TREATING CHRONIC KIDNEY DISEASE WITH A COMBINATION OF SLC6A19 INHIBITOR AND GLP-1 AGONIST

RELATED APPLICATION

This application claims the benefit of priority to U.S. Provisional Patent Application Serial No. 63/633,423, filed April 12, 2024.

BACKGROUND

Chronic kidney disease (CKD) is a condition where the kidneys progressively lose their function to properly filter and remove waste and excess fluids from the body. Two of the most common causes of kidney disease are diabetes and high blood pressure. The disease can progress to end-stage renal failure which can only be treated by dialysis or kidney transplant. Diagnosis of CKD can be based on the measurement of low glomerular filtration rate (GFR), or by significant albuminuria. Patients are categorized into five stages of CKD (1-5), with stages 4-5 being the most severe (GFR <30 mL/min/1.73 m2). Once kidney damage has occurred, it is not reversible. Therapeutics that can slow the progression of chronic kidney disease are the current standard of care, and include antihypertensive agents and diuretics. In addition, GLP-1 (glucagon-like receptor agonists) and GIP (glucose-dependent insulinotropic peptides) have shown efficacy in clinical trials of CKD. Drugs that target these receptors act by mimicking natural hormones that regulate glucose metabolism and appetite. In addition to slowing the progression of CKD, administration of GLP-1 and GIP modulators have shown improvements in hyperglycemia, hypertension, and reducing body weight (BW).

Another kidney transporter that has been linked to CKD is SLC6A19. SLC6A19 is located in the proximal tubule of the kidney and is responsible for reabsorption of amino acids back into the blood. Genome-wide association studies (GWAS) have shown associations between SLC6A19 LOF or missense variants and improvements in biomarkers of kidney function. In addition, preclinical studies suggest that genetic deletion of SLC6A19 may offer some protection in a mouse model of kidney disease.

SUMMARY

One aspect of the invention provides a method of treating or preventing a disease or disorder, comprising co-administering to a patient in need thereof an effective amount of a SLC6A19 inhibitor and an effective amount of a second agent, wherein the second agent comprises a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist, wherein the disease or disorder is selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD).

Another aspect of the invention provides a method for treating or preventing chronic kidney disease (CKD), comprising co-administering to a patient in need thereof an effective amount of a SLC6A19 inhibitor and an effective amount of a GLP-1 agonist.

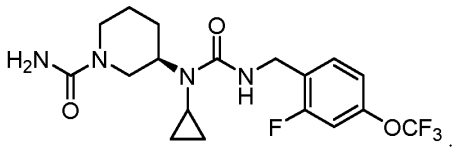
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Another aspect of the invention provides a method for treating or preventing chronic kidney disease (CKD), comprising orally co-administering to a patient in need thereof an effective amount of a SLC6A19 inhibitor and an effective amount of a dual GLP-1/GIP agonist.

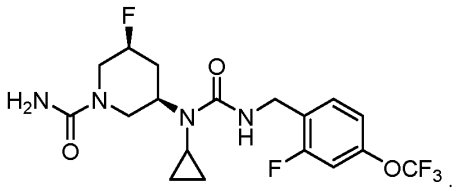
Another aspect of the invention provides a method for treating or preventing nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD), comprising co-administering to a patient in need thereof an effective amount of a SLC6A19 inhibitor and an effective amount of a GLP-1 agonist, a GIP agonist, or a dual GLP-1/GIP agonist.

Another aspect of the invention provides a method for treating or preventing nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD), comprising orally co-administering to a patient in need thereof an effective amount of a SLC6A19 inhibitor and an effective amount of a GLP-1 agonist, a GIP agonist, or a dual GLP-1/GIP agonist.

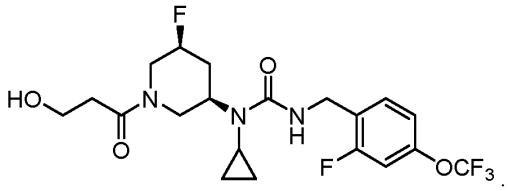
In certain embodiments, the SLC6A19 inhibitor is



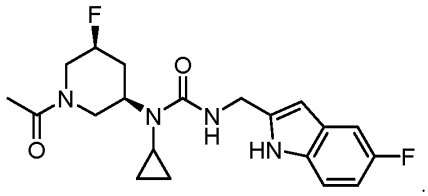
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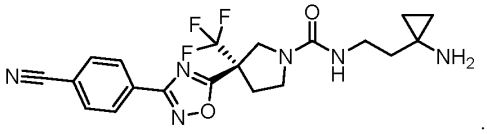
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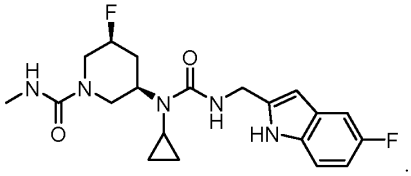
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In some embodiments, the SLC6A19 inhibitor is MZE782 (Maze Therapeutics).

In some embodiments, the SLC6A19 inhibitor is a compound disclosed in WO 2025/049604, WO 2024/112831, WO 2024/112830, or WO 2024/081748, each of which is incorporated herein by reference in its entirety.

In certain embodiments, the GLP-1 agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In certain embodiments, the GIP agonist is selected from Tirzepatide.

In certain embodiments, the dual GLP-1/GIP agonist is selected from Tirzepatide.

In some embodiments, the present disclosure relates to a method of treating or preventing nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD), wherein the SLC6A19 inhibitor is MZE782 (Maze Therapeutics); and the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In some embodiments, the present disclosure relates to a SLC6A19 inhibitor for use in the treatment or prevention of a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD), wherein the treatment or prevention of the disease or disorder further comprises co-administration of an effective amount of a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

In some embodiments, the present disclosure relates to a pharmaceutical composition comprising a SLC6A19 inhibitor and a second agent for use in the treatment or prevention of a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD), wherein the second agent comprises a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

In some embodiments, the present disclosure relates to a composition comprising SLC6A19 inhibitor for use in the treatment or prevention of a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD),

non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD), wherein the treatment or prevention of the disease or disorder further comprises co-administration of an effective amount of a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

In some embodiments, the present disclosure relates to use of a SLC6A19 inhibitor in the manufacture of a medicament for the treatment or prevention of a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD), wherein the treatment or prevention of the disease or disorder further comprises co-administration of an effective amount of a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

In some embodiments, the present disclosure relates to use of a SLC6A19 inhibitor in the manufacture of a medicament for the treatment or prevention of a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD), wherein the medicament further comprises a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features, objects, and advantages of the invention will be apparent from the detailed description, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing total body weight (in grams) of mice raised on either a control diet (Ctrl Diet) or a high fat diet (DIO) and treated daily with either vehicle (Veh), 100 mg/kg (p.o.) compound 5, 10 nmol/kg (s.c.) semaglutide or 100 mg/kg compound 5 + 10 nmol/kg semaglutide starting at day 0. Data represent mean ± S.E.M for 8-12 mice per group.

FIG. 2 is a graph showing percent change in body weight from day 0 of mice raised on either a control diet (Ctrl Diet) or a high fat diet (DIO) and treated daily with either vehicle (Veh), 100 mg/kg (p.o.) compound 5, 10 nmol/kg (s.c.) semaglutide or 100 mg/kg compound 5 + 10 nmol/kg semaglutide. Data represent mean ± S.E.M for 8-12 mice per group.

FIG. 3 is a graph showing fasting blood glucose of mice raised on either a control diet (Ctrl Diet) or a high fat diet (DIO) and treated daily with either vehicle (Veh), 100 mg/kg (p.o.) compound 5, 10 nmol/kg (s.c.) semaglutide or 100 mg/kg compound 5 + 10 nmol/kg semaglutide starting at day 0. Fasting glucose was measured pre-treatment inception (Day -2) and after 14 days of treatment. Data represent mean ± S.E.M for 8-12 mice per group. Two-way ANOVA followed by Tukey's post hoc analysis. * $p < 0.05$, *** $p < 0.001$.

FIG. 4 is a graph showing 120-minute blood glucose area under the curve (AUC) in mice raised on either a control diet (Ctrl Diet) or a high fat diet (DIO) and treated daily with either vehicle (Veh), 100 mg/kg (p.o.) compound 5, 10 nmol/kg (s.c.) semaglutide or 100 mg/kg compound 5 + 10 nmol/kg semaglutide starting at day 0. Data represent mean ± S.E.M for 8-12 mice per group. One-way ANOVA followed by Tukey's post hoc test. *** $p < 0.001$.

FIG. 5 is a graph showing blood glucose concentration following oral glucose challenge in mice raised on either a control diet (Ctrl Diet) or a high fat diet (DIO) and treated daily with either vehicle (Veh), 100 mg/kg (p.o.) compound 5, 10 nmol/kg (s.c.) semaglutide or 100 mg/kg compound 5 + 10 nmol/kg semaglutide starting at day 0. Data represent mean ± S.E.M for 8-12 mice per group. One-way ANOVA followed by Tukey's post hoc test. *** $p < 0.001$.

DETAILED DESCRIPTION

Definitions

For convenience, before further description of the present invention, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

In order for the present invention to be more readily understood, certain terms and phrases are defined below and throughout the specification.

The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with "and/or" should be construed in the same fashion, i.e., "one or more" of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to "A and/or B", when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of" or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e., "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or "exactly one of." "Consisting essentially of," when used in the claims, shall have its ordinary meaning as used in the field of patent law.

As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited.

In the claims, as well as in the specification above, all transitional phrases such as "comprising," "including," "carrying," "having," "containing," "involving," "holding," "composed of," and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases "consisting of" and "consisting essentially of" shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, polymers of the present invention may also be optically active. The present invention contemplates all such compounds, including cis- and trans-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention.

Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

“Geometric isomer" means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon- carbon double bond may be in an E (substituents are on opposite sides of the carbon- carbon double bond) or Z (substituents are oriented on the same side) configuration. "R," "S," "S*," "R*," "E," "Z," "cis," and "trans," indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in “atropisomeric” forms or as “atropisomers.” Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from a mixture of isomers. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods.

If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Percent purity by mole fraction is the ratio of the moles of the enantiomer (or diastereomer) or over the moles of the enantiomer (or diastereomer) plus the moles of its optical isomer. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or

named diastereomer is at least about 60%, about 70%, about 80%, about 90%, about 99% or about 99.9% by mole fraction pure.

When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound or mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers. The invention embraces all of these forms.

Structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds produced by the replacement of a hydrogen with deuterium or tritium, or of a carbon with a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

A “therapeutically effective amount” (or “effective amount”) of a compound with respect to use in treatment, refers to an amount of the compound in a preparation which, when administered as part of a desired dosage regimen (to a mammal, preferably a human) alleviates a symptom, ameliorates a condition, or slows the onset of disease conditions according to clinically acceptable standards for the disorder or condition to be treated or the cosmetic purpose, e.g., at a reasonable benefit/risk ratio applicable to any medical treatment.

The term “prophylactic or therapeutic” treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic, (i.e., it protects the host against developing the unwanted condition), whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic, (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

The term “patient” or “subject” refers to a mammal in need of a particular treatment. In certain embodiments, a patient is a primate, canine, feline, or equine. In certain embodiments, a patient is a human.

The terms “decrease,” “reduce,” “reduced”, “reduction”, “decrease,” and “inhibit” are all used herein generally to mean a decrease by a statistically significant amount relative to a reference. However, for avoidance of doubt, “reduce,” “reduction” or “decrease” or “inhibit” typically means a decrease by at least 10% as compared to a reference level and can include, for example, a decrease by at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, up to and including, for example, the complete absence of the given entity or parameter ascompared to the reference level, or any decrease between 10-99% as compared to the absence of a given treatment.

