any amino acid residue, and (X_{aa7}) is any amino acid residue. The peptide may have an N-terminal cap, a C-terminal cap, or both. In a preferred option the peptide has both an N-terminal cap and a C-terminal cap. In a preferred option the thiol-containing conjugating group is selected from the group consisting of D-Cys, L-Cys, a peptide containing D-Cys, and a peptide containing L-Cys. When the thiol-containing conjugate group is an

amino acid or a peptide, it may have an N-terminal cap, a C-terminal cap, or both. In a preferred option the thiol-containing conjugate group has both an N-terminal cap and a C-terminal cap. In some options the thiol-containing conjugating group is itself a peptide comprising the amino acid sequence of SEQ ID NO:161. In some options the thiol-containing conjugating group and the peptide are the same (i.e., the conjugate is a dimer).

EXEMPLARY COMPOUNDS

[0121] In a preferred option the thiol-containing conjugate group has both an N-terminal cap and a C-terminal cap. In some options the thiol-containing conjugating group is itself a peptide comprising the amino acid sequence of SEQ ID NO:161. In some options the thiol-containing conjugating group and the peptide are the same (i.e., the conjugate is a dimer).

[0122] In another option the compounds are in the form of a conjugate, where the thiol-containing subunit in position X_1 is linked through a disulfide linkage to an L-Cys residue. These compounds have the following structures:



[0123] In the notation used herein, the compound that is linked to the thiol-containing moiety in the X_1 subunit is identified parenthetically, where in these exemplary conjugates the compound L-Cys is indicated (C) is linked to the thiol-containing moiety in the X_1 subunit: Ac-c(C)arrrar-NH_2 (SEQ ID NO:3) and Ac-c(Ac-C)arrrar-NH_2 (SEQ ID NO:141).

[0124] When the described agonists are administered as pharmaceuticals, to humans and animals, they can be given alone or as a pharmaceutical composition containing, for example, 0.1 to 99% (more preferably, 10 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier. In other embodiments, the pharmaceutical composition may contain 0.2-25%, preferably 0.5-5% or 0.5-2%, of active ingredient. These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including, e.g., oral, subcutaneous injection, subcutaneous depot, intravenous injection, intravenous or subcutaneous infusion

[0125] These agonists may be administered to humans and other animals for therapy by any suitable route of administration.

[0126] As described above, the methods of use may be used alone or in combination with other agents and/or modalities. Such other agents and/or modalities include, but are not limited to, dietary phosphate restriction, dialysis, phosphate binders (e.g., aluminum hydroxide, calcium carbonate, calcium acetate, magnesium salts, sevelamer hydrochloride, lanthanum carbonate, polynuclear iron preparation). The particular combination of therapies (agents and/or modalities) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[0127] In one option a described compound is administered at a dose sufficient to reduce phosphorus rebound in a hemodialysis patient. In another option the dose is administered after termination of dialysis.

[0128] A combination treatment of the present invention as defined herein may be achieved by way of the simultaneous, sequential or separate administration of the individual components of said treatment.

EXAMPLES

[0129] The following example is offered to illustrate but not to limit the compounds and methods described herein. Various modifications may be made by the skilled person without departing from the true spirit and scope of the subject matter described herein.

Example 1

[0130] An initial Phase 1 randomized, double-blind, placebo-controlled, single-dose, dose-escalation, two-period cross-over study in ESRD patients on hemodialysis with SHPT was carried out. The study was conducted in part to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous (IV) administration of SEQ ID NO:3 in healthy male volunteers and to inform dose selection for this protocol. This study was a Phase 1b study in hemodialysis

subjects with SHPT.

[0131] Twenty-eight patients on hemodialysis were given a single dose of SEQ ID NO:3 or placebo. Cohorts receiving a 5, 10 or 20 mg dose were studied in a 2-period crossover design while subjects receiving a 40 or 60 mg dose were randomized to SEQ ID NO:3 or placebo with 8 subjects per cohort.

[0132] Immediately following hemodialysis, subjects were admitted to a Phase 1 Unit and observed for 3 days. Baseline laboratory testing was performed 2 hours post hemodialysis. Following injection of SEQ ID NO:3 post dialysis, there is a rapid 60-80% decrease in the levels of intact PTH followed by a dose dependant return towards baseline over the following 48 hours (Fig. 1). There is an associated small (10-16%) decrease in serum calcium.

