METHODS FOR TREATING OR PREVENTING CHRONIC KIDNEY DISEASE

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Patent Application No. 63/037,469, filed on June 10, 2020, and U.S. Provisional Patent Application No. 63/195,411, filed on June 1, 2021, both of which are incorporated herein by reference in their entirety.

BACKGROUND

[0002] Chronic kidney disease describes the gradual loss of kidney function. Kidneys filter wastes and excess fluids from the blood, which are then excreted in the urine. When chronic kidney disease reaches an advanced stage, dangerous levels of fluid, electrolytes, and wastes can build up in the body. Chronic kidney disease can progress to end-stage kidney failure, which is fatal without dialysis or a kidney transplant. New chronic kidney disease medications are needed to treat or prevent this disease.

SUMMARY

[0002a] In an aspect of the present disclosure, there is provided a use of a pharmaceutical composition in the manufacture of a medicament for the treatment or prevention of:
i) chronic kidney disease,
ii) heart failure, or
iii) hypertension, coronary artery disease, Lesch-Nyhan syndrome, Kelley-Seegmiller syndrome, kidney stones, kidney failure, diabetic kidney disease, joint inflammation, arthritis, urolithiasis, plumbism, hyperparathyroidism, psoriasis, sarcoidosis, hypoxanthine-guanine phosphoribosyltransferase **(**HPRT) deficiency, or a combination thereof,
wherein the pharmaceutical composition comprises (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, and at least one inactive ingredient selected from pharmaceutically acceptable carriers, diluents, and excipients.

[0003] In one example, described herein is a method for treating or preventing chronic kidney disease in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof. In some examples is a method for treating chronic kidney disease in an individual in need thereof. In some examples is a method for preventing chronic kidney disease in an individual in need thereof.

[0004] In another example, described herein is a method for treating or preventing heart failure in an individual in need thereof, comprising administering to the individual a therapeutically

effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof. In some examples is a method for treating heart failure in an individual in need thereof. In some examples is a method for preventing heart failure in an individual in need thereof.

[0005] In another example, described herein is a method for treating hypertension, coronary artery disease, Lesch-Nyhan syndrome, Kelley-Seegmiller syndrome, kidney stones, kidney failure, diabetic kidney disease, joint inflammation, arthritis, urolithiasis, plumbism, hyperparathyroidism, psoriasis, sarcoidosis, hypoxanthine-guanine phosphoribosyltransferase **(**HPRT) deficiency, or a combination thereof, in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof. In some examples is a method for treating heart

failure in an individual in need thereof. In some examples is a method for preventing heart failure in an individual in need thereof.

[0006] In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is from about 3 mg to about 1500 mg. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is from about 3 mg to about 600 mg. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is from about 5 mg to about 300 mg. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is from about 10 mg to about 200 mg. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is from about 10 mg to about 100 mg. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered orally. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is taken with food. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is taken without food. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered to the individual once per day. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered to the individual twice per day. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered with at least one additional therapeutic agent. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered with a xanthine oxidase inhibitor. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered with a xanthine oxidase inhibitor selected from allopurinol, oxypurinol, febuxostat, topiroxostat, and inositol. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered with a

sodium-glucose co-transporter-2 (SGLT2) inhibitor. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered with an SGLT2 inhibitor selected from canagliflozin, dapagliflozin, empagliflozin, empagliflozin/linagliptin, empagliflozin/metformin, and dapagliflozin/metformin. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered with a xanthine oxidase inhibitor and a SGLT2 inhibitor. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered with a xanthine oxidase inhibitor and a SGLT2 inhibitor, wherein the xanthine oxidase inhibitor is selected from allopurinol, oxypurinol, febuxostat, topiroxostat, and inositol, and the SGLT2 inhibitor is selected from canagliflozin, dapagliflozin, empagliflozin, empagliflozin/linagliptin, empagliflozin/metformin, and dapagliflozin/metformin.

[0007] In another example is a pharmaceutical composition for use in the treatment or prevention of chronic kidney disease, wherein the pharmaceutical composition comprises a therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone and at least one inactive ingredient selected from pharmaceutically acceptable carriers, diluents, and excipients. In some examples is a pharmaceutical composition for use in the treatment of chronic kidney disease in an individual in need thereof. In some examples is a pharmaceutical composition for use in the prevention of chronic kidney disease in an individual in need thereof.

[0008] In another example is a pharmaceutical composition for use in the treatment or prevention of heart failure, wherein the pharmaceutical composition comprises a therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone and at least one inactive ingredient selected from pharmaceutically acceptable carriers, diluents, and excipients. In some examples is a pharmaceutical composition for use in the treatment of heart failure in an individual in need thereof. In some examples is a pharmaceutical composition for use in the prevention of heart failure in an individual in need thereof.

[0009] In another example is a pharmaceutical composition for use in the treatment of hypertension, coronary artery disease, Lesch-Nyhan syndrome, Kelley-Seegmiller syndrome, kidney stones, kidney failure, diabetic kidney disease, joint inflammation, arthritis, urolithiasis, plumbism, hyperparathyroidism, psoriasis, sarcoidosis, hypoxanthine-guanine phosphoribosyltransferase **(**HPRT) deficiency, or a combination thereof, wherein the pharmaceutical composition comprises a therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-

3-yl-4,5,6,7-d_4)methanone and at least one inactive ingredient selected from pharmaceutically acceptable carriers, diluents, and excipients.

