

METHODS OF TREATING CHRONIC KIDNEY DISEASE (CKD) OR CKD AND
HYPERTENSION WITH LORUNDROSTAT, OR A COMBINATION OF
LORUNDROSTAT AND A SGLT2 INHIBITOR

[0001] This application claims the priority of U.S. Provisional Application No. 63/513,999, filed July 17, 2023, and U.S. Provisional Application No. 63/596,658, filed November 7, 2023, the contents of each of which are hereby incorporated by reference.

[0002] Throughout this application, various publications are referenced, including referenced in parenthesis. The disclosures of all publications mentioned in this application in their entireties are hereby incorporated by reference into this application in order to provide additional description of the art to which this invention pertains and of the features in the art which can be employed with this invention.

FIELD OF THE INVENTION

[0003] This invention relates to methods of treating chronic kidney disease.

BACKGROUND OF THE INVENTION

[0004] Chronic kidney disease (CKD) is a condition in which the ability of the kidneys to work correctly decreases over time.

[0005] Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a class of medications that act by inhibiting sodium-glucose transport protein 2 (SGLT2). SGLT2 is responsible for reabsorbing glucose from the blood that's filtered through the kidneys. By inhibiting SGLT2, these medications prevent the reabsorption of glucose and facilitate its excretion in the urine.

[0006] Studies of sodium–glucose cotransporter 2 (SGLT2) inhibitors in patients with type 2 diabetes investigated the cardiovascular safety of this class of glucose-lowering therapies. In addition to reducing the risk of cardiovascular events, SGLT2 inhibitors reduced the risk of clinically relevant renal outcomes (sustained loss of kidney function, eGFR decline, progression to or worsening of albuminuria, new end-stage kidney disease (ESKD), death from renal causes, and/or a renal composite outcome) compared with placebo, indicating that SGLT2 inhibitors are associated with significantly lower risk of worsening of kidney function (Perkovic et al. 2018, Wanner et al. 2016, and Wiviott et al. 2019). However, these studies were not designed to evaluate treatment benefits in patients with CKD, with only 7–26% of participants having an eGFR of less than 60 mL/min/ 1.73 m². Perkovic, V. et al. (2018), Wanner, C., et al. (2016), and Wiviott, S. et al. (2019). Subsequently, designated kidney outcome trials showed a reduction in the risk of CKD progression with SGLT2 inhibitors in

patients with diabetic kidney disease (DKD) with canagliflozin in CREDENCE and DKD as well as nondiabetic CKD with dapagliflozin in DAPA-CKD. Perkovic, V., et al. (2019), and Heerspink, H. J., et al. (2020).

[0007] Aldosterone is the principal mineralocorticoid in humans, produced in the zona glomerulosa of the adrenal cortex by aldosterone synthase (CYP 11 β 2 beta hydroxylase). Mineralocorticoid receptor-blocking agents (mineralocorticoid receptor antagonists, MRA), such as spironolactone and eplerenone, prevent aldosterone from binding with the mineralocorticoid receptor. A mineralocorticoid receptor antagonist (MRA) is a drug that antagonizes the action of aldosterone at mineralocorticoid receptors. The FIDELIO-DKD trial evaluated the long-term effects of the MRA finerenone on kidney and cardiovascular outcomes and reported a reduced risk of CKD progression in patients with DKD. (Bakris et al. 2020). Finerenone, a selective oral, non-steroidal MRA, lowers risks of CKD progression and cardiovascular events in patients with CKD and T2DM (Bakris et al., 2020). However, the increase in occurrence of hyperkalemia and potential reduction in renal function is a concern in long-term use of an MRA in CKD.

[0008] However, previous studies suggest that some of the effects of aldosterone may occur independently of stimulation of the mineralocorticoid receptor/classic steroid-receptor complex modulation (Grossmann, C., & Gekle, M., 2009; Good, D. W., 2007; Mihailidou, A. S., & Funder, J. W., 2005). In addition, mineralocorticoid receptors are not selective for aldosterone, instead have similar affinity for the glucocorticoids cortisol and corticosterone as well as androgen and progesterone receptors.

[0009] There is a need for improvements in treatment of chronic kidney disease.

SUMMARY OF THE INVENTION

[0010] This invention provides a method of treating chronic kidney disease (CKD) in a subject afflicted with CKD, the method comprising administering to the subject an amount of lorundrostat or a pharmaceutically acceptable salt thereof once per day, wherein the amount is effective to treat CKD in the subject.

[0011] This invention also provides a method of treating chronic kidney disease (CKD) in a subject afflicted with CKD, the method comprising

- (a) receiving an identification of the subject as having:
 - (i) CKD, characterized by the following when taking a stable dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably a maximally tolerated dose of an ACEi or ARB:
 - 1. a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-3500 mg/g or 200-5000mg/g; and/or
 - 2. an estimated glomerular filtration rate (eGFR) of at least 30 or at least 45 mL/min/1.73m² and preferably less than 90 mL/min/1.73m² when taking a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB); or
 - (ii) mild to moderate CKD, characterized by the following when taking a stable dose of an ACEi or ARB, preferably a maximally tolerated dose of an ACEi or ARB:
 - 1. albuminurea, characterized by a 24-hour or first morning urine void UACR of 300-3500 mg/g; and
 - 2. an estimated glomerular filtration rate (eGFR) of at least 45 mL/min/1.73m² and less than 90 mL/min/1.73m²; or
 - (iii) moderate to severe CKD, characterized by the following when taking a stable dose of an ACEi or ARB, preferably a maximally tolerated dose of an ACEi or ARB:
 - 1. albuminurea, characterized by a 24-hour or first morning urine void UACR of 300-3500 mg/g; and

2. an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73m² and less than 45 mL/min/1.73m²; and
- (b) administering to said subject an effective amount of lorundrostat or a pharmaceutically acceptable salt thereof once per day, wherein the amount is effective to treat CKD in the subject.