[0133] Serum phosphorus levels, which were decreased by dialysis, rose rapidly over the first 8 hours to a plateau and then increased more slowly during the remaining interdialytic interval (Fig. 2). In placebo subjects, mean serum phosphorus increased rapidly during the first ~36 hours post-dose after which phosphorus levels tended to plateau at 84% above baseline levels at discharge (Fig. 2). Surprisingly, the rate of return to the plateau level of phosphorus was markedly modified by administration of SEQ ID NO:3. The 5 mg dose had minimal effect, but higher doses markedly decreased the rise of serum phosphorus. At discharge, the mean percent increase from baseline in serum phosphorus in subjects receiving 20-60 mg SEQ ID NO:3 ranged from 23% to 60% and was at least ~24 percentage points lower than placebo.

Example 2

[0134] A Phase 2 study was completed as a double-blind, randomized placebo-controlled, multiple ascending dose study. This study was a single arm, open-label, 12-week, dose titration study with a 4-week follow-up phase to investigate the effect of SEQ ID NO:3 in the treatment of SHPT in hemodialysis subjects with chronic kidney disease-mineral and bone disorder (CKD-MBD). The primary objective of this study was to evaluate the effect of thrice-weekly IV administration of SEQ ID NO:3 in the treatment of SHPT in hemodialysis subjects with CKD-MBD as assessed by percent change in iPTH from baseline during the efficacy period. In addition, secondary objectives were to evaluate the change from baseline in serum cCa (corrected calcium) and phosphorus.

[0135] The starting dose of SEQ ID NO:3 was 5 mg. The dose of SEQ ID NO:3 was titrated to target 150:5 300 pg/mL. Subjects were evaluated for an increase in the SEQ ID NO:3 dose during Week 5 and Week 9. If the subject's most recent cCa was $\geq$ 8.0 mg/dL and there was no ongoing adverse event that precluded a dose increase, then the dose of SEQ ID NO:3 was adjusted as follows: if iPTH $\leq$ 300 pg/mL, then no change in dose; If iPTH > 300 pg/mL, then the dose was increased by 5 mg (i.e., from 5 mg to 10 mg) during Week 5 or increased by 5 mg (i.e., iPTH $\geq$ 300 pg/mL and $\leq$ 450 pg/mL) or 10 mg (iPTH > 450 pg/mL) during Week 9.

[0136] Thirty-two subjects (87%) completed the 12-week treatment period. Five subjects (13/5%) withdrew prior to the end of the treatment period. Of the 32 subjects who completed the 12-week treatment period, 30 subjects entered the open-label extension study and two subjects completed the 4-week follow-up period.

[0137] The primary endpoint was the percent change from baseline in iPTH at the end of the efficacy assessment period. Baseline iPTH level was defined as the average of three iPTH results obtained within 3 weeks of the first dose and prior to the first dose of SEQ ID NO:3. The efficacy assessment period was from 14 days prior to and 3 days after the last dose of SEQ ID NO:3. Secondary endpoints included the proportion of subjects with $\geq$ 30% reduction in iPTH from baseline and the proportion of subjects with iPTH $\geq$ 300 pg/mL during the efficacy assessment period. In addition, the effect of SEQ ID NO:3 on mean change in cCa and phosphorus were evaluated.

[0138] Overall, mean baseline iPTH was 853.4 pg/mL. SEQ ID NO:3 treatment was associated with a 53% mean reduction from baseline in iPTH at the end of the treatment period (95% confidence interval (-60.8, -46.3). Results were similar in the iPTH subgroups (baseline iPTH $\leq$ 700 pg/mL or >700 pg/mL), suggesting that the response was independent of baseline iPTH values.

[0139] When plotted versus time, SEQ ID NO:3 treatment showed a progressive, sustained reduction in predialysis iPTH over the 12-week treatment period. In a secondary responder analysis 89% of subjects achieved $\geq$ 30% reduction in iPTH; the proportion was only slightly lower among subjects with severe disease (i.e., iPTH > 700 pg/mL). Overall, 56% of subjects achieved iPTH $\leq$ 300 pg/mL at the end of the treatment period. Serum calcium levels were adjusted for albumin levels below 4.0 g/dL with the equation: corrected calcium (cCa) = (measured Ca in mg/dL) + [4-(albumin in g/dL)]*0.8. Mean baseline cCa was 10.1 mg/dL and was reduced by 15% at the end of the treatment period. More pronounced decreases in serum cCa were observed in subjects with severe disease.

[0140] Phosphorus measurements were obtained predialysis on protocol specified assessment days. Overall, mean baseline phosphorus was 5.7 mg/dL, with the more severe baseline iPTH subgroup having higher baseline levels. At the end of the efficacy treatment period, the mean percent change from baseline in serum phosphorus was - 10.5%, with the greater reduction experienced in the subjects with more severe disease (Table 3).