[0010] In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is from about 3 mg to about 1500 mg. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is from about 3 mg to about 600 mg. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is from about 5 mg to about 300 mg. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is from about 10 mg to about 200 mg. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is from about 10 mg to about 100 mg. In some examples, the therapeutically effective amount of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is from about 25 mg to about 75 mg. In some examples, the pharmaceutical composition of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered orally. In some examples, the pharmaceutical composition of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is taken with food. In some examples, the pharmaceutical composition of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is taken without food. In some examples, the pharmaceutical composition of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered to the individual once per day. In some examples, the pharmaceutical composition of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered to the individual twice per day. In some examples, the pharmaceutical composition of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered with at least one additional therapeutic agent. In some examples, the pharmaceutical composition of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered with a xanthine oxidase inhibitor. In some examples, the pharmaceutical composition of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered with a xanthine oxidase inhibitor selected from allopurinol, oxypurinol, febuxostat, topiroxostat, and inositol. In some

examples, the pharmaceutical composition of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered with an SGLT2 inhibitor. In some examples, the pharmaceutical composition of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered with an SGLT2 inhibitor selected from canagliflozin, dapagliflozin, empagliflozin, empagliflozin/linagliptin, empagliflozin/metformin, and dapagliflozin/metformin. In some examples, the pharmaceutical composition of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered with a xanthine oxidase inhibitor and an SGLT2 inhibitor. In some examples, the pharmaceutical composition of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, or solvate thereof, is administered with a xanthine oxidase inhibitor and an SGLT2 inhibitor, wherein the xanthine oxidase inhibitor is selected from allopurinol, oxypurinol, febuxostat, topiroxostat, and inositol, and the SGLT2 inhibitor is selected from canagliflozin, dapagliflozin, empagliflozin, empagliflozin/linagliptin, empagliflozin/metformin, and dapagliflozin/metformin.

INCORPORATION BY REFERENCE

[0011] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the extent applicable and relevant and to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE FIGURES

[0012] Fig. 1. Illustrates the mean plasma concentration profiles of Compound 1 following a single oral dose of Compound 1 (15 mg, 50 mg, 100 mg, and 150 mg) in the fasted state.

[0013] Fig. 2. Illustrates the mean plasma concentration profiles of Compound 1 following a single oral dose of Compound 1 at 50 mg in the fasted versus fed state.

[0014] Fig. 3. Illustrates the dose proportionality of Compound 1 AUC following a single oral dose of Compound 1 (15 mg, 50 mg, 100 mg, and 150 mg) in the fasted state.

[0015] Fig. 4. Illustrates the dose proportionality of Compound 1 Cmax following a single oral dose of Compound 1 (15 mg, 50 mg, 100 mg, and 150 mg) in the fasted state.

[0016] Fig. 5. Illustrates mean serum uric acid levels (mg/dL) following a single oral dose of Compound 1 at various doses under fasted conditions.

[0017] Fig. 6. Illustrates mean time-matched (Day-1) percent change in serum uric acid concentration from baseline following a single oral dose of Compound 1 at various doses under fasted conditions.

CLAIMS

We Claim:

1. Use of a pharmaceutical composition in the manufacture of a medicament for the treatment or prevention of:

   i) chronic kidney disease,

   ii) heart failure, or

   iii) hypertension, coronary artery disease, Lesch-Nyhan syndrome, Kelley-Seegmiller syndrome, kidney stones, kidney failure, diabetic kidney disease, joint inflammation, arthritis, urolithiasis, plumbism, hyperparathyroidism, psoriasis, sarcoidosis, hypoxanthine-guanine phosphoribosyltransferase **(**HPRT) deficiency, or a combination thereof,

   wherein the pharmaceutical composition comprises (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone, and at least one inactive ingredient selected from pharmaceutically acceptable carriers, diluents, and excipients.
2. The use of claim 1, for the treatment of chronic kidney disease in an individual in need thereof.
3. The use of claim 1, for the treatment of heart failure in an individual in need thereof.
4. The use of claim 1, wherein from about 10 mg to about 200 mg of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone is to be administered.
5. The use of claim 1, wherein from about 10 mg to about 100 mg of (3,5-dibromo-4-hydroxyphenyl)(2-(1-hydroxyethyl)benzofuran-3-yl-4,5,6,7-d_4)methanone is to be administered.
6. The use of claim 1, formulated for oral administration.
7. The use of claim 1, wherein the pharmaceutical composition is to be taken with food.
8. The use of claim 1, wherein the pharmaceutical composition is to be taken without food.
9. The use of claim 1, wherein the pharmaceutical composition is to be administered once per day.
10. The use of any one of claims 1-9, wherein the pharmaceutical composition is to be administered to an individual in need thereof, and a xanthine oxidase inhibitor is to be further administered.
11. The use of claim 10, wherein the xanthine oxidase inhibitor is allopurinol, oxypurinol, febuxostat, topiroxostat, or inositol.

12. The use of any one of claims 1-9, wherein the pharmaceutical composition is to be administered to an individual in need thereof, and an SGLT2 inhibitor is to be further administered.
13. The use of claim 12, wherein the SGLT2 inhibitor is canagliflozin, dapagliflozin, empagliflozin, empagliflozin/linagliptin, empagliflozin/metformin, or dapagliflozin/metformin.