[0012] This invention also provides a method of treating hypertension in a subject afflicted with hypertension and CKD, the method comprising:

- (a) receiving an identification of the subject as having:
 - (i) hypertension, preferably characterized by a systolic blood pressure of between 135-180 mmHg, inclusive;
 - (ii) CKD, characterized by one of the following:
 1. CKD, characterized by the following when taking stable dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably a maximally tolerated dose of an ACEi or ARB:
 - a. a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-3500 mg/g or 200-5000mg/g; and/or
 - b. an estimated glomerular filtration rate (eGFR) of at least 30 or at least 45 mL/min/1.73m² and preferably less than 90 mL/min/1.73m² when taking a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB); or
 2. mild to moderate CKD, characterized by the following when taking a stable dose of an ACEi or ARB, preferably a maximally tolerated dose of an ACEi or ARB:
 - a. albuminurea, characterized by a 24-hour or first morning urine void UACR of 300-3500 mg/g; and
 - b. an estimated glomerular filtration rate (eGFR) of at least 45 mL/min/1.73m² and less than 90 mL/min/1.73m²; or
 3. moderate to severe CKD, characterized by the following when taking a stable dose of an ACEi or ARB, preferably a maximally tolerated dose of an ACEi or ARB:

- a. albuminuria, characterized by a 24-hour or first morning urine void UACR of 300-3500 mg/g; and
 - b. an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73m² and less than 45 mL/min/1.73m²; and
- (b) administering to said subject an effective amount of lorundrostat or a pharmaceutically acceptable salt thereof once per day, wherein the amount is effective to treat hypertension in the subject.

[0013] This invention also provides a method of identifying a subject for treatment with lorundrostat or pharmaceutically acceptable salt thereof, the method comprising:

- (a) measuring the subject's 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) and/or an estimated glomerular filtration rate (eGFR);
- (b) selecting a subject who, when taking a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), has:
 - (i) chronic kidney disease (CKD), characterized by:
 - 1. a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-3500 mg/g or 200-5000mg/g; and/or
 - 2. an estimated glomerular filtration rate (eGFR) of at least 30 or at least 45 mL/min/1.73m² and 1 preferably less than 90 mL/min/1.73m²;
 - (ii) mild to moderate CKD, characterized by:
 - 1. albuminuria, characterized by a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 300-3500 mg/g; and
 - 2. an estimated glomerular filtration rate (eGFR) of at least 45 mL/min/1.73m² and less than 90 mL/min/1.73m²; or
 - (iii) moderate to severe CKD, characterized by:
 - 1. albuminuria, characterized by a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 300-3500 mg/g; and

2. an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73m² and less than 45 mL/min/1.73m²;

thereby identifying said subject for treatment with lorundrostat or pharmaceutically acceptable salt thereof.

[0014] This invention also provides a method of identifying a subject for treatment with a sodium-glucose cotransporter 2 (SGLT2) inhibitor and lorundrostat or pharmaceutically acceptable salt thereof, the method comprising:

- (a) measuring the subject's 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) and/or an estimated glomerular filtration rate (eGFR);
- (b) selecting a subject who, when taking a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), has:
 - (i) chronic kidney disease (CKD), characterized by:
 1. a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-3500 mg/g or 200-5000mg/g; and/or
 2. an estimated glomerular filtration rate (eGFR) of at least 30 or at least 45 mL/min/1.73m² and preferably less than 90 mL/min/1.73m²;
 - (ii) chronic kidney disease (CKD), characterized by:
 1. a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-3500 mg/g; and/or
 2. an estimated glomerular filtration rate (eGFR) of at least 45 mL/min/1.73m² and less than 90 mL/min/1.73m²;
 - (iii) mild to moderate CKD, characterized by:
 1. albuminuria, characterized by a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 300-3500 mg/g; and
 2. an estimated glomerular filtration rate (eGFR) of at least 45 mL/min/1.73m² and less than 90 mL/min/1.73m²; or
 - (iv) moderate to severe CKD, characterized by:

1. albuminuria, characterized by a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 300-3500 mg/g; and
2. an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73m² and less than 45 mL/min/1.73m²;

thereby identifying said subject for treatment with a sodium-glucose cotransporter 2 (SGLT2) and lorundrostat or pharmaceutically acceptable salt thereof.

[0015] This invention also provides lorundrostat or a pharmaceutically acceptable salt thereof for use in treating chronic kidney disease (CKD) in a subject afflicted with CKD, wherein said use is in combination with a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably wherein the SGLT2 inhibitor is dapagliflozin.

[0016] This invention also provides use of lorundrostat or pharmaceutically acceptable salt thereof for treating chronic kidney disease (CKD) in a subject afflicted with CKD in combination with a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably wherein the SGLT2 inhibitor is dapagliflozin.

[0017] This invention also provides lorundrostat or a pharmaceutically acceptable salt thereof for use in treating chronic kidney disease (CKD) in a subject afflicted with CKD, wherein said use is in combination with a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably wherein the SGLT2 inhibitor is dapagliflozin.

[0018] This invention also provides use of lorundrostat or pharmaceutically acceptable salt thereof for treating chronic kidney disease (CKD) in a subject afflicted with CKD in combination with a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably wherein the SGLT2 inhibitor is dapagliflozin.

[0019] This invention also provides a package comprising:

- (a) a first pharmaceutical composition comprising an amount of lorundrostat or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier;

- (b) a second pharmaceutical composition comprising an amount of sodium-glucose cotransporter 2 (SGLT2) inhibitor;
- (c) optionally, a third pharmaceutical composition comprising an amount of an angiotensin-converting enzyme inhibitor (ACEi); and
- (d) optionally, a fourth pharmaceutical composition comprising an amount of an angiotensin receptor blocker (ARB)
- (e) instructions for use of the first and second pharmaceutical compositions, and third and fourth pharmaceutical compositions, if present, together to treat a subject afflicted with CKD, or CKD and hypertension.

[0020] This invention also provides a package comprising:

- (a) a first pharmaceutical composition comprising an amount of lorundrostat or pharmaceutically acceptable salt thereof, an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and a pharmaceutically acceptable carrier; and
- (b) optionally, a second pharmaceutical composition comprising an amount of an angiotensin-converting enzyme inhibitor (ACEi) and/or an amount of an angiotensin receptor blocker (ARB) and a pharmaceutically acceptable carrier;
- (c) instructions for use of the pharmaceutical composition(s) to treat a subject afflicted with chronic kidney disease (CKD) or CKD and hypertension.

[0021] This invention also provides a pharmaceutical composition comprising:

- (a) an amount of lorundrostat or a pharmaceutically acceptable salt thereof;
- (b) an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor or a pharmaceutically acceptable salt thereof;
- (c) optionally an amount of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) or a pharmaceutically acceptable salt thereof;

wherein the lorundrostat or pharmaceutically acceptable salt thereof, SGLT2 inhibitor, and ACEi or ARB, if present, are administered simultaneously, contemporaneously or concomitantly.