The terms “increased”, “increase” or “enhance” or “activate” are all used herein to generally mean an increase by a statically significant amount; for the avoidance of any doubt, the terms “increased”, “increase” or “enhance” or “activate” means an increase of at least 10% as compared to a reference level, for example an increase of at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least about 90% or up to and including a 100% increase or any increase between 10-100% as compared to a reference level, or at least about a 2-fold, or at least about a 3-fold, or at least about a 4-fold, or at least about a 5-fold or at least about a 10-fold increase, or any increase between 2-fold and 10-fold or greater as compared to a reference level.

As used herein, a therapeutic that “prevents” or “reduces the risk of developing” a disease, disorder, or condition refers to a compound that, in a statistical sample, reduces the occurrence of the disease, disorder, or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.

The term “treating” includes prophylactic and/or therapeutic treatments. The term “prophylactic or therapeutic” treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic (i.e., it protects the host against developing the

unwanted condition), whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic, (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

As used herein, the term "modulate" includes up-regulation and down-regulation, e.g., enhancing or inhibiting a response.

As used herein, the terms "co-administration" and "conjoint administration" refer to any form of administration of two or more different therapeutic agents such that the second agent is administered while the previously administered therapeutic agent is still effective in the body (e.g., the two agents are simultaneously effective in the patient, which may include synergistic effects of the two agents). For example, the different therapeutic compounds can be administered either in the same formulation or in separate formulations, either concomitantly or sequentially. Thus, an individual who receives such treatment can benefit from a combined effect of different therapeutic agents.

As used herein, the term "SLC6A19 inhibitor" includes any agent, e.g. a small molecule, which inihibits Solute Carrier Family 6 Member 19 (SLC6A19). Such inhibitors include, but are not limited to, Compounds 1 to 6 disclosed herein and compound MZE782 (developed by Maze Therapeutics).

As used herein, the term "GLP-1 agonist" or "GLP-1 receptor agonist" includes any agent, e.g., a peptide, which is an agonist of, i.e. agent which activates, glucagon-like peptide 1 (GLP-1). Such agonists include, but are not limited to, Tirzepatide, Semaglutide, Dulaglutide, Exanatide, Liraglutide, and Lixisenatide.

As used herein, the term "GIP agonist" includes any agent, e.g., a peptide, which is an agonist of, i.e. agent which activates, gastric inhibitory peptide (GIP). Such agonists include, but are not limited to, Tirzepatide.

As used herein, the term "dual GLP-1/GIP agonist" includes any agent, e.g., a peptide, which is an agonist of, i.e. agent which activates, glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP). Such dual agonists include, but are not limited to, Tirzepatide.

Methods of Treatment

One aspect of the invention provides a method of treating or preventing a disease or disorder, comprising co-administering to a patient in need thereof an effective amount of a SLC6A19 inhibitor and an effective amount of a second agent, wherein the second agent comprises a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist, wherein the

disease or disorder is selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD).

In some embodiments, the disease or disorder is type 1 or type 2 diabetes mellitus.

In some embodiments, the disease or disorder is type 2 diabetes mellitus.

In some embodiments, the disease or disorder is obesity.

In some embodiments, the disease or disorder is nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD).

In some embodiments, the disease or disorder is chronic kidney disease.

In some embodiments, the SLC6A19 inhibitor and the second agent are co-administered.

In some embodiments, the treatment reduces the risk of developing and/or delays the progression of type 1 or type 2 diabetes mellitus or obesity in the patient.

In some embodiments, the treatment reduces excess body weight and maintains weight reduction in a patient who is obese.

In some embodiments, the patient is an adult patient.

In some embodiments, the patient is an elderly patient.

In some embodiments, the patient is a pediatric patient.

In some embodiments, the SLC6A19 inhibitor is administered conjointly with the second agent.

In some embodiments, the SLC6A19 inhibitor and the second agent are simultaneously administered to the patient.

In some embodiments, the SLC6A19 inhibitor and the second agent are administered in the same formulation.

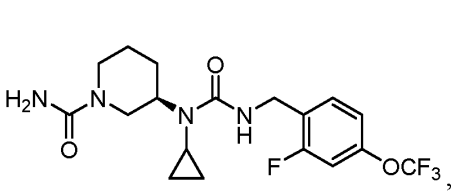
In some embodiments, the SLC6A19 inhibitor and the second agent are administered in separate formulations.

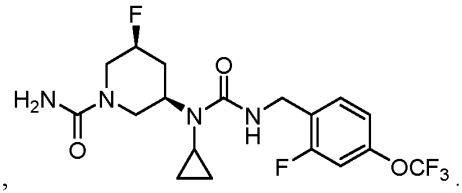
In some embodiments, the SLC6A19 inhibitor and the second agent are sequentially administered to the patient.

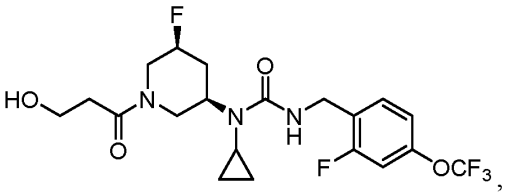
In some embodiments, the SLC6A19 inhibitor and the second agent are administered orally.

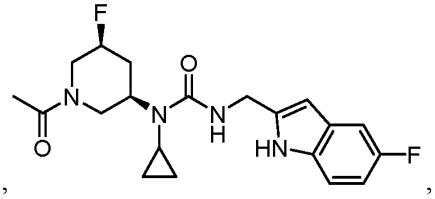
In some embodiments, the SLC6A19 inhibitor is administered orally; and the second agent is administered by subcutaneous injection.

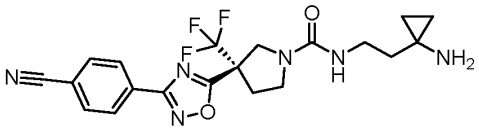
In some embodiments, the SLC6A19 inhibitor is selected from:

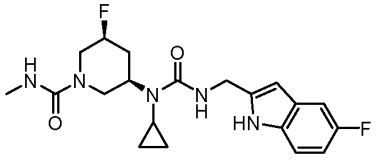

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, and


, or a pharmaceutically acceptable salt thereof.

In some embodiments, the SLC6A19 inhibitor is MZE782 (Maze Therapeutics).

In some embodiments, the SLC6A19 inhibitor is a compound disclosed in WO 2025/049604, WO 2024/112831, WO 2024/112830, or WO 2024/081748, each of which is incorporated herein by reference in its entirety.

In some embodiments, the second agent is a GLP-1 receptor agonist.

In some embodiments, the second agent comprises a GLP-1 receptor agonist and an amylin receptor agonist.

In some embodiments, the second agent comprises a GLP-1 receptor agonist and a glucagon agonist.

In some embodiments, the second agent comprises a GLP-1 receptor agonist and a GIP antagonist.

In some embodiments, the second agent comprises a GLP-1 receptor agonist and a dual amylin/calcitonin receptor agonist (DACRA).

In some embodiments, the second agent comprises a GLP-1 receptor agonist and a GLP-2 receptor agonist.

In some embodiments, the second agent comprises a GLP-1 receptor agonist and an activin receptor II inhibitor.

In some embodiments, the second agent is a GLP-1 receptor agonist.

In some embodiments, the GLP-1 receptor agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, Lixisenatide, Orforglipron, combination of Semaglutide and Cagrilintide, combination of Semaglutide and Bimagrumab, Survodutide, Retatrutide, Danuglipron, Lotiglipron, Mazdutide, Maridebart cafraglutide, Efinopegdutide, Pemvidutide, and Dapiglutide.

In some embodiments, the GLP-1 receptor agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In some embodiments, the second agent is a dual GLP-1/glucagon agonist. As used herein, the term "dual GLP-1/glucagon agonist" includes any agent, e.g., a peptide, which is an agonist of, i.e. agent which activates, glucagon-like peptide 1 receptor (GLP-1) and glucagon receptor.

In some embodiments, the second agent is a dual GLP-1/amylin receptor agonist. As used herein, the term "dual GLP-1/amylin receptor agonist" includes any agent, e.g., a peptide, which is an agonist of, i.e. agent which activates, glucagon-like peptide 1 receptor (GLP-1) and and amylin receptor.

In some embodiments, the second agent is a triple GLP-1/GIP /glucagon agonist. As used herein, the term "triple GLP-1/GIP /glucagon agonist" includes any agent, e.g., a peptide, which is an agonist of, i.e. agent which activates, glucagon-like peptide 1 receptor (GLP-1), glucose-dependent insulinotropic polypeptide receptor (GIP), and glucagon receptor.

In some embodiments, the second agent comprises a dual GLP-1/GIP agonist and a glucagon agonist.

In some embodiments, the second agent comprises a dual GLP-1/glucagon agonist and a GIP agonist.

In some embodiments, the second agent is a triple GLP-1/amylin/calcitonin receptor agonist. As used herein, the term "triple GLP-1/amylin/calcitonin receptor agonist" includes any agent, e.g., a peptide, which is an agonist of, i.e. agent which activates, glucagon-like peptide 1 receptor (GLP-1), amylin receptor, and calcitonin receptor.

In some embodiments, the second agent comprises a GLP-1 receptor agonist and a dual amylin/calcitonin receptor agonist. As used herein, the term "dual amylin/calcitonin

receptor agonist" includes any agent, e.g., a peptide, which is an agonist of, i.e. agent which activates, amylin receptor and calcitonin receptor.

In some embodiments, the second agent is a dual GLP-1/GLP-2 receptor agonist. As used herein, the term "dual GLP-1/GLP-2 receptor agonist" includes any agent, e.g., a peptide, which is an agonist of, i.e. agent which activates, glucagon-like peptide 1 receptor (GLP-1) and glucagon-like peptide 2 receptor (GLP-2).

In some embodiments, the second agent is a dual GLP-1 receptor agonist/activin receptor II inhibitor. As used herein, the term "dual GLP-1 receptor agonist/activin receptor II inhibitor" includes any agent, e.g., a peptide, which is an agonist of, i.e. agent which activates, glucagon-like peptide 1 receptor (GLP-1) and inhibits activin receptor II.

In some embodiments, the second agent is a GIP agonist.

In some embodiments, the second agent is a GIP agonist.

In some embodiments, the GIP agonist is Tirzepatide.

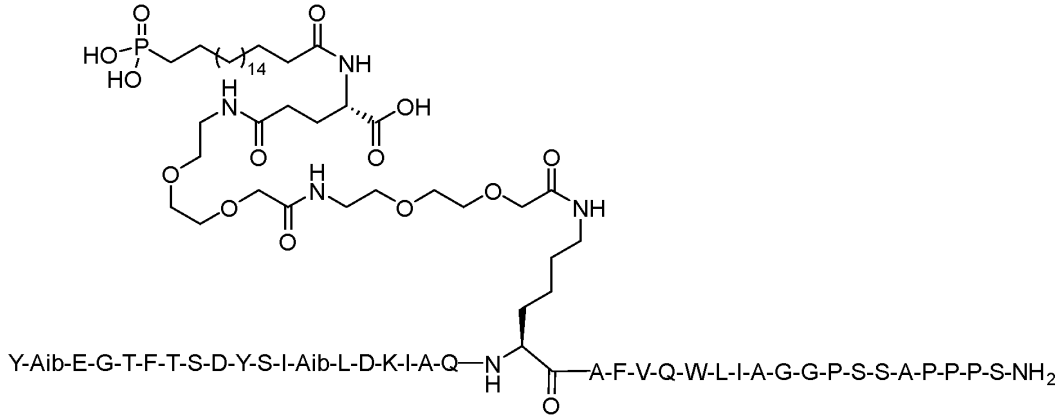
In some embodiments, the second agent is a dual GLP-1/GIP agonist.