Table 3

Serum Phosphorus (P) in	iPTH ≤ 700	iPTH > 700	Total
mg/dL	N=22	N = 15	N = 37
Baseline	5.1	6.5	5.7
EOT	4.7	5.5	5.0
Mean percent Change (%)	-7.7	-14.5	-10.5
95% CI of Mean percent Change	-17.7, 2.3	-23.4, -5.6	-17.2, -3.9

[0141] Overall, with the exception of the one phosphorus mean percent change in the lower iPTH subgroup, all pre-specified primary and secondary endpoints analyses showed significant reductions in iPTH, cCa and phosphorus across both subgroups.

SEQUENCE LISTING

[0142]

<110> Karim, Felix Bell, Gregory

<120> Therapeutic Agents for Regulating Serum PHosphorus

<130> 63200.8021.WO00

<140> Not yet assigned
<141> Filed herewith

<150> US 61/494,874
<151> 2011-06-08

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<400> 16

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<223> C-terminal amidation

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1 5

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<400> 18

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<400> 19

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<223> Xaa = D-Ala

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<400> 20

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<400> 21

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<400> 22

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<400> 23

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<220>
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<400> 28

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa

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<400> 31

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<400> 32

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<400> 34

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<400> 35

Cys Xaa Xaa Xaa Xaa Xaa Xaa
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<400> 36

Xaa Xaa Arg Xaa Xaa Xaa Xaa
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<210> 37
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Xaa Xaa Xaa Arg Xaa Xaa Xaa
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<400> 38

Xaa Xaa Xaa Xaa Arg Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Ala Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa Arg
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<400> 42

Xaa Gly Xaa Xaa Xaa Gly Xaa
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<210> 43
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<220>
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<400> 43

Xaa Ala Xaa Xaa Xaa Ala Xaa
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<212> PRT
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<400> 44

Cys Xaa Arg Xaa Arg Xaa Arg
1 5

<210> 45
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<400> 45

Cys His Asp Ala Pro Ile Gly Tyr Asp
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<210> 46
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<212> PRT
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<400> 46

Cys Pro Asp Tyr His Asp Ala Gly Ile
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Cys Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg
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<400> 48

Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg
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<211> 8
<212> PRT
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<400> 49

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<222> (12)
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<400> 50

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Gly Xaa Xaa Xaa Gly Xaa
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Xaa Ala Xaa Xaa Xaa Ala Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<400> 72

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<400> 73

Xaa Xaa Xaa Xaa Xaa Xaa Xaa

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Cys Ala Arg Arg Arg Ala Arg
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 78
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<400> 78

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> 79
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<400> 79

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> 80
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> 81
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<400> 81

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> 84
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<223> Xaa = D-Ile

<220>
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<223> Xaa = D-Ala

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<400> 115

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<211> 7
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<220>
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<222> (4)
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<222> (6)
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<400> 116

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<211> 7
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<223> Xaa = D-Arg

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<400> 117

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<223> Xaa = D-Arg

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<400> 118

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<223> Xaa = D-Ala

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<400> 119

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1 5

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<223> Xaa = D-Arg

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<400> 120

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<223> N-terminal acetylation

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<223> Xaa = N-methylalanine (Nma)

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<221> VARIANT
<222> (6)
<223> Xaa = D-Ala

<220>
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<400> 121

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<220>
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<220>
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<223> N-terminal acetylation

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<222> (2)
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<220>
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<400> 122

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<220>
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<220>
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<222> (6)
<223> Xaa = D-Ala

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<400> 123

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<223> N-terminal acetylation

<220>
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<222> (2)
<223> Xaa = D-Ala

<220>
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<222> (3), (4), (5), (7)
<223> Xaa = D-Arg

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<223> Xaa = 2-aminoisobutyric acid (Aib)

<220>
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<400> 124

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<211> 7
<212> PRT
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<220>
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<223> N-terminal acetylation

<220>
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<223> Xaa = N-methylglycine (sarcosine)

<220>
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<223> Xaa = D-Arg

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<400> 125

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<223> N-terminal acetylation

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<223> Xaa = D-Ala

<220>
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<222> (6)
<223> Xaa = N-methylglycine (sarcosine)

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<400> 126

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<223> Xaa = N-methylalanine (Nma)