[0022] This invention also provides a pharmaceutical composition comprising an amount of lorundrostat or pharmaceutically acceptable salt thereof for use in treating chronic kidney

disease (CKD) or CKD and hypertension in a subject afflicted with CKD or CKD and hypertension in combination with an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an amount of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

[0023] This invention also provides a pharmaceutical composition in unit dosage form, useful in treating a subject afflicted with chronic kidney disease (CKD) or CKD and hypertension, which comprises:

- (a) an amount of lorundrostat or a pharmaceutically acceptable salt thereof;
- (b) an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor or a pharmaceutically acceptable salt thereof; and
- (c) optionally an amount of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) or a pharmaceutically acceptable salt thereof;

wherein the respective amounts of said lorundrostat or pharmaceutically acceptable salt thereof, said SGLT2 inhibitor, and said ACEi or ARB, if present, in said composition are effective, upon concomitant administration to said subject of one or more of said unit dosage forms of said composition, to treat the subject.

[0024] This invention also provides a therapeutic package for dispensing to, or for use in dispensing to, a subject afflicted with chronic kidney disease (CKD) or CKD and hypertension, which comprises:

- (a) one or more unit doses, each such unit dose comprising:
 - (i) an amount of lorundrostat or a pharmaceutically acceptable salt thereof;
 - (ii) an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor or a pharmaceutically acceptable salt thereof; and
 - (iii) optionally an amount of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) or a pharmaceutically acceptable salt thereof;

wherein the respective amounts of said lorundrostat or pharmaceutically acceptable salt thereof, said SGLT2 inhibitor, and said ACEi or ARB, if present, in said unit doses are effective, upon concomitant administration to said subject, to treat CKD or CKD and hypertension in the subject, and

- (b) a finished pharmaceutical container therefor, said container containing said unit dose or unit doses, said container further containing or comprising labeling directing the use of said package in the treatment of said subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] Figure 1: Estimate of time above IC₅₀ for various doses of lorundrostat HBr based on PKPD modeling from SAD study.

[0026] Figure 2: Study Flow. Abbreviations: OLE, Open-Label Extension; QD, once daily.

DETAILED DESCRIPTION OF THE INVENTION

Methods

[0027] This invention provides a method of treating chronic kidney disease (CKD) in a subject afflicted with CKD, the method comprising administering to the subject an amount of lorundrostat or a pharmaceutically acceptable salt thereof once per day, wherein the amount is effective to treat CKD in the subject.

[0028] This invention provides a method of treating hypertension in a subject afflicted with hypertension and CKD, the method comprising administering to the subject an amount of lorundrostat or a pharmaceutically acceptable salt thereof once per day, wherein the amount is effective to treat hypertension in the subject.

[0029] This invention also provides a method of treating chronic kidney disease (CKD) in a subject afflicted with CKD, the method comprising

- (a) receiving an identification of the subject as having:
 - (i) CKD, characterized by the following when stable dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably a maximally tolerated dose of an ACEi or ARB:
 - 1. a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-3500 mg/g or 200-5000mg/g; and/or
 - 2. an estimated glomerular filtration rate (eGFR) of at least 30 or at least 45 mL/min/1.73m² and preferably less than 90 mL/min/1.73m²;
 - (ii) mild to moderate CKD, characterized by the following when taking a stable dose of an ACEi or ARB, preferably a maximally tolerated dose of an ACEi or ARB:
 - 1. albuminuria, characterized by a 24-hour or first morning urine void UACR of 300-3500 mg/g; and
 - 2. an estimated glomerular filtration rate (eGFR) of at least 30 or at least 45 mL/min/1.73m² and preferably less than 90 mL/min/1.73m²; or

- (iii) moderate to severe CKD, characterized by the following when taking a stable dose of an ACEi or ARB, preferably a maximally tolerated dose of an ACEi or ARB:
 1. albuminuria, characterized by a 24-hour or first morning urine void UACR of 300-3500 mg/g; and
 2. an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73m² and less than 45 mL/min/1.73m²; and
- (b) administering to said subject an effective amount of lorundrostat or a pharmaceutically acceptable salt thereof once per day, wherein the amount is effective to treat CKD in the subject.

[0030] In an embodiment of the above method, step (a) comprises receiving an identification of the subject as:

- (a) having hypertension, preferably characterized by a systolic blood pressure of between 135-180 mmHg, inclusive;
- (b) not having Type 1 diabetes;
- (c) having a serum cortisol of between 3 µg/dL and 22 µg/dL in the morning;
- (d) having a body mass index (BMI) of 18-40 kg/m²;
- (e) having a serum potassium of less than 4.8 mmol/L; and/or
- (f) having a serum sodium of greater than 135 mmol/L, preferably wherein said serum sodium measurement is corrected for hyperglycemia, if present.

[0031] This invention also provides a method of treating hypertension in a subject afflicted with hypertension and CKD, the method comprising:

- (a) receiving an identification of the subject as having:
 - (i) hypertension, preferably characterized by a systolic blood pressure of between 135-180 mmHg, inclusive;
 - (ii) CKD, characterized by one of the following:
 1. CKD, characterized by the following when taking stable dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably a maximally tolerated dose of an ACEi or ARB:
 - a. a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-3500 mg/g or 200-5000mg/g; and/or

- b. an estimated glomerular filtration rate (eGFR) of at least 30 or at least 45 mL/min/1.73m² and preferably less than 90 mL/min/1.73m² when taking a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB); or
 - 2. mild to moderate CKD, characterized by the following when taking a stable dose of an ACEi or ARB, preferably a maximally tolerated dose of an ACEi or ARB:
 - a. albuminuria, characterized by a 24-hour or first morning urine void UACR of 300-3500 mg/g; and
 - b. an estimated glomerular filtration rate (eGFR) of at least 45 mL/min/1.73m² and less than 90 mL/min/1.73m²; or
 - 3. moderate to severe CKD, characterized by the following when taking a stable dose of an ACEi or ARB, preferably a maximally tolerated dose of an ACEi or ARB:
 - a. albuminuria, characterized by a 24-hour or first morning urine void UACR of 300-3500 mg/g; and
 - b. an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73m² and less than 45 mL/min/1.73m²; and
- (b) administering to said subject an effective amount of lorundrostat or a pharmaceutically acceptable salt thereof once per day, wherein the amount is effective to treat hypertension in the subject.

[0032] In embodiments of the invention, the subject afflicted with CKD is being treated with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB).

[0033] In embodiments of the invention, the subject afflicted with CKD is being treated with a maximally tolerated dose of an ACEi or ARB.