In some embodiments, the dual GLP-1/GIP agonist is Tirzepatide.

In some embodiments, the GLP-1/GIP agonist is VK2735 (developed by Viking Therapeutics).

In some embodiments, the GLP-1/GIP agonist is a compound disclosed in WO 2024/192219, WO 2024/020388, WO 2024/020372, WO 2023/141044, WO 2023/044290, or WO 2022159395, each of which is incorporated herein by reference in its entirety.

In some embodiments, the GLP-1/GIP agonist is



(SEQ ID NO: 1).

In some embodiments, the GLP-1/GIP agonist is SCO-094 (developed by Scohia Pharma).

In some embodiments, the GLP-1/GIP agonist is a compound disclosed in WO 2014/192284, which is incorporated herein by reference in its entirety.

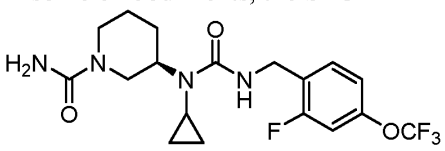
In some embodiments, the GLP-1/GIP agonist is selected from H-Tyr-Aib-Glu-Gly-Thr-αMePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Ala-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH_2 (SEQ ID NO: 2),
H-Tyr-Aib-Glu-Gly-Thr-αMePhe-Thr-Ser-Asp-Tyr-Aib-Ile-Aib-Leu-Asp-Lys-Gln-Ala-Gln-Ala-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH_2 (SEQ ID NO: 3),
H-Tyr-Aib-Glu-Gly-Thr-αMePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Gln-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH_2 (SEQ ID NO: 4), and
H-Tyr-Aib-Glu-Gly-Thr-αMePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Gln-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2 (SEQ ID NO: 5).

In some embodiments, the GLP-1/GIP agonist is CT-388 (Carmot Therapeutics).

In some embodiments, the GLP-1/GIP agonist is CT-996 (Carmot Therapeutics).

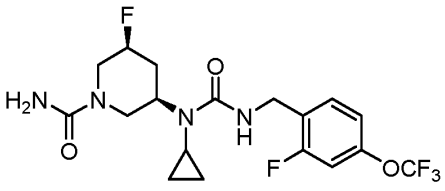
In some embodiments, the GLP-1/GIP agonist is a compound disclosed in WO 2019/183577, WO 2022/241287, WO 2024/243243, WO 2024/226540, WO 2022/235717, or WO 2024/026338, each of which is incorporated herein by reference in its entirety.

In some embodiments, the SLC6A19 inhibitor is



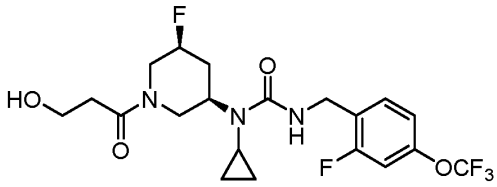
, or a pharmaceutically acceptable salt thereof; and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In some embodiments, the SLC6A19 inhibitor is



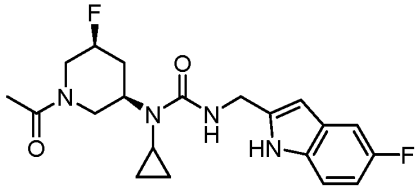
, or a pharmaceutically acceptable salt thereof; and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In some embodiments, the SLC6A19 inhibitor is



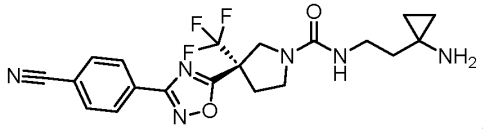
, or a pharmaceutically acceptable salt and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In some embodiments, the SLC6A19 inhibitor is



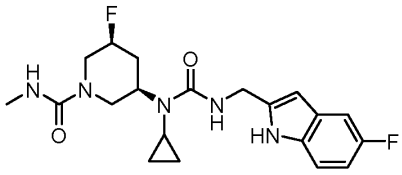
, or a pharmaceutically acceptable salt thereof; and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In some embodiments, the SLC6A19 inhibitor is



, or a pharmaceutically acceptable salt thereof; and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In some embodiments, the SLC6A19 inhibitor is



, or a pharmaceutically acceptable salt thereof; and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In some embodiments, the SLC6A19 inhibitor is MZE782 (developed by Maze Therapeutics); and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In some embodiments, the SLC6A19 inhibitor is a compound disclosed in WO 2025/049604, WO 2024/112831, WO 2024/112830, or WO 2024/081748, each of which is incorporated herein by reference in its entirety; and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In certain embodiments, the amounts of the SLC6A19 inhibitor and the second agent, taken together, are therapeutically effective to treat or prevent type 1 or type 2 diabetes mellitus, obesity, chronic kidney disease (CKD), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), or Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD).

The SLC6A19 inhibitor and the the second agent may be administered simultaneously or sequentially. When administered simultaneously, they can be administered in the same or separate formulations, but if separately they are administered substantially at the same time. The SLC6A19 inhibitor and the second agent are administered sequentially with one another when the administration of the SLC6A19 inhibitor and the second agent is temporally separated. The separation in time between the administration of these compounds may be a matter of minutes or it may be longer.

Based on the distinct mechanisms of SLC6A19 and GLP-1/GIP agonists, the combination of an SLC6A19 inhibitor and an GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist provides increased protection against CKD than compared to each single agent alone.

One aspect of the invention provides a method of treating or preventing chronic kidney disease, comprising co-administering to a patient in need thereof an effective amount of a SLC6A19 inhibitor and an effective amount of a GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist.

In certain embodiments, a SLC6A19 inhibitor and a GLP-1 agonist are co-administered. In certain embodiments, a SLC6A19 inhibitor and a GIP agonist are co-administered. In certain embodiments, a SLC6A19 inhibitor and a dual GLP-1/GIP agonist are co-administered.

In certain embodiments, the chronic kidney disease is stage 1. In certain embodiments, the chronic kidney disease is stage 2. In certain embodiments, the chronic kidney disease is stage 3. In certain embodiments, the chronic kidney disease is stage 4. In certain embodiments, the chronic kidney disease is stage 5.

In certain embodiments, the patient is also afflicted with type 1 or type 2 diabetes mellitus, cardiovascular disease, and/or obesity,

In certain embodiments, the chronic kidney disease is at risk of progression.

In certain embodiments, the treatment reduces the risk of developing and/or delays the progression of the chronic kidney disease in the patient.

Another aspect of the invention provides a method of treating or preventing nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD), comprising co-administering to a patient in need thereof an effective amount of a SLC6A19 inhibitor and an effective amount of a GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist.

In certain embodiments, a SLC6A19 inhibitor and a GLP-1 agonist are co-administered.

In certain embodiments, a SLC6A19 inhibitor and a GIP agonist are co-administered.

In certain embodiments, a SLC6A19 inhibitor and a dual GLP-1/GIP agonist are co-administered.

In certain embodiments, the treatment reduces the risk of developing and/or delays the progression of the nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD) in the patient.

In certain embodiments, the treatment reduces the risk of sustained decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease, cardiovascular death, and/or hospitalization in a patient with chronic kidney disease at risk of progression.

In certain embodiments, the treatment reduces the risk of cardiovascular death, hospitalization for heart failure, and/or urgent heart failure visits in a patient with heart failure.

In certain embodiments, the treatment reduces the risk of hospitalization for heart failure in a patient with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors.

In certain embodiments, the treatment reduces the risk of major adverse cardiovascular events (e.g., cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in a patient with established cardiovascular disease and either obesity or overweight.

In certain embodiments, the treatment reduces excess body weight and maintains weight reduction in a patient who is obese.

In certain embodiments, the treatment reduces or delays the loss of estimated glomerular filtration rate (eGFR), the progression to end stage renal disease/kidney failure in the patient, and/or the risk of progression to renal death in the patient.

In certain embodiments, the patient is an adult patient.

In certain embodiments, the patient is an elderly patient.

In certain embodiments, the patient is a pediatric patient.

In certain embodiments, the SLC6A19 inhibitor is administered conjointly with the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist.

In certain embodiments, the SLC6A19 inhibitor and the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist are simultaneously administered to the patient.

In certain embodiments, the SLC6A19 inhibitor and the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist are administered in the same formulation.

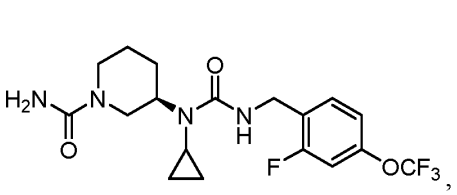
In certain embodiments, the SLC6A19 inhibitor and the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist are administered in separate formulations.

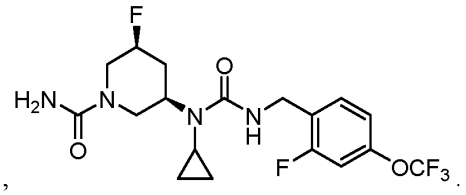
In certain embodiments, the SLC6A19 inhibitor and the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist are sequentially administered to the patient.

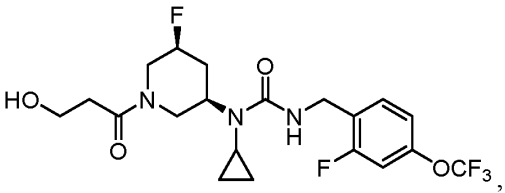
In certain embodiments, the SLC6A19 inhibitor and the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist are administered orally.

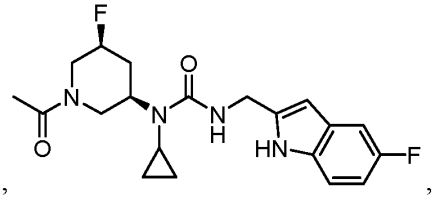
In certain embodiments, the SLC6A19 inhibitor is administered orally and the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist is administered by subcutaneous injection.

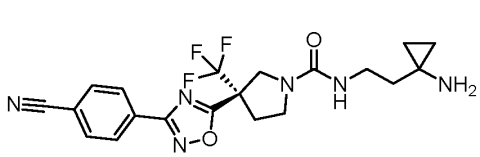
In certain embodiments, the SLC6A19 inhibitor is selected from:

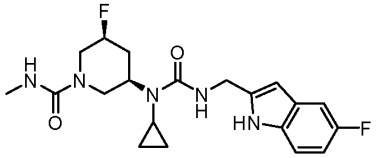

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, or a pharmaceutically acceptable salt thereof.

In some embodiments, the SLC6A19 inhibitor is MZE782 (Maze Therapeutics).

In some embodiments, the SLC6A19 inhibitor is a compound disclosed in WO 2025/049604, WO 2024/112831, WO 2024/112830, or WO 2024/081748, each of which is incorporated herein by reference in its entirety.

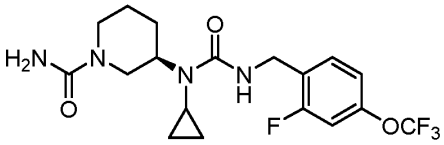
In certain embodiments, the GLP-1 receptor agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, Lixisenatide, Orforglipron, combination of Semaglutide and Cagrilintide, combination of Semaglutide and Bimagrumab, Survodutide, Retatrutide, Danuglipron, Lotiglipron, Mazdutide, Maridebart cafraglutide, Efinopegdutide, Pemvidutide, and Dapiglutide.

In certain embodiments, the GLP-1 agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In certain embodiments, the GIP agonist is Tirzepatide.