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<223> Xaa = D-Arg

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<223> Xaa = D-Ala

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<400> 127

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<400> 128

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<400> 129

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<400> 130

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<400> 132

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<400> 133

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<400> 134

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<400> 136

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<223> Xaa = D-Norleucine (dNLeu)

<220>
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<220>
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<400> 138

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<223> Xaa = D-Cys

<220>
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<223> N-terminal acetylation

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<223> Bond with D-homocysteine (dHcy)

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<222> (7)
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<400> 139

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 140
<211> 7
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<220>
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<223> Xaa = D-Cys

<220>
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<223> Xaa = D-Arg

<220>
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<400> 140

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 141
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<220>
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<223> C-terminal amidation

<400> 141

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 142
<211> 7
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<220>
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<220>
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<220>
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<222> (1)..(1)
<223> Bond with D-Cysteine

<220>
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<400> 142

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 143
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<220>
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<223> Xaa = D-Cys

<220>
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<222> (1)..(1)
<223> Bond with Polyethylene glycol

<220>
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<400> 143

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 144
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<213> Artificial Sequence

<220>
<223> Synthetic peptide

<220>
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<222> (1)..(1)
<223> Bond with Polyethylene glycol

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<222> (7)
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 145

Cys Glu Glu Glu Glu Glu Glu
1 5

<210> 146
<211> 7
<212> PRT
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<220>
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<220>
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<223> N-terminal acetylation

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<220>
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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Claims

1. A composition for use in treating chronic kidney disease-mineral and bone disorder (CKD-MBD) in a patient receiving hemodialysis, the composition comprising a compound comprising Ac-c(C)arrrar-NH_2 (SEQ ID NO:3); wherein the serum phosphate level of the patient is assessed and found to be above the normal range; wherein the composition is administered within the period beginning 15 minutes prior to completion of hemodialysis and ending 3 hours after completion of hemodialysis; wherein the patient has been diagnosed with hyperphosphatemia; and wherein said administering is effective to maintain a post-hemodialysis serum phosphorus level that is lower than a pre-hemodialysis serum phosphorus level for a period of at least 6 hours after dialysis such that the patient's serum phosphorus increases by less than 10% in the first 6 hours after dialysis.

2. The composition for use according to claim 1, wherein the compound comprises a pharmaceutically acceptable salt of SEQ ID NO:3.

3. The composition for use according to claim 2, wherein the salt is a hydrochloride salt.

4. The composition for use according to any one of claims 1-3, wherein the compound is administered during the rinse back procedure at the end of dialysis.

5. The composition for use according to any one of claims 1-4, wherein the patient is being treated with a phosphate binding agent.

6. The composition for use according to any one of claims 1-5, wherein said administering is effective to maintain a post-hemodialysis serum phosphorus level that is at least 10% lower than a pre-hemodialysis serum phosphorus level for an inter dialytic period.

7. The composition for use according to any one of claims 1-5, wherein the patient is being treated for secondary hyperparathyroidism or primary hyperparathyroidism.

8. The composition according to any one of claims 1 -4, wherein the patient is not being treated with a phosphate binding agent.

Patentansprüche

1. Zusammensetzung zur Verwendung bei der Behandlung einer Störung des Mineral- und Knochenstoffwechsels bei chronischer Nierenerkrankung (CKD-MBD) bei einem Hämodialysepatienten, wobei die Zusammensetzung eine Verbindung umfassend Ac-c(C)arrrar-NH_2 (SEQ ID NO:3) umfasst;
wobei der Phosphatgehalt im Serum des Patienten bewertet und für oberhalb des Normalbereichs befunden wird; wobei die Zusammensetzung innerhalb des Zeitraums verabreicht wird, der 15 Minuten vor Abschluss der Hämodialyse beginnt und 3 Stunden nach Abschluss der Hämodialyse endet; wobei bei dem Patienten Hyperphosphatämie diagnostiziert worden ist; und wobei die Verabreichung dafür wirksam ist, einen Phosphatgehalt im Serum nach der Hämodialyse beizubehalten, der für einen Zeitraum von mindestens 6 Stunden nach der Dialyse niedriger ist als ein Phosphatgehalt im Serum vor der Hämodialyse, sodass der Phosphatgehalt im Serum des Patienten in den ersten 6 Stunden nach der Dialyse um weniger als 10 % ansteigt.

2. Zusammensetzung zur Verwendung nach Anspruch 1, wobei die Zusammensetzung ein pharmazeutisch unbedenkliches Salz von SEQ ID NO:3 umfasst.