[0034] In embodiments of the invention:

- (a) the amount of the ACEi or ARB when administered with the lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the ACEi or ARB inhibitor that is effective to treat CKD when the ACEi or ARB inhibitor is administered alone;

- (b) the amount of the ACEi or ARB when administered with the lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the ACEi or ARB that is effective to treat CKD when the ACEi or ARB inhibitor is administered in the absence of administration of the lorundrostat or a pharmaceutically acceptable salt thereof; and/or
- (c) the amount of the ACEi or ARB that is effective to treat CKD when administered in the absence of administration of the lorundrostat or pharmaceutically acceptable salt thereof causes one or more adverse effects in the subject, wherein the one or more adverse effects are not caused by the amounts of the ACEi or ARB, and lorundrostat or pharmaceutically acceptable salt thereof that are effective to treat CKD when administered together.

[0035] In embodiments of the invention, the amount of lorundrostat or pharmaceutically acceptable salt thereof when administered together with the ACEi or ARB are more effective to treat the subject than when each agent at the same amount is administered alone.

[0037] In embodiments of the invention, the amount of lorundrostat or pharmaceutically acceptable salt thereof is:

- (a) 10-15 mg per day, preferably 12.5 mg per day;
- (b) 20-30 mg per day, preferably 25 mg per day; or
- (c) 40-60 mg per day, preferably 50 mg per day.

[0038] In embodiments of the invention, the lorundrostat or a pharmaceutically acceptable salt thereof is administered in the morning.

[0039] In embodiments of the invention, the lorundrostat or a pharmaceutically acceptable salt thereof administered daily:

- (a) for at least one week;
- (b) for at least two weeks;
- (c) for at least four weeks;
- (d) for at least eight weeks; or
- (e) For at least 12 weeks.

[0040] In embodiments of the invention, the lorundrostat or pharmaceutically acceptable salt thereof is the monohydrobromide salt of lorundrostat.

[0042] In embodiments of the invention, the method further comprises administering to the subject an amount of a sodium–glucose cotransporter 2 (SGLT2) inhibitor once per day, wherein the amount of the SGLT2 inhibitor and the amount of lorundrostat or pharmaceutically acceptable salt thereof taken together are sufficient to treat CKD in the subject.

[0043] In embodiments of the invention, the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof are administered in a combined pharmaceutical composition.

[0044] In embodiments of the invention, the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof are administered simultaneously, contemporaneously or concomitantly.

[0045] In embodiments of the invention, the subject afflicted with CKD is being treated with a angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB).

[0046] In embodiments of the invention, the subject afflicted with CKD is being treated with a maximally tolerated dose of an ACEi or ARB.

[0047] In embodiments of the invention:

- (a) the amount of the ACEi or ARB when administered with the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the ACEi or ARB inhibitor that is effective to treat CKD when the ACEi or ARB inhibitor is administered alone;
- (b) the amount of the ACEi or ARB when administered with the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the ACEi or ARB that is effective to treat CKD when the ACEi or ARB inhibitor is administered in the absence of administration of the SGLT2 inhibitor and/or lorundrostat or pharmaceutically acceptable salt thereof; and/or
- (c) the amount of the ACEi or ARB that is effective to treat CKD when administered in the absence of administration of the SGLT2 inhibitor and/or lorundrostat or pharmaceutically acceptable salt thereof causes one or more adverse effects in the subject, wherein the one or more adverse effects are not caused by the amounts of the ACEi or ARB, SGLT2 inhibitor and

lorundrostat or pharmaceutically acceptable salt thereof that are effective to treat CKD when administered together.

[0048] In embodiments of the invention:

- (a) the amounts of the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof when taken together are effective to achieve a greater than additive therapeutic result in treating the subject;
- (b) the amount of the SGLT2 inhibitor is lower than the amount of the SGLT2 inhibitor that is effective to treat CKD when the SGLT2 inhibitor is administered alone;
- (c) the amount of lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the lorundrostat or pharmaceutically acceptable salt thereof that is effective to treat CKD when lorundrostat or pharmaceutically acceptable salt thereof is administered alone;
- (d) the amount of the SGLT2 inhibitor is lower than the amount of the SGLT2 inhibitor that is effective to treat CKD when the SGLT2 inhibitor is administered in the absence of administration of lorundrostat or pharmaceutically acceptable salt thereof; and/or
- (e) the amount of the SGLT2 inhibitor that is effective to treat CKD when administered in the absence of administration of lorundrostat or pharmaceutically acceptable salt thereof causes one or more adverse effects in the subject, wherein the one or more adverse effects are not caused by the amounts of the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof that are effective to treat CKD when administered together.

[0049] In embodiments of the invention, the amount of the SGLT2 inhibitor, and the amount of lorundrostat or pharmaceutically acceptable salt thereof when administered together are more effective to treat the subject than when each agent at the same amount is administered alone.

[0050] In embodiments of the invention, the SGLT2 inhibitor is selected from the group consisting of dapagliflozin, empagliflozin, ipragliflozin, luseogliflozin, canagliflozin, ertugliflozin and bexagliflozin.

[0051] In embodiments of the invention, the SGLT2 inhibitor is dapagliflozin.

[0052] In embodiments of the invention, the amount of dapagliflozin is 8-12 mg per day, preferably 10 mg per day.

[0054] In embodiments of the invention, the SGLT2 inhibitor and the lorundrostat or pharmaceutically acceptable salt thereof are administered in the morning.

[0055] In embodiments of the invention, the SGLT2 inhibitor and the lorundrostat or pharmaceutically acceptable salt thereof:

- (a) are administered daily for at least one week;
- (b) are administered daily for at least two weeks;
- (c) are administered daily for at least four weeks; or
- (d) are administered daily for at least eight weeks.

[0057] In embodiments of the invention, the method is effective to:

- (a) treat proteinuria in the subject, preferably wherein the method is effective to treat albuminuria in the subject; and/or
- (b) attenuate progression of nephropathy.

[0058] In embodiments of the invention:

- (a) the subject's 24-hour or first morning urine void urine albumin-to-creatinine ratio (UACR) is reduced relative to the subject's 24-hour or first morning urine void UACR prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered;
- (b) the subject's 24-hour total urine albumin (TUA) is reduced relative to the subject's TUA prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered;
- (c) the subject's 24-hour urinary protein to creatinine ratio (UPCR) is reduced relative to the subject's UPCR prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered; and/or
- (d) the subject's 24-hour urine protein is reduced relative to the subject's 24-hour urine protein prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered.