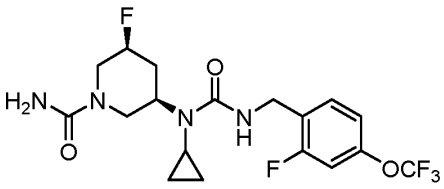
In certain embodiments, the dual GLP-1/GIP agonist is Tirzepatide.

In certain embodiments, the SLC6A19 inhibitor is



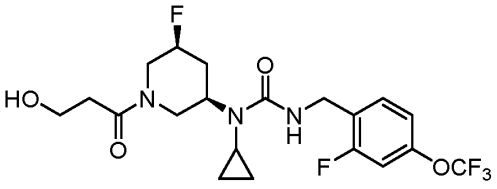
, or a pharmaceutically acceptable salt thereof; and the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In certain embodiments, the SLC6A19 inhibitor is



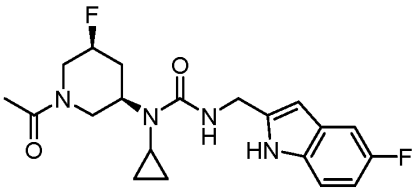
, or a pharmaceutically acceptable salt thereof; and the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In certain embodiments, the SLC6A19 inhibitor is



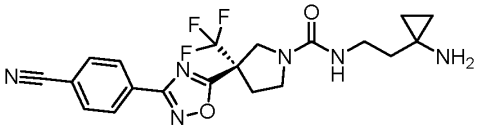
, or a pharmaceutically acceptable salt and the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In certain embodiments, the SLC6A19 inhibitor is



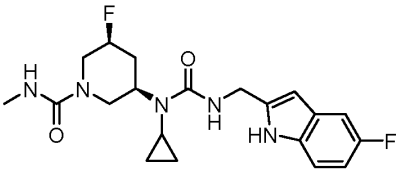
, or a pharmaceutically acceptable salt thereof; and the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In certain embodiments, the SLC6A19 inhibitor is



, or a pharmaceutically acceptable salt thereof; and the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In certain embodiments, the SLC6A19 inhibitor is



, or a pharmaceutically acceptable salt thereof; and the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In some embodiments, the SLC6A19 inhibitor is MZE782 (developed by Maze Therapeutics); and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In some embodiments, the SLC6A19 inhibitor is a compound disclosed in WO 2025/049604, WO 2024/112831, WO 2024/112830, or WO 2024/081748, each of which is incorporated herein by reference in its entirety; and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In some embodiments, the SLC6A19 inhibitor is MZE782 (Maze Therapeutics); and the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

In some embodiments, the present disclosure relates to a SLC6A19 inhibitor for use in the treatment or prevention of a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis

(NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), and chronic kidney disease, wherein the treatment or prevention of the disease or disorder further comprises co-administration of an effective amount of a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

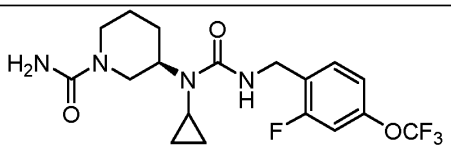
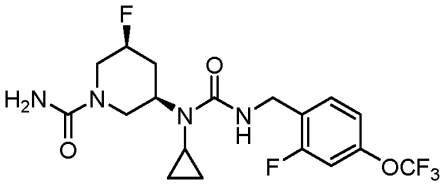
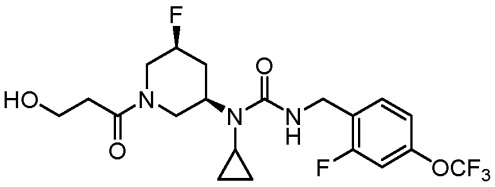
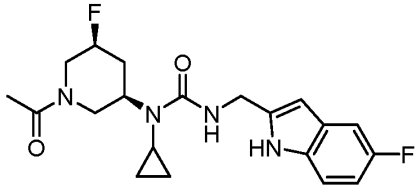
In some embodiments, the present disclosure relates to a pharmaceutical composition comprising SLC6A19 inhibitor and a second agent for use in the treatment or prevention of a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD)ase, wherein the second agent comprises a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

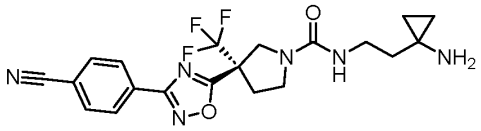
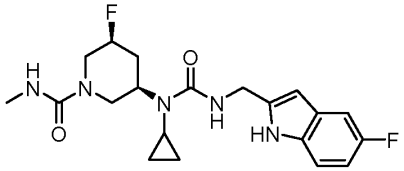
In some embodiments, the present disclosure relates to a composition comprising a SLC6A19 inhibitor for use in the treatment or prevention of a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD), wherein the treatment or prevention of the disease or disorder further comprises co-administration of an effective amount of a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

In some embodiments, the present disclosure relates to use of a SLC6A19 inhibitor in the manufacture of a medicament for the treatment or prevention of a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD), wherein the treatment or prevention of the disease or disorder further comprises co-administration of an effective amount of a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

In some embodiments, the present disclosure relates to use of a SLC6A19 inhibitor in the manufacture of a medicament for the treatment or prevention of a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD), wherein the medicament further comprises a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

In certain embodiments, the SLC6A19 inhibitor is selected from the following Table:

#	Structure	Name
1	 SLC6A19 IC_{50} = <500 nM	(R)-3-(1-cyclopropyl-3-(2-fluoro-4-(trifluoromethoxy)benzyl)ureido)piperidine-1-carboxamide
2	 SLC6A19 IC_{50} = <500 nM	(3R,5S)-3-(1-cyclopropyl-3-(2-fluoro-4-(trifluoromethoxy)benzyl)ureido)-5-fluoropiperidine-1-carboxamide
3	 SLC6A19 IC_{50} = <500 nM	1-cyclopropyl-1-((3R,5S)-5-fluoro-1-(3-hydroxypropanoyl)piperidin-3-yl)-3-(2-fluoro-4-(trifluoromethoxy)benzyl)urea
4	 SLC6A19 IC_{50} = <500 nM	1-((3R,5S)-1-acetyl-5-fluoropiperidin-3-yl)-1-cyclopropyl-3-((5-fluoro-1H-indol-2-yl)methyl)urea

5	 SLC6A19 IC_{50} = <1,500 nM	(S)-N-(2-(1-aminocyclopropyl)ethyl)-3-(3-(4-cyanophenyl)-1,2,4-oxadiazol-5-yl)-3-(trifluoromethyl)pyrrolidine-1-carboxamide
6	 SLC6A19 IC_{50} = <500 nM	(3R,5S)-3-(1-cyclopropyl-3-((5-fluoro-1H-indol-2-yl)methyl)ureido)-5-fluoro-N-methylpiperidine-1-carboxamide

In certain embodiments, the amount of the SLC6A19 inhibitor and the GLP-1 agonist or GIP agonist, taken together, are therapeutically effective to treat or prevent chronic kidney disease (CKD), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD).

In certain embodiments, the amount of the SLC6A19 inhibitor and the GIP agonist, taken together, are therapeutically effective to treat or prevent chronic kidney disease (CKD), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD).

In certain embodiments, the amount of the SLC6A19 inhibitor and the dual GLP-1/GIP agonist, taken together, are therapeutically effective to treat or prevent chronic kidney disease (CKD), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD).

In certain embodiments, the amount of the SLC6A19 inhibitor and the GLP-1 agonist or GIP agonist, taken together, are therapeutically effective to treat or prevent a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic

Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD).

In certain embodiments, the amount of the SLC6A19 inhibitor and the GIP agonist, taken together, are therapeutically effective to treat or prevent a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD).

In certain embodiments, the amount of the SLC6A19 inhibitor and the dual GLP-1/GIP agonist, taken together, are therapeutically effective to treat or prevent a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD).

The SLC6A19 inhibitor and the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist may be administered simultaneously or sequentially. When administered simultaneously, they can be administered in the same or separate formulations, but they are administered substantially at the same time. The SLC6A19 inhibitor and the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist are administered sequentially with one another when the administration of the SLC6A19 inhibitor and the GLP-1 agonist, GIP agonist, or dual GLP-1/GIP agonist is temporally separated. The separation in time between the administration of these compounds may be a matter of minutes or it may be longer.

Pharmaceutical Compositions

In certain embodiments, the invention relates to a pharmaceutical composition, comprising the SLC6A19 inhibitor, the GLP-1 agonist, and a pharmaceutically acceptable carrier for treating or preventing chronic kidney disease (CKD), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy,

glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD).

In certain embodiments, the invention relates to a pharmaceutical composition, comprising the SLC6A19 inhibitor, the GIP agonist, and a pharmaceutically acceptable carrier for treating or preventing chronic kidney disease (CKD), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD).

In certain embodiments, the invention relates to a pharmaceutical composition, comprising the SLC6A19 inhibitor, the dual GLP-1/GIP agonist, and a pharmaceutically acceptable carrier for treating or preventing chronic kidney disease (CKD), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD).

In certain embodiments, the invention relates to a first pharmaceutical composition, comprising a SLC6A19 inhibitor and a pharmaceutically acceptable carrier and a second pharmaceutical composition comprising a GLP-1 agonist and a pharmaceutically acceptable carrier, for treating or preventing chronic kidney disease (CKD), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD).

In certain embodiments, the invention relates to a first pharmaceutical composition, comprising a SLC6A19 inhibitor and a pharmaceutically acceptable carrier and a second pharmaceutical composition comprising a GIP agonist, and a pharmaceutically acceptable carrier, for treating or preventing chronic kidney disease (CKD), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD).

In certain embodiments, the invention relates to a first pharmaceutical composition, comprising a SLC6A19 inhibitor and a pharmaceutically acceptable carrier and a second pharmaceutical composition comprising a dual GLP-1/GIP agonist, and a pharmaceutically acceptable carrier, for treating or preventing chronic kidney disease (CKD), nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy,

glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD).

In certain embodiments, the invention relates to a pharmaceutical composition, comprising the SLC6A19 inhibitor, the GLP-1 agonist, and a pharmaceutically acceptable carrier for treating or preventing a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD).

In certain embodiments, the invention relates to a pharmaceutical composition, comprising the SLC6A19 inhibitor, the GIP agonist, and a pharmaceutically acceptable carrier for treating or preventing a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD).

In certain embodiments, the invention relates to a first pharmaceutical composition, comprising a SLC6A19 inhibitor and a pharmaceutically acceptable carrier and a second pharmaceutical composition comprising a GLP-1 agonist and a pharmaceutically acceptable carrier, for treating or preventing a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD).

In certain embodiments, the invention relates to a first pharmaceutical composition, comprising a SLC6A19 inhibitor and a pharmaceutically acceptable carrier and a second pharmaceutical composition comprising a GIP agonist, and a pharmaceutically acceptable carrier, for treating or preventing a disease or disorder selected from type 1 or type 2 diabetes

mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD).

In certain embodiments, the invention relates to a first pharmaceutical composition, comprising a SLC6A19 inhibitor and a pharmaceutically acceptable carrier and a second pharmaceutical composition comprising a dual GLP-1/GIP agonist, and a pharmaceutically acceptable carrier, for treating or preventing a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD).

In certain embodiments, the pharmaceutical composition is formulated as a tablet. In other embodiment, the pharmaceutical composition is formulated as a suspension.