3. Zusammensetzung zur Verwendung nach Anspruch 2, wobei das Salz ein Hydrochloridsalz ist.

4. Zusammensetzung zur Verwendung nach einem der Ansprüche 1-3, wobei die Zusammensetzung während eines Rückspülungsvorgangs am Ende der Dialyse verabreicht wird.

5. Zusammensetzung zur Verwendung nach einem der Ansprüche 1-4, wobei der Patient mit einem phosphatbindenden Mittel behandelt wird.

6. Zusammensetzung zur Verwendung nach einem der Ansprüche 1-5, wobei die Verabreichung dafür wirksam ist, einen Phosphatgehalt im Serum nach der Hämodialyse beizubehalten, der für einen interdialytischen Zeitraum mindestens 10 % niedriger ist als ein Phosphatgehalt im Serum vor der Hämodialyse.

7. Zusammensetzung zur Verwendung nach einem der Ansprüche 1-5, wobei der Patient aufgrund von sekundärem Hyperparathyreoidismus oder primärem Hyperparathyreoidismus behandelt wird.

8. Zusammensetzung nach einem der Ansprüche 1-4, wobei der Patient nicht mit einem phosphatbindenden Mittel behandelt wird.

Revendications

1. Composition pour une utilisation dans le traitement des troubles minéraux et osseux de la maladie rénale chronique (TMO-MRC) chez un patient recevant une hémodialyse, la composition comprenant un composé comprenant Ac-c(C)arrrar-NH_2 (SEQ ID NO : 3) ;
dans laquelle le taux de phosphate sérique du patient est estimé et trouvé supérieur à la plage normale ;
dans laquelle la composition est administrée au sein de la période débutant 15 minutes avant le terme de l'hémodialyse et se terminant 3 heures après le terme de l'hémodialyse ; dans laquelle le patient a été diagnostiqué avec une hyperphosphatémie ; et dans laquelle ladite administration est efficace pour maintenir un taux de phosphore sérique post-hémodialyse qui est inférieur à un taux de phosphore sérique pré-hémodialyse pendant une période d'au moins 6 heures après la dialyse de telle façon que le phosphore sérique du patient augmente de moins de 10 % au cours des 6 premières heures après la dialyse.

2. Composition pour une utilisation selon la revendication 1, dans laquelle le composé comprend un sel pharmaceutiquement acceptable de SEQ ID NO : 3.

3. Composition pour une utilisation selon la revendication 2, dans laquelle le sel est un sel chlorhydrate.

4. Composition pour une utilisation selon l'une quelconque des revendications 1 à 3, dans laquelle le composé est administré durant la procédure de rétro-rinçage à la fin de la dialyse.

5. Composition pour une utilisation selon l'une quelconque des revendications 1 à 4, dans laquelle le patient est traité avec un agent de liaison des phosphates.

6. Composition pour une utilisation selon l'une quelconque des revendications 1 à 5, dans laquelle ladite administration est efficace pour maintenir un taux de phosphore sérique post-hémodialyse qui est au moins de 10 % inférieur à un taux de phosphore sérique pré-hémodialyse pendant une période interdialytique.

7. Composition pour une utilisation selon l'une quelconque des revendications 1 à 5, dans laquelle le patient est traité pour une hyperparathyroïdie secondaire ou une hyperparathyroïdie primaire.

8. Composition selon l'une quelconque des revendications 1 à 4, dans laquelle le patient n'est pas traité avec un agent de liaison des phosphates.