[0059] In embodiments of the invention:

- (a) the subject's 24-hour or first morning urine void urine albumin-to-creatinine ratio (UACR) is reduced by at least 30%, by at least 40%, by between 30%

and 70%, by between 30% and 60%, by between 30% and 50%, by between 40% and 80%, by between 40% and 70%, by between 40% and 60%, relative to the subject's 24-hour or first morning urine void UACR prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered;

- (b) the subject's 24-hour total urine albumin (TUA) is reduced by at least 30%, by at least 40%, by between 30% and 70%, by between 30% and 60%, by between 30% and 50%, by between 40% and 80%, by between 40% and 70%, by between 40% and 60%, relative to the subject's TUA prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered;
- (c) the subject's 24-hour urinary protein to creatinine ratio (UPCR) is reduced by at least 30%, by at least 40%, by between 30% and 70%, by between 30% and 60%, by between 30% and 50%, by between 40% and 80%, by between 40% and 70%, by between 40% and 60%, relative to the subject's UPCR prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered; and/or
- (d) the subject's 24-hour urine protein is reduced by at least 30%, by at least 40%, by between 30% and 70%, by between 30% and 60%, by between 30% and 50%, by between 40% and 80%, by between 40% and 70%, by between 40% and 60%, relative to the subject's 24-hour urine protein prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered.

[0060] In embodiments of the invention, the subject's aldosterone level follows a substantially normal circadian rhythm.

[0061] In embodiments of the invention:

- (a) the amount of the lorundrostat or pharmaceutically acceptable salt thereof inhibits CYP 11 β 2 beta hydroxylase activity for a duration that is sufficient to maintain a state of sodium and volume depletion in the subject;
- (b) the method does not produce a persistent state of hyperkalemia or mild non-anion gap metabolic acidosis in the subject;
- (c) the lorundrostat or pharmaceutically acceptable salt thereof does not substantially accumulate in the subject, preferably wherein the lack of

substantial accumulation of the lorundrostat or pharmaceutically acceptable salt thereof in the subject allows for the subject's aldosterone levels to return to pre-drug baseline within 24-48 hours of the lorundrostat or pharmaceutically acceptable salt thereof being administered, more preferably within 16-24 hours of the lorundrostat or pharmaceutically acceptable salt thereof being administered;

- (d) the subject's potassium levels are generally maintained in a clinically normal range, preferably wherein the subject's potassium levels are mildly elevated relative to the subject's potassium levels prior to administration of the lorundrostat or pharmaceutically acceptable salt thereof, more preferably wherein the subject's potassium levels are elevated by 0.35 mmol/L or less, more preferably wherein the subject's potassium levels are maintained below a level of 5.5 mmol/L, more preferably wherein the subject's potassium levels are maintained between 3.5 mEq/l to 5.1 mEq/l; and/or
- (e) the lorundrostat or pharmaceutically acceptable salt thereof is administered to the subject in an amount which:
 - (i) suppresses aldosterone production in the subject;
 - (ii) increases serum and/or plasma potassium levels in the subject; and/or
 - (iii) increases plasma renin activity (PRA) in the subject; preferably wherein:
 - (i) serum and/or plasma aldosterone AUC-24 is reduced in the subject by at least 25% relative to the aldosterone levels in the subject prior to administration of the lorundrostat or pharmaceutically acceptable salt thereof;
 - (ii) serum and/or plasma potassium levels in the subject are increased by at least 0.2 mMol/L relative to the serum and/or plasma potassium levels in the subject prior to administration of the lorundrostat or pharmaceutically acceptable salt thereof; and/or
 - (iii) PRA in the subject is increased by at least 5 ng/ml/hr relative to the PRA in the subject prior to administration of the lorundrostat or pharmaceutically acceptable salt thereof.

[0063] In embodiments of the invention, the subject is afflicted by CKD characterized by one or more or all of the following:

- (a) a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-3500 mg/g or 200-5000mg/g;
- (b) an estimated glomerular filtration rate (eGFR) of at least 25 mL/min/1.73m², preferably at least 30 mL/min/1.73m², more preferably at least 30 mL/min/1.73m² and less than 90 mL/min/1.73m²;
- (c) nephropathy;
- (d) proteinuria such as albuminuria;
- (e) urine sediment abnormalities;
- (f) abnormalities such as electrolyte abnormalities due to tubular disorders;
- (g) abnormalities detected by histology; and
- (h) structural abnormalities detected by imaging.

[0064] In embodiments of the invention, the subject is afflicted by mild to moderate CKD, characterized by:

- (a) an eGFR of at least 45 mL/min/1.73 m² and less than 90 mL/min/1.73 m²; and
- (b) albuminurea characterized by a UACR of ≥ 300 mg/g to 3500 mg/g.

[0065] In embodiments of the invention, the subject is afflicted by moderate to severe CKD, characterized by:

- (a) an eGFR of at least 30 mL/min/1.73 m² and less than 45 mL/min/1.73 m²; and
- (b) albuminurea characterized by a UACR of ≥ 300 mg/g to 3500 mg/g.

[0066] In embodiments of the invention, the subject is also afflicted with hypertension, preferably wherein the subject has systolic blood pressure of at least 120 mmHg and a systolic blood pressure of at least 80 mmHg, more preferably wherein the subject has a systolic blood pressure of between 135-180 mmHg, inclusive.

[0067] In embodiments of the invention, the method is effective to:

- (a) reduce the subject's systolic blood pressure by at least 10 mmHg, by 10-55 mmHg, by 10-50 mmHg, by 10-45 mmHg, by 10-40 mmHg, by 10-35 mmHg, by 10-30 mmHg, by 10-25 mmHg, by 10-20 mmHg, or by 10-15 mmHg, relative to the subject's systolic blood pressure prior to

administration of the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof for a period of at least eight weeks; and/or

- (b) reduce the subject's diastolic blood by at least 5 mmHg, by 5-25 mmHg, by 5-20 mmHg, or by 5-15 mmHg relative to the subject's diastolic blood pressure prior to administration of the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof for a period of at least eight weeks;
- (c) reduce the subject's average systolic blood pressure during sleep relative to
 - (i) the subject's average systolic blood pressure during sleep prior to receiving the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof for a period of at least eight weeks;
 - (ii) the subject's average systolic blood pressure during sleep prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof for a period of at least eight weeks; and/or
 - (iii) the subject's average daytime systolic blood pressure.
- (d) reduce the subject's average systolic blood pressure during sleep by at least 10%, by between 10% and 40%, by between 10% and 30%, or by between 10% and 20% relative to the subject's average daytime systolic blood pressure;
- (e) reduce the subject's average systolic blood pressure during sleep by at least 8 mmHg, by at least 10mmHg, by between 8 and 55 mmHg, by between 10 and 45 mmHg, or by between 10 and 25 mmHg, relative to the subject's average systolic blood pressure during sleep prior to receiving the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof for a period of at least eight weeks; and/or
- (f) reduce the subject's average systolic blood pressure during sleep by at least 8 mmHg, by at least 10mmHg, by between 8 and 55 mmHg, by between 10 and 45 mmHg, or by between 10 and 25 mmHg, relative to the subject's average systolic blood pressure during sleep prior to receiving lorundrostat or pharmaceutically acceptable salt thereof for a period of at least eight weeks.