The compositions and methods of the present invention may be utilized to treat a subject in need thereof. In certain embodiments, the subject is a mammal such as a human, or a non-human mammal. When administered to subject, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound of the invention and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil, or injectable organic esters. In preferred embodiments, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free, or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, suspension, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The

composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

A pharmaceutically acceptable carrier can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a compound such as a compound of the invention. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation or pharmaceutical composition can be a self-emulsifying drug delivery system or a self-microemulsifying drug delivery system. The pharmaceutical composition (preparation) also can be a liposome or other polymer matrix, which can have incorporated therein, for example, a compound of the invention. Liposomes, for example, which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase “pharmaceutically acceptable excipient” or “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject chemical from one organ or portion of the body, to another organ or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation, not injurious to the patient, and substantially non-pyrogenic. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose, and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin,

sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations. In certain embodiments, pharmaceutical compositions of the present invention are non-pyrogenic, i.e., do not induce significant temperature elevations when administered to a patient.

The term "pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of the compound(s). These salts can be prepared in situ during the final isolation and purification of the compound(s), or by separately reacting a purified compound(s) in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci*. 66:1-19.)

In other cases, the compounds useful in the methods of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic inorganic and organic base addition salts of a compound(s). These salts can likewise be prepared in situ during the final isolation and purification of the compound(s), or by separately reacting the purified compound(s) in its free acid form with a suitable base, such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like (see, for example, Berge et al., *supra*).

The term "pharmaceutically acceptable cocrystals" refers to solid coformers that do not form formal ionic interactions with the small molecule.

For any compound described herein the therapeutically effective amount can be initially determined from animal models. A therapeutically effective dose can also be determined from human data for compounds which have been tested in humans and for

compounds which are known to exhibit similar pharmacological activities, such as other related active agents. Higher doses may be required for parenteral administration. The applied dose can be adjusted based on the relative bioavailability and potency of the administered compound. Adjusting the dose to achieve maximal efficacy based on the methods described above and other methods as are well-known in the art is well within the capabilities of the ordinarily skilled artisan.

The formulations of the invention can be administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients.

For use in therapy, an effective amount of the compound can be administered to a subject by any mode that delivers the compound to the desired surface. Administering a pharmaceutical composition may be accomplished by any means known to the skilled artisan. Routes of administration include but are not limited to intravenous, intramuscular, intraperitoneal, intravesical (urinary bladder), oral, subcutaneous, direct injection (for example, into a tumor or abscess), mucosal (e.g., topical to eye), inhalation, and topical.

For intravenous and other parenteral routes of administration, a compound of the invention can be formulated as a lyophilized preparation, as a lyophilized preparation of liposome-intercalated or -encapsulated active compound, as a lipid complex in aqueous suspension, or as a salt complex. Lyophilized formulations are generally reconstituted in suitable aqueous solution, e.g., in sterile water or saline, shortly prior to administration.

For oral administration, the compounds can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained as solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Optionally the oral formulations may

also be formulated in saline or buffers, e.g., EDTA for neutralizing internal acid conditions or may be administered without any carriers.

Also specifically contemplated are oral dosage forms of the above component or components. The component or components may be chemically modified so that oral delivery of the derivative is efficacious. Generally, the chemical modification contemplated is the attachment of at least one moiety to the component molecule itself, where said moiety permits (a) inhibition of acid hydrolysis; and (b) uptake into the blood stream from the stomach or intestine. Also desired is the increase in overall stability of the component or components and increase in circulation time in the body. Examples of such moieties include: polyethylene glycol, copolymers of ethylene glycol and propylene glycol, carboxymethyl cellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone and polyproline. Abuchowski and Davis, "Soluble Polymer-Enzyme Adducts", In: Enzymes as Drugs, Hocenberg and Roberts, eds., Wiley-Interscience, New York, N.Y., pp. 367-383 (1981); Newmark et al., *J Appl Biochem* 4:185-9 (1982). Other polymers that could be used are poly-1,3-dioxolane and poly-1,3,6-tioxocane. For pharmaceutical usage, as indicated above, polyethylene glycol moieties are suitable.

For the component (or derivative) the location of release may be the stomach, the small intestine (the duodenum, the jejunum, or the ileum), or the large intestine. One skilled in the art has available formulations which will not dissolve in the stomach, yet will release the material in the duodenum or elsewhere in the intestine. Preferably, the release will avoid the deleterious effects of the stomach environment, either by protection of the compound of the invention (or derivative) or by release of the biologically active material beyond the stomach environment, such as in the intestine.

To ensure full gastric resistance a coating impermeable to at least pH 5.0 is essential. Examples of the more common inert ingredients that are used as enteric coatings are cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), HPMCP 50, HPMCP 55, polyvinyl acetate phthalate (PVAP), Eudragit L30D, Aquateric, cellulose acetate phthalate (CAP), Eudragit L, Eudragit S, and shellac. These coatings may be used as mixed films.

A coating or mixture of coatings can also be used on tablets, which are not intended for protection against the stomach. This can include sugar coatings, or coatings which make the tablet easier to swallow. Capsules may consist of a hard shell (such as gelatin) for delivery of dry therapeutic (e.g., powder); for liquid forms, a soft gelatin shell may be used.

The shell material of cachets could be thick starch or other edible paper. For pills, lozenges, molded tablets or tablet triturates, moist massing techniques can be used.

The therapeutic can be included in the formulation as fine multi-particulates in the form of granules or pellets of particle size about 1 mm. The formulation of the material for capsule administration could also be as a powder, lightly compressed plugs or even as tablets. The therapeutic could be prepared by compression.

Colorants and flavoring agents may all be included. For example, the compound of the invention (or derivative) may be formulated (such as by liposome or microsphere encapsulation) and then further contained within an edible product, such as a refrigerated beverage containing colorants and flavoring agents.

One may dilute or increase the volume of the therapeutic with an inert material. These diluents could include carbohydrates, especially mannitol, α-lactose, anhydrous lactose, cellulose, sucrose, modified dextrans and starch. Certain inorganic salts may be also be used as fillers including calcium triphosphate, magnesium carbonate and sodium chloride. Some commercially available diluents are Fast-Flo, Emdex, STA-Rx 1500, Emcompress and Avicell.

Disintegrants may be included in the formulation of the therapeutic into a solid dosage form. Materials used as disintegrates include but are not limited to starch, including the commercial disintegrant based on starch, Explotab. Sodium starch glycolate, Amberlite, sodium carboxymethylcellulose, ultramylopectin, sodium alginate, gelatin, orange peel, acid carboxymethyl cellulose, natural sponge and bentonite may all be used. Another form of the disintegrants are the insoluble cationic exchange resins. Powdered gums may be used as disintegrants and as binders and these can include powdered gums such as agar, Karaya or tragacanth. Alginic acid and its sodium salt are also useful as disintegrants.

Binders may be used to hold the therapeutic agent together to form a hard tablet and include materials from natural products such as acacia, tragacanth, starch and gelatin. Others include methyl cellulose (MC), ethyl cellulose (EC) and carboxymethyl cellulose (CMC). Polyvinyl pyrrolidone (PVP) and hydroxypropylmethyl cellulose (HPMC) could both be used in alcoholic solutions to granulate the therapeutic.

An anti-frictional agent may be included in the formulation of the therapeutic to prevent sticking during the formulation process. Lubricants may be used as a layer between the therapeutic and the die wall, and these can include but are not limited to; stearic acid including its magnesium and calcium salts, polytetrafluoroethylene (PTFE), liquid paraffin,

vegetable oils and waxes. Soluble lubricants may also be used such as sodium lauryl sulfate, magnesium lauryl sulfate, polyethylene glycol of various molecular weights, Carbowax 4000 and 6000.

Glidants that might improve the flow properties of the drug during formulation and to aid rearrangement during compression might be added. The glidants may include starch, talc, pyrogenic silica and hydrated silicoaluminate.

To aid dissolution of the therapeutic into the aqueous environment a surfactant might be added as a wetting agent. Surfactants may include anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate. Cationic detergents which can be used and can include benzalkonium chloride and benzethonium chloride. Potential non-ionic detergents that could be included in the formulation as surfactants include lauromacrogol 400, polyoxyl 40 stearate, polyoxyethylene hydrogenated castor oil 10, 50 and 60, glycerol monostearate, polysorbate 40, 60, 65 and 80, sucrose fatty acid ester, methyl cellulose and carboxymethyl cellulose. These surfactants could be present in the formulation of the compound of the invention or derivative either alone or as a mixture in different ratios.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Microspheres formulated for oral administration may also be used. Such microspheres have been well defined in the art. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For topical administration, the compound may be formulated as solutions, gels, ointments, creams, suspensions, etc. as are well-known in the art. Systemic formulations include those designed for administration by injection, e.g., subcutaneous, intravenous, intramuscular, intrathecal or intraperitoneal injection, as well as those designed for transdermal, transmucosal oral or pulmonary administration.

For administration by inhalation, compounds for use according to the present invention may be conveniently delivered in the form of an aerosol spray presentation from

pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Also contemplated herein is pulmonary delivery of the compounds disclosed herein (or salts thereof). The compound is delivered to the lungs of a mammal while inhaling and traverses across the lung epithelial lining to the blood stream. Other reports of inhaled molecules include Adjei et al., *Pharm Res* 7:565-569 (1990); Adjei et al., *Int J Pharmaceutics* 63:135-144 (1990) (leuprolide acetate); Braquet et al., *J Cardiovasc Pharmacol* 13(suppl. 5):143-146 (1989) (endothelin-1); Hubbard et al., *Annal Int Med* 3:206-212 (1989) (α1-antitrypsin); Smith et al., 1989, *J Clin Invest* 84:1145-1146 (a-1-proteinase); Oswein et al., 1990, "Aerosolization of Proteins", Proceedings of Symposium on Respiratory Drug Delivery II, Keystone, Colorado, March, (recombinant human growth hormone); Debs et al., 1988, *J Immunol* 140:3482-3488 (interferon-gamma and tumor necrosis factor alpha) and Platz et al., U.S. Pat. No. 5,284,656 (granulocyte colony stimulating factor; incorporated by reference). A method and composition for pulmonary delivery of drugs for systemic effect is described in U.S. Pat. No. 5,451,569 (incorporated by reference), issued Sep. 19, 1995 to Wong et al.

Contemplated for use in the practice of this invention are a wide range of mechanical devices designed for pulmonary delivery of therapeutic products, including but not limited to nebulizers, metered dose inhalers, and powder inhalers, all of which are familiar to those skilled in the art.

Some specific examples of commercially available devices suitable for the practice of this invention are the Ultravent nebulizer, manufactured by Mallinckrodt, Inc., St. Louis, Mo.; the Acorn II nebulizer, manufactured by Marquest Medical Products, Englewood, Colo.; the Ventolin metered dose inhaler, manufactured by Glaxo Inc., Research Triangle Park, North Carolina; and the Spinhaler powder inhaler, manufactured by Fisons Corp., Bedford, Mass.

All such devices require the use of formulations suitable for the dispensing of the compounds of the invention. Typically, each formulation is specific to the type of device employed and may involve the use of an appropriate propellant material, in addition to the usual diluents, adjuvants and/or carriers useful in therapy. Also, the use of liposomes,

microcapsules or microspheres, inclusion complexes, or other types of carriers is contemplated. Chemically modified compound of the invention may also be prepared in different formulations depending on the type of chemical modification or the type of device employed.

Formulations suitable for use with a nebulizer, either jet or ultrasonic, will typically comprise a compound of the invention (or derivative) dissolved in water at a concentration of about 0.1 to 25 mg of biologically active compound of the invention per mL of solution. The formulation may also include a buffer and a simple sugar (e.g., for inhibitor stabilization and regulation of osmotic pressure). The nebulizer formulation may also contain a surfactant, to reduce or prevent surface induced aggregation of the compound of the invention caused by atomization of the solution in forming the aerosol.