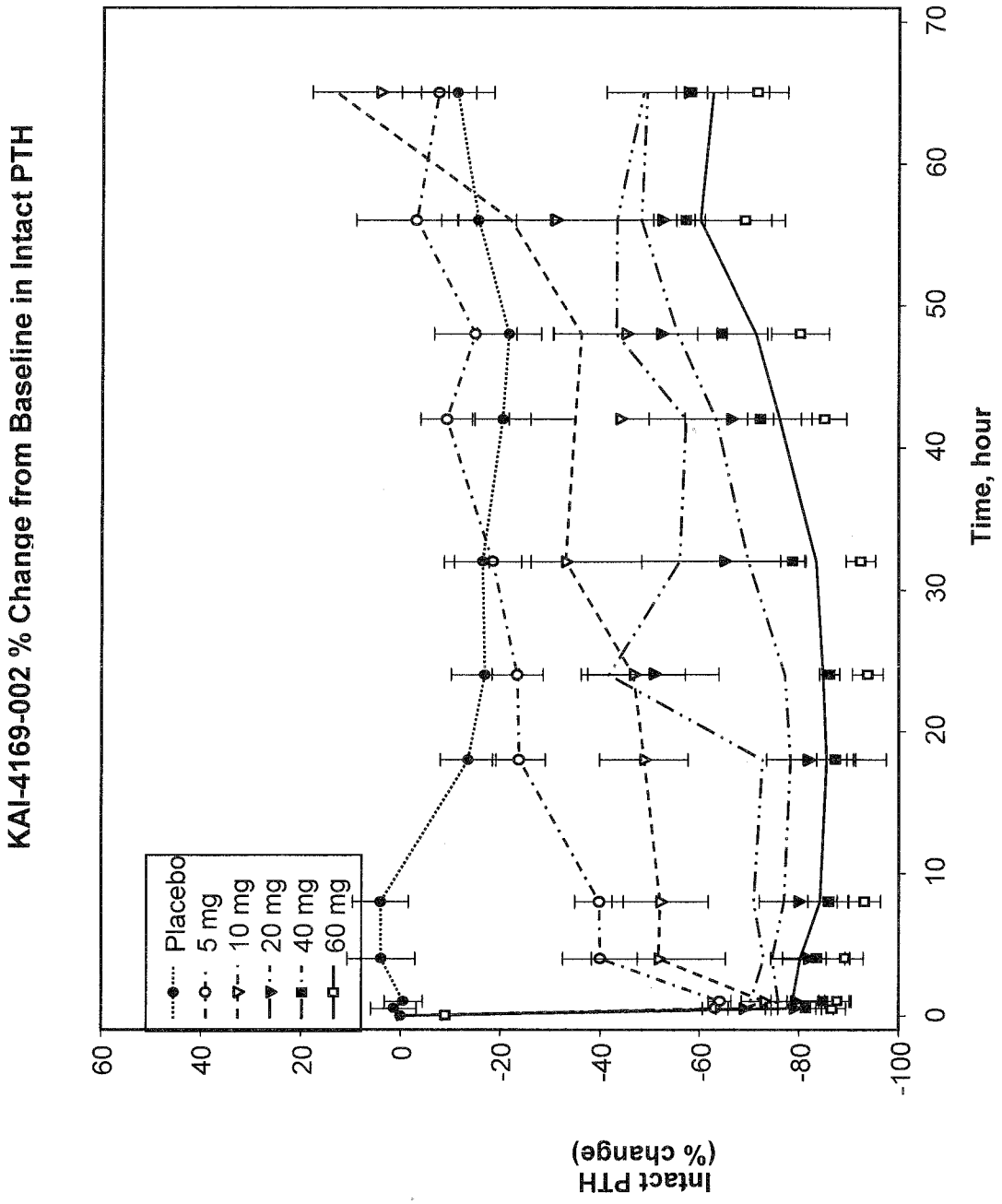
KAI-4169-002 % Change from Baseline in Intact PTH
Placebo
5 mg
10 mg
20 mg
40 mg
60 mg
Intact PTH (% change)
60
40
20
0
-20
-40
-60
-80
-100
0
10
20
30
40
50
60
70
Time, hour