[0068] In embodiments of the invention, the amount of the ACEi or ARB when administered with the lorundrostat or pharmaceutically acceptable salt thereof is lower than the

amount of the ACEi or ARB inhibitor that is effective to treat CKD and/or hypertension when the ACEi or ARB inhibitor is administered alone;

[0069] In embodiments of the invention, the amount of the ACEi or ARB when administered with the lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the ACEi or ARB that is effective to treat CKD and/or hypertension when the ACEi or ARB inhibitor is administered in the absence of administration of the lorundrostat or a pharmaceutically acceptable salt thereof; and/or

[0070] In embodiments of the invention, the amount of the ACEi or ARB that is effective to treat CKD and/or hypertension when administered in the absence of administration of the lorundrostat or pharmaceutically acceptable salt thereof causes one or more adverse effects in the subject, wherein the one or more adverse effects are not caused by the amounts of the ACEi or ARB, and lorundrostat or pharmaceutically acceptable salt thereof that are effective to treat CKD and/or hypertension when administered together.

[0071] In embodiments of the invention, the amount of lorundrostat or pharmaceutically acceptable salt thereof when administered together with the ACEi or ARB are more effective to treat CKD and/or hypertension in the subject than when each agent at the same amount is administered alone.

[0072] In embodiments of the invention, the subject is also afflicted with Type 2 diabetes mellitus (T2DM).

[0073] In embodiments of the invention, the subject:

- (a) is not afflicted with Type 2 diabetes mellitus (T2DM); and/or
- (b) is not afflicted with Type 1 diabetes.

[0074] In embodiments of the invention, the subject does not have primary aldosteronism.

[0076] This invention also provides a method of identifying a subject for treatment with lorundrostat or pharmaceutically acceptable salt thereof, the method comprising:

- (a) measuring the subject's 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) and/or an estimated glomerular filtration rate (eGFR);
- (b) selecting a subject who, when taking a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), has:
 - (i) chronic kidney disease (CKD), characterized by:

1. a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-3500 mg/g or 200-5000mg/g; and/or
 2. an estimated glomerular filtration rate (eGFR) of at least 30 or at least 45 mL/min/1.73m² and preferably less than 90 mL/min/1.73m²;
- (ii) mild to moderate CKD, characterized by:
1. albuminuria, characterized by a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 300-3500 mg/g; and
 2. an estimated glomerular filtration rate (eGFR) of at least 45 mL/min/1.73m² and less than 90 mL/min/1.73m²; or
- (iii) moderate to severe CKD, characterized by:
1. albuminuria, characterized by a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 300-3500 mg/g; and
 2. an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73m² and less than 45 mL/min/1.73m²;

thereby identifying said subject for treatment with lorundrostat or pharmaceutically acceptable salt thereof.

[0077] In an embodiment, step (a) further comprises measuring the subject's systolic blood pressure and step (b) further comprises selecting a subject who has hypertension, preferably characterized by a systolic blood pressure of 135-180 mmHg.

[0078] In embodiments of the invention, the subject is identified for treatment with:

- (a) 10-15 mg per day of lorundrostat or a pharmaceutically acceptable salt thereof, preferably 12.5 mg per day of lorundrostat or a pharmaceutically acceptable salt thereof;
- (b) 20-30 mg per day of lorundrostat or pharmaceutically acceptable salt thereof, preferably 25 mg per day of lorundrostat or pharmaceutically acceptable salt thereof; or
- (c) 40-60 mg per day per day of lorundrostat or pharmaceutically acceptable salt thereof, preferably 50 mg per day of lorundrostat or pharmaceutically acceptable salt thereof.

[0079] This invention also provides a method of identifying a subject for treatment with a sodium-glucose cotransporter 2 (SGLT2) inhibitor and lorundrostat or pharmaceutically acceptable salt thereof, the method comprising:

- (a) measuring the subject's 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) and/or an estimated glomerular filtration rate (eGFR);
- (b) selecting a subject who, when taking a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), has:
 - (i) chronic kidney disease (CKD), characterized by:
 - 1. a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-3500 mg/g or 200-5000mg/g; and/or
 - 2. an estimated glomerular filtration rate (eGFR) of at least 30 or at least 45 mL/min/1.73m² and preferably less than 90 mL/min/1.73m²;
 - (ii) mild to moderate CKD, characterized by:
 - 1. albuminuria, characterized by a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 300-3500 mg/g; and
 - 2. an estimated glomerular filtration rate (eGFR) of at least 45 mL/min/1.73m² and less than 90 mL/min/1.73m²; or
 - (iii) moderate to severe CKD, characterized by:
 - 1. albuminuria, characterized by a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 300-3500 mg/g; and
 - 2. an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73m² and less than 45 mL/min/1.73m²;

thereby identifying said subject for treatment with a sodium-glucose cotransporter 2 (SGLT2) and lorundrostat or pharmaceutically acceptable salt thereof.

[0080] In embodiments of the invention, the SGLT2 inhibitor is selected from the group consisting of dapagliflozin, empagliflozin, ipragliflozin, luseogliflozin, canagliflozin, ertugliflozin and bexagliflozin.