Formulations for use with a metered-dose inhaler device will generally comprise a finely divided powder containing the compound of the invention (or derivative) suspended in a propellant with the aid of a surfactant. The propellant may be any conventional material employed for this purpose, such as a chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol, and 1,1,1,2-tetrafluoroethane, or combinations thereof. Suitable surfactants include sorbitan trioleate and soya lecithin. Oleic acid may also be useful as a surfactant.

Formulations for dispensing from a powder inhaler device will comprise a finely divided dry powder containing compound of the invention (or derivative) and may also include a bulking agent, such as lactose, sorbitol, sucrose, or mannitol in amounts which facilitate dispersal of the powder from the device, e.g., 50 to 90% by weight of the formulation. The compound of the invention (or derivative) should advantageously be prepared in particulate form with an average particle size of less than 10 micrometers (μm), most preferably 0.5 to 5 μm, for most effective delivery to the deep lung.

Nasal delivery of a pharmaceutical composition of the present invention is also contemplated. Nasal delivery allows the passage of a pharmaceutical composition of the present invention to the blood stream directly after administering the therapeutic product to the nose, without the necessity for deposition of the product in the lung. Formulations for nasal delivery include those with dextran or cyclodextran.

For nasal administration, a useful device is a small, hard bottle to which a metered dose sprayer is attached. In one embodiment, the metered dose is delivered by drawing the

pharmaceutical composition of the present invention solution into a chamber of defined volume, which chamber has an aperture dimensioned to aerosolize and aerosol formulation by forming a spray when a liquid in the chamber is compressed. The chamber is compressed to administer the pharmaceutical composition of the present invention. In a specific embodiment, the chamber is a piston arrangement. Such devices are commercially available.

Alternatively, a plastic squeeze bottle with an aperture or opening dimensioned to aerosolize an aerosol formulation by forming a spray when squeezed is used. The opening is usually found in the top of the bottle, and the top is generally tapered to partially fit in the nasal passages for efficient administration of the aerosol formulation. Preferably, the nasal inhaler will provide a metered amount of the aerosol formulation, for administration of a measured dose of the drug.

The compounds, when it is desirable to deliver them systemically, may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethylcellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active compounds may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal or vaginal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described above, a compound may also be formulated as a depot preparation. Such long acting formulations may be formulated with suitable

polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Suitable liquid or solid pharmaceutical preparation forms are, for example, aqueous or saline solutions for inhalation, microencapsulated, encochleated, coated onto microscopic gold particles, contained in liposomes, nebulized, aerosols, pellets for implantation into the skin, or dried onto a sharp object to be scratched into the skin. The pharmaceutical compositions also include granules, powders, tablets, coated tablets, (micro)capsules, suppositories, syrups, emulsions, suspensions, creams, drops or preparations with protracted release of active compounds, in whose preparation excipients and additives and/or auxiliaries such as disintegrants, binders, coating agents, swelling agents, lubricants, flavorings, sweeteners or solubilizers are customarily used as described above. The pharmaceutical compositions are suitable for use in a variety of drug delivery systems. For a brief review of methods for drug delivery, see Langer R, *Science* 249:1527-33 (1990).

The compound of the invention and optionally other therapeutics may be administered *per se* (neat) or in the form of a pharmaceutically acceptable salt or cocrystal. When used in medicine the salts or cocrystals should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts or cocrystals may conveniently be used to prepare pharmaceutically acceptable salts or cocrystals thereof. Such salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulphonic, tartaric, citric, methane sulphonic, formic, malonic, succinic, naphthalene-2-sulphonic, and benzene sulphonic. Also, such salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group.

Suitable buffering agents include: acetic acid and a salt (1-2% w/v); citric acid and a salt (1-3% w/v); boric acid and a salt (0.5-2.5% w/v); and phosphoric acid and a salt (0.8-2% w/v). Suitable preservatives include benzalkonium chloride (0.003-0.03% w/v); chlorobutanol (0.3-0.9% w/v); parabens (0.01-0.25% w/v) and thimerosal (0.004-0.02% w/v).

Pharmaceutical compositions of the invention contain an effective amount of a compound as described herein and optionally therapeutic agents included in a pharmaceutically acceptable carrier. The term “pharmaceutically acceptable carrier” means

one or more compatible solid or liquid filler, diluents or encapsulating substances which are suitable for administration to a human or other vertebrate animal. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being commingled with the compounds of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficiency.

The therapeutic agent(s), including specifically but not limited to a compound of the invention, may be provided in particles. Particles as used herein means nanoparticles or microparticles (or in some instances larger particles) which can consist in whole or in part of the compound of the invention or the other therapeutic agent(s) as described herein. The particles may contain the therapeutic agent(s) in a core surrounded by a coating, including, but not limited to, an enteric coating. The therapeutic agent(s) also may be dispersed throughout the particles. The therapeutic agent(s) also may be adsorbed into the particles. The particles may be of any order release kinetics, including zero-order release, first-order release, second-order release, delayed release, sustained release, immediate release, and any combination thereof, etc. The particle may include, in addition to the therapeutic agent(s), any of those materials routinely used in the art of pharmacy and medicine, including, but not limited to, erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof. The particles may be microcapsules which contain the compound of the invention in a solution or in a semi-solid state. The particles may be of virtually any shape.

Both non-biodegradable and biodegradable polymeric materials can be used in the manufacture of particles for delivering the therapeutic agent(s). Such polymers may be natural or synthetic polymers. The polymer is selected based on the period of time over which release is desired. Bioadhesive polymers of particular interest include bioerodible hydrogels described in Sawhney H S et al. (1993) *Macromolecules* 26:581-7, the teachings of which are incorporated herein. These include polyhyaluronic acids, casein, gelatin, glutin, polyanhydrides, polyacrylic acid, alginate, chitosan, poly(methyl methacrylates), poly(ethyl methacrylates), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate).

The therapeutic agent(s) may be contained in controlled release systems. The term "controlled release" is intended to refer to any drug-containing formulation in which the manner and profile of drug release from the formulation are controlled. This refers to immediate as well as non-immediate release formulations, with non-immediate release formulations including but not limited to sustained release and delayed release formulations. The term "sustained release" (also referred to as "extended release") is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period. The term "delayed release" is used in its conventional sense to refer to a drug formulation in which there is a time delay between administration of the formulation and the release of the drug there from. "Delayed release" may or may not involve gradual release of drug over an extended period of time, and thus may or may not be "sustained release."

Use of a long-term sustained release implant may be particularly suitable for treatment of chronic conditions. "Long-term" release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 7 days, and preferably 30-60 days. Long-term sustained release implants are well-known to those of ordinary skill in the art and include some of the release systems described above.

It will be understood by one of ordinary skill in the relevant arts that other suitable modifications and adaptations to the compositions and methods described herein are readily apparent from the description of the invention contained herein in view of information known to the ordinarily skilled artisan, and may be made without departing from the scope of the invention or any embodiment thereof. Having now described the present invention in detail, the same will be more clearly understood by reference to the following examples, which are included herewith for purposes of illustration only and are not intended to be limiting of the invention.

EXAMPLES

The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

Example 1. Combination Studies

An SLC6A19 inhibitor and a GLP-1 agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to treat or prevent chronic kidney disease in the patient.

An SLC6A19 inhibitor and a GLP-1 agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to treat chronic kidney disease in the patient.

An SLC6A19 inhibitor and a GLP-1 agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to prevent chronic kidney disease in the patient.

An SLC6A19 inhibitor and a GLP-1 agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to reduce the risk of developing and/or delay the progression of chronic kidney disease in the patient.

An SLC6A19 inhibitor and a GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to treat or prevent chronic kidney disease in the patient.

An SLC6A19 inhibitor and a GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to treat chronic kidney disease in the patient.

An SLC6A19 inhibitor and a GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to prevent chronic kidney disease in the patient.

An SLC6A19 inhibitor and a GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to reduce the risk of developing and/or delay the progression of chronic kidney disease in the patient.

An SLC6A19 inhibitor and a dual GLP-1/GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to treat or prevent chronic kidney disease in the patient.

An SLC6A19 inhibitor and a dual GLP-1/GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to treat chronic kidney disease in the patient.

An SLC6A19 inhibitor and a dual GLP-1/GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to prevent chronic kidney disease in the patient.

An SLC6A19 inhibitor and a dual GLP-1/GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to reduce the risk of developing and/or delay the progression of chronic kidney disease in the patient.

An SLC6A19 inhibitor and a GLP-1 agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to treat or prevent nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD) in the patient.

An SLC6A19 inhibitor and a GLP-1 agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to treat nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD) in the patient.

An SLC6A19 inhibitor and a GLP-1 agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to prevent nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD) in the patient.

An SLC6A19 inhibitor and a GLP-1 agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to reduce the risk of developing and/or delay the progression of nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD) in the patient.

An SLC6A19 inhibitor and a GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to treat or prevent nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD) in the patient.

An SLC6A19 inhibitor and a GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to treat nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD) in the patient.

An SLC6A19 inhibitor and a GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to prevent nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD) in the patient.

An SLC6A19 inhibitor and a GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to reduce the risk of developing and/or delay the progression of nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD) in the patient.

An SLC6A19 inhibitor and a dual GLP-1/GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to treat or prevent nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD) disease in the patient.

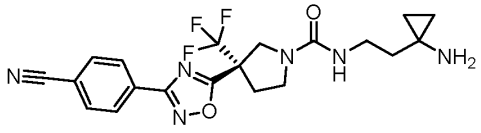
An SLC6A19 inhibitor and a dual GLP-1/GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to treat nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD) in the patient.

An SLC6A19 inhibitor and a dual GLP-1/GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to prevent nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD) in the patient.

An SLC6A19 inhibitor and a dual GLP-1/GIP agonist are co-administered to a patient in need thereof. The co-administration of the combination is effective to reduce the risk of developing and/or delay the progression of nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD) in the patient.

Example 2. Study of co-administration of Compound 5 and semaglutide.

Compound 5:



In vitro transport activity: Human SLC6A19 IC_{50} <1500 nM; Mouse SLC6A19 IC_{50} <100 nM.

Materials and Methods

Male C57Bl/6 mice were raised on a high fat diet to induce an obesity phenotype (diet-induced obesity, DIO). At age of 20-22 weeks, mice were acclimatized to handling and sham dosing approximately one week prior to study initiation. Starting on day 0, dosing was initiated. Mice were dosed once daily with either a) vehicle (p.o. 0.5% methocellulose + 0.1% Tween-80, s.c. PBS), b) 100 mg/kg Example 5 (p.o. dosing), c) 10 nmol/kg semaglutide (s.c. dosing), or d) 100 mg/kg Example 5 (p.o.) + 10 nmol/kg semaglutide (s.c.). Male C57Bl/6 mice fed a regular diet and dosed with vehicle were used as a control group. Body weight was assessed daily.

To measure fasting blood glucose, mice were fasted for 6 hours two days before treatment inception and after 14 days of treatment. After 6 hours of fasting, blood was taken from the tail vein and blood glucose measurement using Accu-Chek Guide.

To measure glucose tolerance, mice were fasted for 16 hours overnight prior to oral administration of 2g/kg glucose. Blood glucose levels were measured using Accu-Chek Guide prior to glucose administration at 0 min and 15, 30, 60 and 120 minutes after glucose administration.

The results of the study are shown in FIGs. 1-5.

INCORPORATION BY REFERENCE

All of the U.S. patents and U.S. and PCT published patent applications cited herein are hereby incorporated by reference.

EQUIVALENTS

The foregoing written specification is sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by examples provided, since the examples are intended as a single illustration of one aspect of the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall

within the scope of the appended claims. The advantages and objects of the invention are not necessarily encompassed by each embodiment of the invention.