Fig. 1

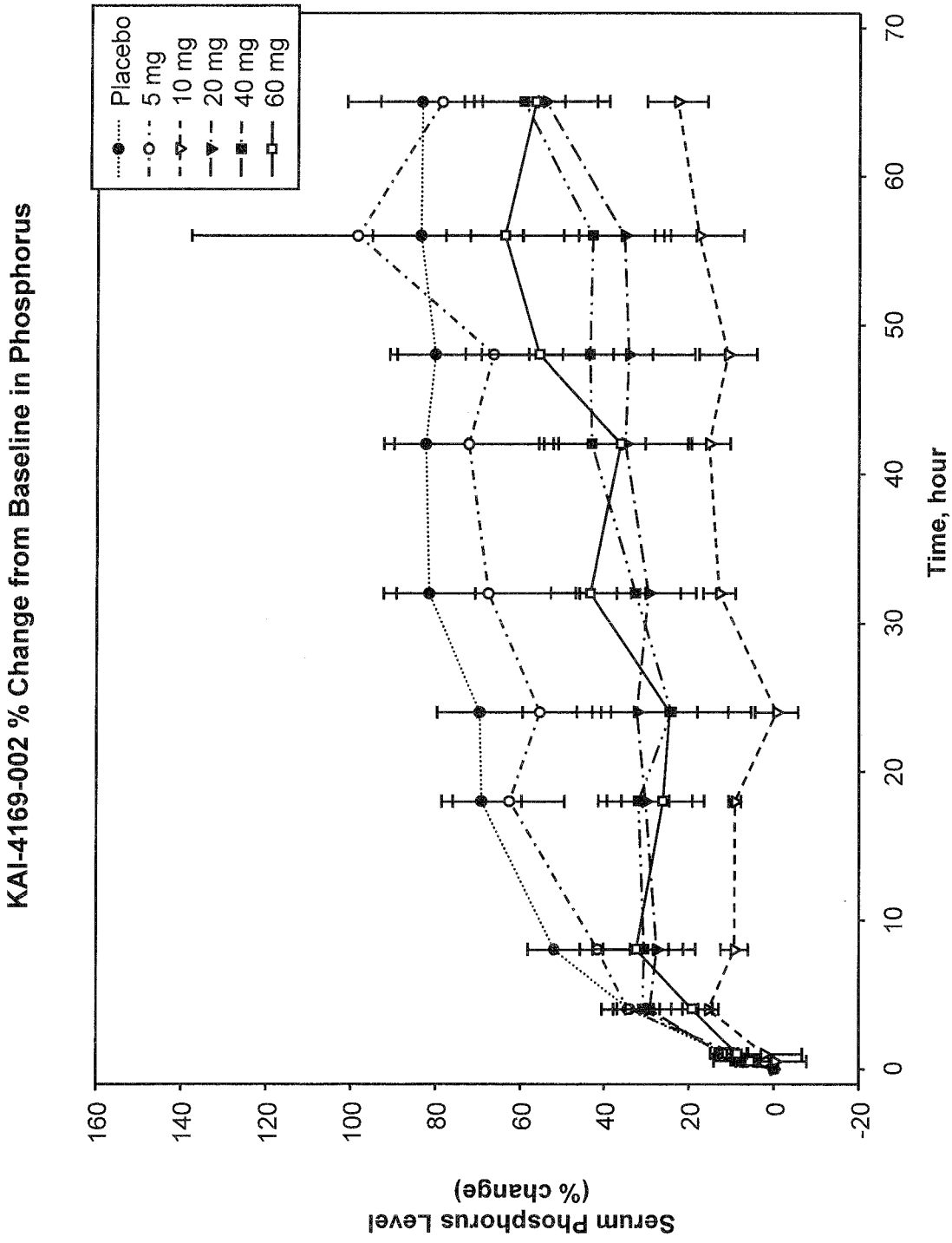
KAI-4169-002 % Change from Baseline in Phosphorus
Placebo
5 mg
10 mg
20 mg
40 mg
60 mg
Serum Phosphorus Level
(% change)
160
140
120
100
80
60
40
20
0
-20
0
10
20
30
40
50
60
70
Time, hour