- [0081] In embodiments of the invention, the SGLT2 inhibitor is dapagliflozin.
- [0082] In embodiments of the invention, the subject is identified for treatment with:
- (a) 10-15 mg per day of lorundrostat or a pharmaceutically acceptable salt thereof, preferably 12.5 mg per day of lorundrostat or a pharmaceutically acceptable salt thereof, and 8-12 mg per day of dapagliflozin, preferably 10 mg per day of dapagliflozin;
 - (b) 20-30 mg per day of lorundrostat or pharmaceutically acceptable salt thereof, preferably 25 mg per day of lorundrostat or a pharmaceutically acceptable salt thereof, and 8-12 mg per day of dapagliflozin, preferably 10 mg per day of dapagliflozin; or
 - (c) 40-60 mg per day per day of lorundrostat or a pharmaceutically acceptable salt thereof, preferably 50 mg per day of lorundrostat or a pharmaceutically acceptable salt thereof, and 8-12 mg per day of dapagliflozin, preferably 10 mg per day of dapagliflozin.
- [0083] In embodiments of the invention, the lorundrostat or pharmaceutically acceptable salt thereof is the monohydrobromide salt of lorundrostat.
- [0085] In embodiments of the methods of identifying a subject for treatment, step (b) further comprises selecting a subject without Type 1 diabetes.
- [0086] In embodiments of the methods of identifying a subject for treatment:
- (a) step (a) further comprises measuring the subject's serum cortisol in the morning, and step b) further comprises selecting a subject with a serum cortisol of between 3 µg/dL and 22 µg/dL;
 - (b) step (a) further comprises determining the subject's body mass index (BMI), and step (b) further comprises selecting a subject with a BMI of 18-40 kg/m²;
 - (c) step (a) further comprises measuring the subject's serum potassium, and step (b) further comprises selecting a subject with a serum potassium of less than 4.8 mmol/L;
 - (d) step (a) further comprises measuring the subject's serum sodium, and step (b) further comprises selecting a subject with a serum sodium of greater than 135 mmol/L.

- (e) step a) further comprises measuring the subject's systolic blood pressure, and step b) further comprises selecting a subject with hypertension, preferably characterized by a systolic blood pressure of at least 135 mmHg, more preferably between 135 mmHg and 180 mmHg, inclusive.

Compositions

[0087] This invention also provides lorundrostat or a pharmaceutically acceptable salt thereof for use in any one of the methods described herein.

[0088] This invention also provides a pharmaceutical composition comprising lorundrostat or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier for use in any one of the methods described herein.

[0089] This invention also provides a lorundrostat or a pharmaceutically acceptable salt thereof for use in treating chronic kidney disease (CKD) in a subject afflicted with CKD, wherein said use is in combination with a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably wherein the SGLT2 inhibitor is dapagliflozin.

[0090] This invention also provides use of lorundrostat or pharmaceutically acceptable salt thereof for treating chronic kidney disease (CKD) in a subject afflicted with CKD in combination with a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably wherein the SGLT2 inhibitor is dapagliflozin.

[0091] This invention also provides a lorundrostat or a pharmaceutically acceptable salt thereof for use in treating chronic kidney disease (CKD) and hypertension in a subject afflicted with CKD and hypertension, wherein said use is in combination with a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably wherein the SGLT2 inhibitor is dapagliflozin.

[0092] This invention also provides use of lorundrostat or pharmaceutically acceptable salt thereof for treating chronic kidney disease (CKD) and hypertension in a subject afflicted with CKD and hypertension, in combination with a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably wherein the SGLT2 inhibitor is dapagliflozin.

[0093] This invention also provides a lorundrostat or a pharmaceutically acceptable salt thereof for use in treating hypertension in a subject afflicted with CKD and hypertension, wherein said use is in combination with a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably wherein the SGLT2 inhibitor is dapagliflozin.

[0094] This invention also provides use of lorundrostat or pharmaceutically acceptable salt thereof for treating hypertension in a subject afflicted with CKD and hypertension, in combination with a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably wherein the SGLT2 inhibitor is dapagliflozin.

[0095] This invention also provides a package comprising:

- (a) a first pharmaceutical composition comprising an amount of lorundrostat or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier;
- (b) a second pharmaceutical composition comprising an amount of sodium-glucose cotransporter 2 (SGLT2) inhibitor;
- (c) optionally, a third pharmaceutical composition comprising an amount of an angiotensin-converting enzyme inhibitor (ACEi); and
- (d) optionally, a fourth pharmaceutical composition comprising an amount of an angiotensin receptor blocker (ARB)
- (e) instructions for use of the first and second pharmaceutical compositions, and third and fourth pharmaceutical compositions, if present, together to treat a subject afflicted with CKD, or CKD and hypertension.

[0096] This invention also provides a package comprising:

- (a) a first pharmaceutical composition comprising an amount of lorundrostat or pharmaceutically acceptable salt thereof, an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and a pharmaceutically acceptable carrier; and
- (b) optionally, a second pharmaceutical composition comprising an amount of an angiotensin-converting enzyme inhibitor (ACEi) and/or an amount of an angiotensin receptor blocker (ARB) and a pharmaceutically acceptable carrier; and

- (c) instructions for use of the pharmaceutical composition(s) to treat a subject afflicted with chronic kidney disease (CKD) or CKD and hypertension.

[0097] This invention also provides a pharmaceutical composition comprising:

- (a) an amount of lorundrostat or a pharmaceutically acceptable salt thereof;
- (b) an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor or a pharmaceutically acceptable salt thereof;
- (c) optionally an amount of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) or a pharmaceutically acceptable salt thereof;

wherein the lorundrostat or pharmaceutically acceptable salt thereof, SGLT2 inhibitor, and ACEi or ARB, if present, are administered simultaneously, contemporaneously or concomitantly.

[0098] This invention also provides a pharmaceutical composition comprising an amount of lorundrostat or pharmaceutically acceptable salt thereof for use in treating chronic kidney disease (CKD) or CKD and hypertension in a subject afflicted with CKD or CKD and hypertension in combination with an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an amount of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

[0099] This invention also provides a pharmaceutical composition comprising an amount of lorundrostat or pharmaceutically acceptable salt thereof for use in treating hypertension in a subject afflicted with CKD or CKD and hypertension in combination with an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an amount of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).

[0100] This invention also provides a pharmaceutical composition in unit dosage form, useful in treating a subject afflicted with chronic kidney disease (CKD) or CKD and hypertension, which comprises:

- (a) an amount of lorundrostat or a pharmaceutically acceptable salt thereof;
- (b) an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor or a pharmaceutically acceptable salt thereof; and
- (c) optionally an amount of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) or a pharmaceutically acceptable salt thereof;

wherein the respective amounts of said lorundrostat or pharmaceutically acceptable salt thereof, said SGLT2 inhibitor, and said ACEi or ARB, if present, in said composition are effective, upon concomitant administration to said subject of one or more of said unit dosage forms of said composition, to treat the subject.