What is claimed is:

1. A method of treating or preventing a disease or disorder, comprising co-administering to a patient in need thereof an effective amount of a SLC6A19 inhibitor and an effective amount of a second agent, wherein the second agent comprises a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist, wherein the disease or disorder is selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD).

2. The method of claim 1, wherein the disease or disorder is type 1 or type 2 diabetes mellitus.

3. The method of claim 1, wherein the disease or disorder is type 2 diabetes mellitus.

4. The method of claim 1, wherein the disease or disorder is obesity.

5. The method of claim 1, wherein the disease or disorder is nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD).

6. The method of claim 1, wherein the disease or disorder is chronic kidney disease.

7. The method of any one of claims 1-6, wherein the SLC6A19 inhibitor and the second agent are co-administered.

8. The method of any one of claims 1-7, wherein the treatment reduces the risk of developing and/or delays the progression of type 1 or type 2 diabetes mellitus or obesity in the patient.

9. The method of any one of claims 1-8, wherein the treatment reduces excess body weight and maintains weight reduction in a patient who is obese.

10. The method of any one of claims 1-9, wherein the patient is an adult patient.

11. The method of claim 10, wherein the patient is an elderly patient.

12. The method of any one of claims 1-9, wherein the patient is a pediatric patient.

13. The method of any one of claims 1-12, wherein the SLC6A19 inhibitor is administered conjointly with the second agent.

14. The method of any one of claims 1-12, wherein the SLC6A19 inhibitor and the second agent are simultaneously administered to the patient.

15. The method of claim 14, wherein the SLC6A19 inhibitor and the second agent are administered in the same formulation.

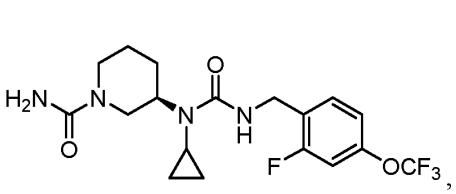
16. The method of claim 14, wherein the SLC6A19 inhibitor and the second agent are administered in separate formulations.

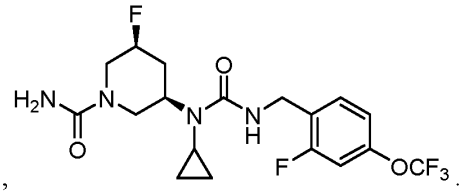
17. The method of any one of claims 1-13, wherein the SLC6A19 inhibitor and the second agent are sequentially administered to the patient.

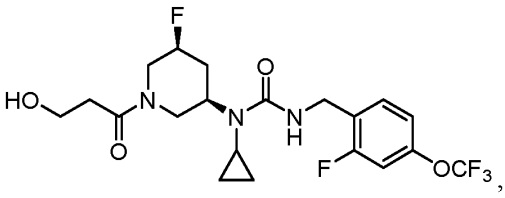
18. The method of any one of claims 1-17, wherein the SLC6A19 inhibitor and the second agent are administered orally.

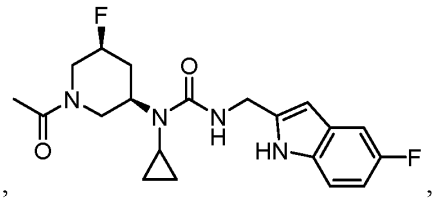
19. The method of any one of claims 1-17, wherein the SLC6A19 inhibitor is administered orally; and the second agent is administered by subcutaneous injection.

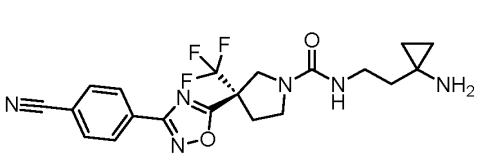
20. The method of any one of claims 1-19, wherein the SLC6A19 inhibitor is selected from:

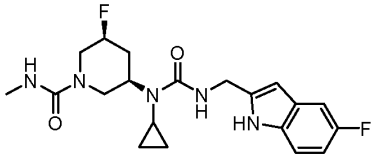

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,


,


, and


, or a pharmaceutically acceptable salt thereof.

21. The method of any one of claims 1-19, wherein the SLC6A19 inhibitor is MZE782 (Maze Therapeutics); or a compound disclosed in WO 2025/049604, WO 2024/112831, WO 2024/112830, or WO 2024/081748.

22. The method of any one of claims 1-21, wherein the second agent comprises a GLP-1 receptor agonist.

23. The method of any one of claims 1-21, wherein the second agent comprises a GLP-1 receptor agonist and an amylin receptor agonist.

24. The method of any one of claims 1-21, wherein the second agent comprises a GLP-1 receptor agonist and a glucagon agonist.

25. The method of any one of claims 1-21, wherein the second agent comprises a GLP-1 receptor agonist and a GIP antagonist.

26. The method of any one of claims 1-21, wherein the second agent comprises a GLP-1 receptor agonist and a dual amylin/calcitonin receptor agonist (DACRA).

27. The method of any one of claims 1-21, wherein the second agent comprises a GLP-1 receptor agonist and a GLP-2 receptor agonist.

28. The method of any one of claims 1-21, wherein the second agent comprises a GLP-1 receptor agonist and an activin receptor II inhibitor.

29. The method of any one of claims 1-21, wherein the second agent is a GLP-1 receptor agonist.

30. The method of any one of claims 22-29, wherein the GLP-1 receptor agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, Lixisenatide, Orforglipron, combination of Semaglutide and Cagrilintide, combination of Semaglutide and Bimagrumab, Survodutide, Retatrutide, Danuglipron, Lotiglipron, Mazdutide, Maridebart cafraglutide, Efinopegdutide, Pemvidutide, and Dapiglutide.

31. The method of claim 30, wherein the GLP-1 receptor agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

32. The method of any one of claims 1-21, wherein the second agent is a dual GLP-1/amylin receptor agonist.

33. The method of any one of claims 1-21, wherein the second agent is a dual GLP-1/glucagon agonist.

34. The method of any one of claims 1-21, wherein the second agent is a triple GLP-1/GIP /glucagon agonist.

35. The method of any one of claims 1-21, wherein the second agent comprises a dual GLP-1/GIP agonist and a glucagon agonist.

36. The method of any one of claims 1-21, wherein the second agent comprises a dual GLP-1/glucagon agonist and a GIP agonist.

37. The method of any one of claims 1-21, wherein the second agent is a triple GLP-1/amylin/calcitonin receptor agonist.

38. The method of any one of claims 1-21, wherein the second agent is a dual GLP-1/GLP-2 receptor agonist.

39. The method of any one of claims 1-21, wherein the second agent is a dual GLP-1 receptor agonist/activin receptor II inhibitor.

40. The method of any one of claims 1-21, wherein the second agent comprises a GIP agonist.

41. The method of any one of claims 1-21, wherein the second agent is a GIP agonist.

42. The method of claim 40 or 41, wherein the GIP agonist is Tirzepatide.

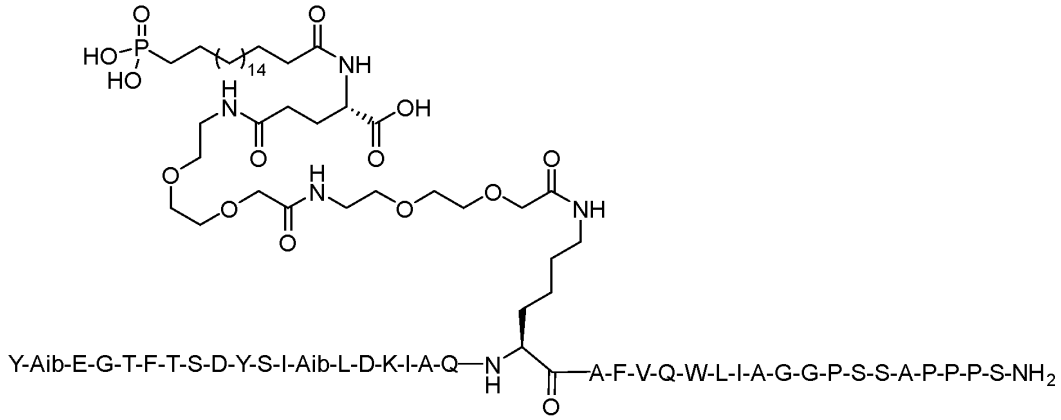
43. The method of any one of claims 1-21, wherein the second agent comprises a dual GLP-1/GIP agonist.

44. The method of any one of claims 1-21, wherein the second agent is a dual GLP-1/GIP agonist.

45. The method of claim 43 or 44, wherein the dual GLP-1/GIP agonist is Tirzepatide.

46. The method of claim 43 or 44, wherein the GLP-1/GIP agonist is VK2735 (Viking Therapeutics).

47. The method of claim 43 or 44, wherein the GLP-1/GIP agonist is



(SEQ ID NO: 1).

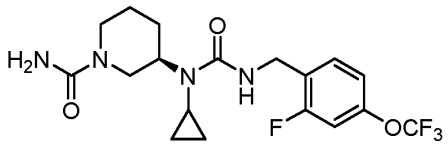
48. The method of claim 43 or 44, wherein the GLP-1/GIP agonist is SCO-094 (Scohia Pharma).

49. The method of claim 43 or 44, wherein the GLP-1/GIP agonist is selected from H-Tyr-Aib-Glu-Gly-Thr-αMePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Ala-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH_2 (SEQ ID NO: 2),
H-Tyr-Aib-Glu-Gly-Thr-αMePhe-Thr-Ser-Asp-Tyr-Aib-Ile-Aib-Leu-Asp-Lys-Gln-Ala-Gln-Ala-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH_2 (SEQ ID NO: 3),
H-Tyr-Aib-Glu-Gly-Thr-αMePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Gln-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH_2 (SEQ ID NO: 4), and
H-Tyr-Aib-Glu-Gly-Thr-αMePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Gln-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH_2 (SEQ ID NO: 5).

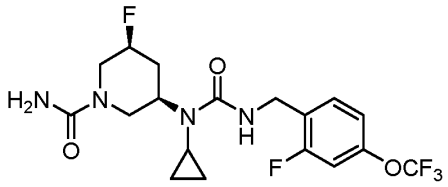
50. The method of claim 43 or 44, wherein the GLP-1/GIP agonist is CT-388 (Carmot Therapeutics).