Fig. 2

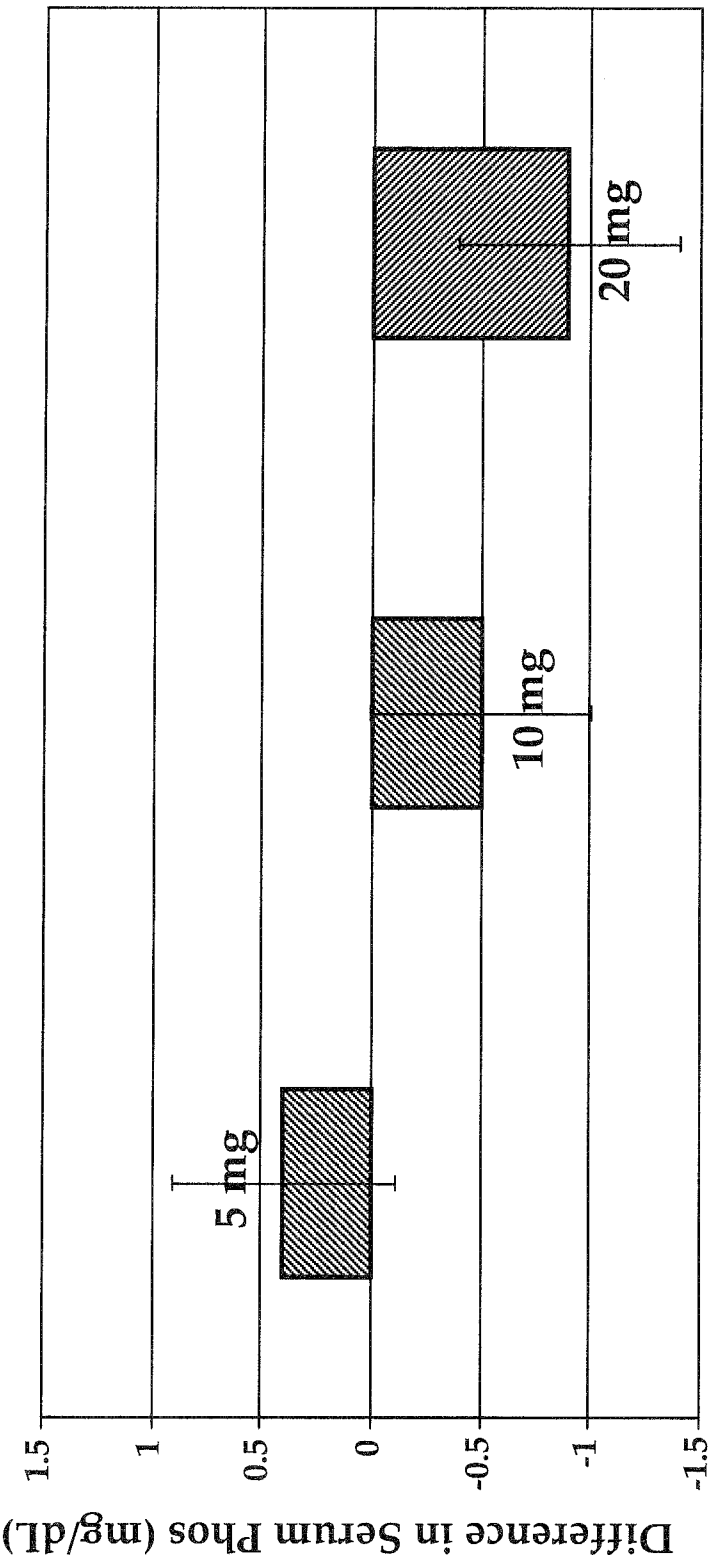
Difference in Serum Phos (mg/dL)
1.5
1
0.5
0
-0.5
-1
-1.5
5 mg
10 mg
20 mg
Dose Group

Fig. 3

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

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- US 6031003 A **[0079] [0082]**
- US 20110028394 A **[0079] [0082]**
- US 20090023652 A **[0079] [0082]**
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SZABADALMI IGÉNYPONTOK

1. Készítmény a krónikus veseelégtelenségben kialakuló csont és ásványianyagcsere-zavar (CKD-MBD) kezelésében való felhasználásra hemodialízisben részesülő betegnél, ahol a készítmény Ac-c(C)arrrar-NH_2-t (SEQ ID NO:3) tartalmazó vegyületet tartalmaz;
   ahol a beteg szérumfoszfátszintjét megvizsgálták és a normál tartomány fölöttinek találták;
   ahol a készítmény beadása a 15 perccel a hemodialízis befejezése előtt kezdődő és 3 órával utána befejeződő időszakon belül történik; ahol a beteget hiperfoszfatémiával diagnosztizálták; és ahol a készítmény említett beadása elég hatékony ahhoz, hogy a szérum hemodialízis utáni foszforszintjét a hemodialízis előtti szintnél alacsonyabban tartsa a dialízis után legalább 6 órán keresztül úgy, hogy a beteg szérumfoszforszintje 10%-nál kisebb mértékben növekszik a dialízis utáni első 6 órában.

2. Az 1. igénypont szerinti felhasználásra szánt készítmény, ahol a készítmény tartalmazza a SEQ ID NO:3 egy gyógyászatilag elfogadható sóját.

3. A 2. igénypont szerinti felhasználásra szánt készítmény, ahol a só hidroklorid só.

4. Az 1-3. igénypontok bármelyike szerinti felhasználásra szánt készítmény, ahol a vegyület beadása a dialízis végén végzett visszaöblítési eljárás alatt történik.

5. Az 1-4. igénypontok bármelyike szerinti felhasználásra szánt készítmény, ahol a beteget foszfátkötő szerrel kezelik.

6. Az 1-5. igénypontok bármelyike szerinti felhasználásra szánt készítmény, ahol a készítmény említett beadása elég hatékony ahhoz, hogy a szérum hemodialízis utáni foszforszintjét a hemodialízis előtti szintnél legalább 10%-kal alacsonyabban tartsa egy interdialitikus időszakra.

7. Az 1-5. igénypontok bármelyike szerinti felhasználásra szánt készítmény, ahol a beteget szekunder hyperparathyreosis vagy primer hyperparathyreosis betegséggel kezelik.

8. Az 1-4. igénypontok bármelyike szerinti készítmény, ahol a beteget nem kezelik foszfátkötő szerrel.