51. The method of claim 43 or 44, wherein the GLP-1/GIP agonist is CT-996 (Carmot Therapeutics).

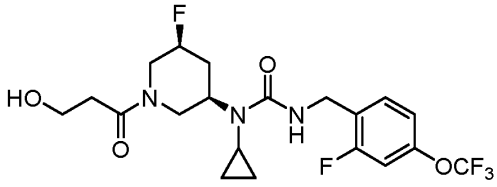
52. The method of claim 20, wherein the SLC6A19 inhibitor is

, or a pharmaceutically acceptable salt thereof; and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

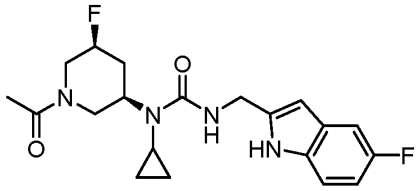
53. The method of claim 20, wherein the SLC6A19 inhibitor is

, or a pharmaceutically acceptable salt thereof; and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

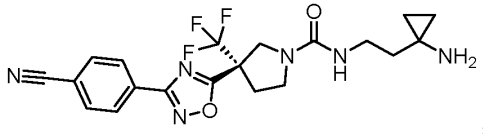
54. The method of claim 20, wherein the SLC6A19 inhibitor is

, or a pharmaceutically acceptable salt and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

55. The method of claim 20, wherein the SLC6A19 inhibitor is

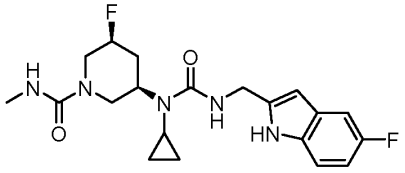
, or a pharmaceutically acceptable salt thereof; and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

56. The method of claim 20, wherein the SLC6A19 inhibitor is



, or a pharmaceutically acceptable salt thereof; and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

57. The method of claim 20, wherein the SLC6A19 inhibitor is



, or a pharmaceutically acceptable salt thereof; and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

58. The method of claim 21, wherein the SLC6A19 inhibitor is MZE782 (Maze Therapeutics), or a compound disclosed in WO 2025/049604, WO 2024/112831, WO 2024/112830, or WO 2024/081748; and the second agent is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

59. A method of treating or preventing chronic kidney disease, comprising co-administering to a patient in need thereof an effective amount of a SLC6A19 inhibitor and an effective amount of a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

60. The method of claim 59, wherein a SLC6A19 inhibitor and a GLP-1 receptor agonist are co-administered.

61. The method of claim 59, wherein a SLC6A19 inhibitor and a GIP agonist are co-administered.

62. The method of claim 59, wherein a SLC6A19 inhibitor and a dual GLP-1/GIP agonist are co-administered.

63. The method of any one of claims 59-62, wherein the chronic kidney disease is stage 1.

64. The method of any one of claims 59-62, wherein the chronic kidney disease is stage 2.

65. The method of any one of claims 59-62, wherein the chronic kidney disease is stage 3.

66. The method of any one of claims 59-62, wherein the chronic kidney disease is stage 4.

67. The method of any one of claims 59-62, wherein the chronic kidney disease is stage 5.

68. The method of any one of claims 59-67, wherein the patient is also afflicted with type 1 or type 2 diabetes mellitus, cardiovascular disease, and/or obesity.

69. The method of any one of claims 59-68, wherein the chronic kidney disease is at risk of progression.

70. The method of claim 69, wherein the treatment reduces the risk of developing and/or delays the progression of the chronic kidney disease in the patient.

71. A method of treating or preventing nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD), comprising co-administering to a patient in need thereof an effective amount of a SLC6A19 inhibitor and an effective amount of a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

72. The method of claim 71, wherein a SLC6A19 inhibitor and a GLP-1 receptor agonist are co-administered.

73. The method of claim 71, wherein a SLC6A19 inhibitor and a GIP agonist are co-administered.

74. The method of claim 71, wherein a SLC6A19 inhibitor and a dual GLP-1/GIP agonist are co-administered.

75. The method of any one of claims 71-74, wherein the treatment reduces the risk of developing and/or delays the progression of the nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, or Pyruvate Dehydrogenase Complex Deficiency (PDCD) in the patient.

76. The method of any one of claims 59-75, wherein the treatment reduces the risk of sustained decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease, cardiovascular death, and/or hospitalization in a patient with chronic kidney disease at risk of progression.

77. The method of any one of claims 59-75, wherein the treatment reduces the risk of cardiovascular death, hospitalization for heart failure, and/or urgent heart failure visits in a patient with heart failure.

78. The method of any one of claims 59-75, wherein the treatment reduces the risk of hospitalization for heart failure in a patient with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors.

79. The method of any one of claims 59-75, wherein the treatment reduces the risk of major adverse cardiovascular events (e.g., cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in a patient with established cardiovascular disease and either obesity or overweight.

80. The method of any one of claims 59-75, wherein the treatment reduces excess body weight and maintains weight reduction in a patient who is obese.

81. The method of any one of claims 59-75, wherein the treatment reduces or delays the loss of estimated glomerular filtration rate (eGFR), the progression to end stage renal disease/kidney failure in the patient, and/or the risk of progression to renal death in the patient.

82. The method of any one of claims 59-81, wherein the patient is an adult patient.

83. The method of claim 82, wherein the patient is an elderly patient.

84. The method of any one of claims 59-81, wherein the patient is a pediatric patient.

85. The method of any one of claims 59-84, wherein the SLC6A19 inhibitor is administered conjointly with the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

86. The method of any one of claims 59-84, wherein the SLC6A19 inhibitor and the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist are simultaneously administered to the patient.

87. The method of claim 86, wherein the SLC6A19 inhibitor and the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist are administered in the same formulation.

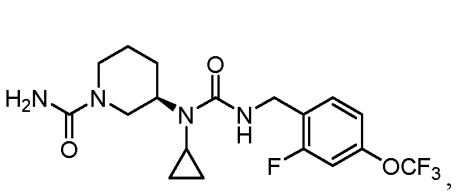
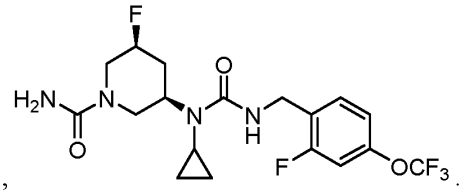
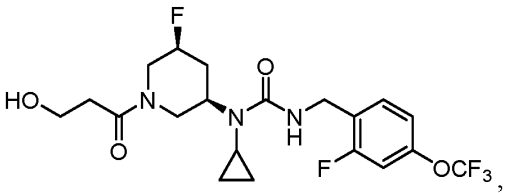
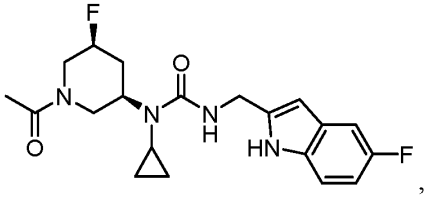
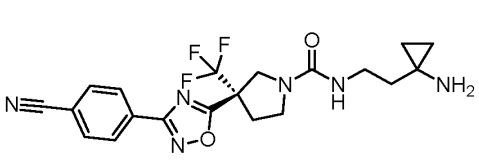
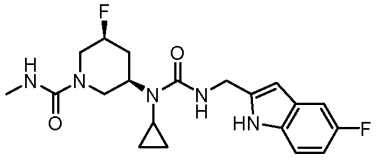
88. The method of claim 86, wherein the SLC6A19 inhibitor and the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist are administered in separate formulations.

89. The method of any one of claims 59-84, wherein the SLC6A19 inhibitor and the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist are sequentially administered to the patient.

90. The method of any one of claims 59-89, wherein the SLC6A19 inhibitor and the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist are administered orally.

91. The method of any one of claims 59-84, wherein the SLC6A19 inhibitor is administered orally and the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist is administered by subcutaneous injection.

92. The method of any one of claims 59-91, wherein the SLC6A19 inhibitor is selected from:






, and

, or a pharmaceutically acceptable salt thereof.

93. The method of any one of claims 59-91, wherein the SLC6A19 inhibitor is MZE782 (Maze Therapeutics); or a compound disclosed in WO 2025/049604, WO 2024/112831, WO 2024/112830, or WO 2024/081748.

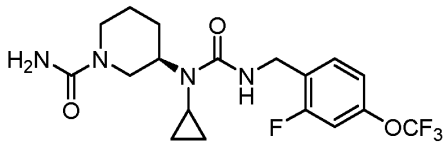
94. The method of any one of claims 59-93, wherein the GLP-1 receptor agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, Lixisenatide, Orforglipron, combination of Semaglutide and Cagrilintide, combination of Semaglutide and Bimagrumab, Survodutide, Retatrutide, Danuglipron, Lotiglipron, Mazdutide, Maridebart cafraglutide, Efinopegdutide, Pemvidutide, and Dapiglutide.

95. The method of any one of claims 59-94, wherein the GLP-1 receptor agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

96. The method of any one of claims 59-93, wherein the GIP agonist is Tirzepatide.

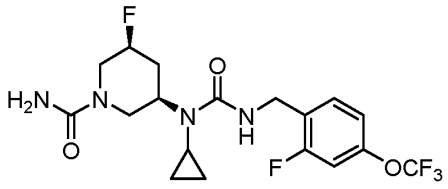
97. The method of any one of claims 59-93, wherein the dual GLP-1/GIP agonist is Tirzepatide.

98. The method of any one of claims 59-92, wherein the SLC6A19 inhibitor is



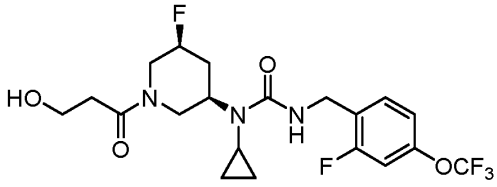
, or a pharmaceutically acceptable salt thereof; and the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

99. The method of any one of claims 59-92, wherein the SLC6A19 inhibitor is



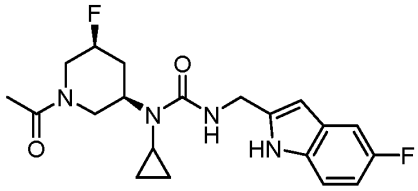
, or a pharmaceutically acceptable salt thereof; and the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

100. The method of any one of claims 59-92, wherein the SLC6A19 inhibitor is



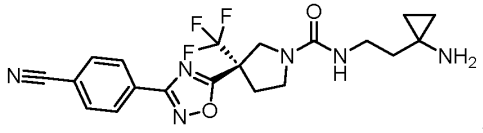
, or a pharmaceutically acceptable salt and the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

101. The method of any one of claims 59-92, wherein the SLC6A19 inhibitor is



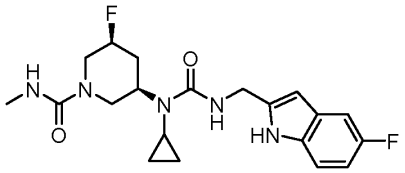
, or a pharmaceutically acceptable salt thereof; and the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

102. The method of any one of claims 59-92, wherein the SLC6A19 inhibitor is



, or a pharmaceutically acceptable salt thereof; and the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

103. The method of any one of claims 59-92, wherein the SLC6A19 inhibitor is



, or a pharmaceutically acceptable salt thereof; and the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

104. The method of any one of claims 59-91, wherein the SLC6A19 inhibitor is MZE782 (Maze Therapeutics) or a compound disclosed in WO 2025/049604, WO 2024/112831, WO 2024/112830, or WO 2024/081748; and the GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist is selected from Tirzepatide, Semaglutide, Dulaglutide, Exenatide, Liraglutide, and Lixisenatide.

105. A SLC6A19 inhibitor for use in the treatment or prevention of a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD), wherein

the treatment or prevention of the disease or disorder further comprises co-administration of an effective amount of a second agent comprising a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

106. A pharmaceutical composition comprising a SLC6A19 inhibitor and a second agent for use in the treatment or prevention of a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD), wherein

the second agent comprises a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

107. A composition comprising SLC6A19 inhibitor for use in the treatment or prevention of a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD), wherein

the treatment or prevention of the disease or disorder further comprises co-administration of an effective amount of a second agent comprising a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

108. Use of a SLC6A19 inhibitor in the manufacture of a medicament for the treatment or prevention of a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD), wherein

the treatment or prevention of the disease or disorder further comprises co-administration of an effective amount of a second agent comprising a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.

109. Use of a SLC6A19 inhibitor in the manufacture of a medicament for the treatment or prevention of a disease or disorder selected from type 1 or type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), diabetic nephropathy, glomerulosclerosis, glaucoma, Alport Syndrome, Pyruvate Dehydrogenase Complex Deficiency (PDCD), chronic kidney disease, IgA nephropathy (IgAN), nephropathic cystinosis, Focal Segmental Glomerulosclerosis (FSGS), Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Acute Kidney Injury (AKI) to CKD transition – acute kidney disease (AKD), wherein the medicament further comprises a second agent comprising a GLP-1 receptor agonist, GIP agonist, or dual GLP-1/GIP agonist.