[0101] This invention also provides a therapeutic package for dispensing to, or for use in dispensing to, a subject afflicted with chronic kidney disease (CKD) or CKD and hypertension, which comprises:

- (a) one or more unit doses, each such unit dose comprising:
 - (i) an amount of lorundrostat or a pharmaceutically acceptable salt thereof;
 - (ii) an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor or a pharmaceutically acceptable salt thereof; and
 - (iii) optionally an amount of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) or a pharmaceutically acceptable salt thereof;

wherein the respective amounts of said lorundrostat or pharmaceutically acceptable salt thereof, said SGLT2 inhibitor, and said ACEi or ARB, if present, in said unit doses are effective, upon concomitant administration to said subject, to treat CKD in the subject, and

- (b) a finished pharmaceutical container therefor, said container containing said unit dose or unit doses, said container further containing or comprising labeling directing the use of said package in the treatment of said subject.

[0102] In embodiments of the package, pharmaceutical composition, or therapeutic package of the invention, the SGLT2 inhibitor is dapagliflozin.

[0103] In embodiments of the package, pharmaceutical composition, or therapeutic package, the lorundrostat or pharmaceutically acceptable salt thereof is the monohydrobromide salt of lorundrostat.

[0104] In embodiments of the package, pharmaceutical composition, or therapeutic package, the pharmaceutical composition, unit dose, or unit dosage form comprises 10-15 mg, 20-30 mg, or 40-60 mg of lorundrostat or pharmaceutically acceptable salt thereof, preferably 12.5 mg, 25 mg, or 50 mg of lorundrostat or pharmaceutically acceptable salt thereof, and 8-12 mg of dapagliflozin, preferably 10 mg of dapagliflozin.

Definitions

[0105] Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

[0106] In the discussion unless otherwise stated, adjectives such as “substantially” and “about” modifying a condition or relationship characteristic of a feature or features of an embodiment of the invention, are understood to mean that the condition or characteristic is defined to within tolerances that are acceptable for operation of the embodiment for an application for which it is intended. In embodiments, about means within a standard deviation using measurements generally acceptable in the art. In embodiments, about means a range extending to +/- 10% of the specified value. In embodiments, about includes the specified value. Unless otherwise indicated, the word “or” in the specification and claims is considered to be the inclusive “or” rather than the exclusive or, and indicates at least one of and any combination of items it conjoins.

[0107] It should be understood that the terms “a” and “an” as used above and elsewhere herein refer to “one or more” of the enumerated components. It will be clear to one of ordinary skill in the art that the use of the singular includes the plural unless specifically stated otherwise. Therefore, the terms “a,” “an” and “at least one” are used interchangeably in this application.

[0108] For purposes of better understanding the present teachings and in no way limiting the scope of the teachings, unless otherwise indicated, all numbers expressing quantities, percentages or proportions, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term “about.” Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0109] In the description and claims of the present application, each of the verbs, “comprise,” “include” and “have” and conjugates thereof, are used to indicate that the object

or objects of the verb are not necessarily a complete listing of components, elements or parts of the subject or subjects of the verb. Other terms as used herein are meant to be defined by their well-known meanings in the art.

[0110] Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health. Chronic kidney disease (CKD) is classified into 5 stages depending on the amount of damage the kidney has sustained. CKD is classified by Kidney Disease: Improving Global Outcomes (KDIGO) into 5 stages (Chen et al., 2019; Kovesdy, 2022). Stage 3 consists of mild-to-moderate decrease in kidney function and is further divided into CKD Stage 3a (eGFR 45-59 mL/min/1.73 m²) and 3b (eGFR 30-44 mL/min/1.73 m²). Stage 4 (eGFR 15-29 mL/min/1.73 m²) consists of severe decrease in kidney function (Chen et al., 2019).

[0111] “CYP11β2”, “Cyp11B2”, or “CYP11β2 beta hydroxylase” is a cytochrome P450 enzyme, encoded by the CYP11B2 gene in humans, which catalyzes a series of reactions leading from 11-deoxycorticosterone (i.e., an aldosterone precursor) to aldosterone. Thus, it is referred to in the art as “aldosterone synthase.” Cyp11B2 is mainly expressed in an adrenal cortex spherical layer and a level of plasma aldosterone is regulated by enzymatic activity of Cyp11B2 present in the adrenal gland. Aldosterone is expressed in other tissues, such as cardiovascular, kidney, adipose, and brain.

[0112] “CYP11β1”, “Cyp11B1” or “CYP11β1 beta hydroxylase” is a cytochrome P450 enzyme, encoded by the CYP11B1 gene in humans, which is involved in the biosynthesis of adrenal corticosteroids. It is referred to in the art as “steroid 11β-hydroxylase.”

[0113] An “inhibitor” refers to a compound (e.g. compounds described herein) that reduces activity when compared to a control, such as absence of the compound or a compound with known inactivity. An inhibitor can be a small molecule inhibitor, an antibody inhibitor, a protein inhibitor, a biomolecule inhibitor, a natural ligand, and the like. An “inhibitor” may be in the form of a pharmaceutically acceptable salt, e.g. of the compounds described herein.

[0114] As used herein “lorundrostat” refers to *N*-[*trans*-4-(acetylamino)cyclohexyl]-2-{4-[5-(4-methylphenyl)-1,2,4-triazin-3-yl]piperazin-1-yl}acetamide. As used herein “lorundrostat HBr” refers to the hydrobromide salt of lorundrostat, i.e. *N*-[*trans*-4-(acetylamino)cyclohexyl]-2-{4-[5-(4-methylphenyl)-1,2,4-triazin-3-yl]piperazin-1-yl}acetamide monohydrobromide. Weights and/or strengths of “lorundrostat” and “the

compound” of the invention refer to the weight of the free base in the monohydrobromide salt and not the weight of the salt.

[0115] Lorundrostat can be made by the processes described, for example, in US Patent No. 10,029,993 and European Publication No. 3549935, the disclosures of which are incorporated by reference herein in their entirety.

[0116] As used herein “dapagliflozin” refers to D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4ethoxyphenyl)methyl]phenyl]-, (1S)-, compounded with (2S)-1,2-propanediol, hydrate (1:1:1).

[0117] “Treating” or “treatment” as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject’s condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (i.e., not worsening) the state of disease, prevention of a disease’s transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. In other words, “treatment” as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease’s spread; relieve the disease’s symptoms, fully or partially remove the disease’s underlying cause, shorten a disease’s duration, or do a combination of these things.

[0118] “Treating” and “treatment” as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of an active agent. The administering step may be a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of active agent, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In embodiments, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient. In embodiments, the treating or treatment is not prophylactic treatment.

[0119] An “angiotensin-converting enzyme inhibitor”, “ACE inhibitor” or “ACEi” refers to a hypertension medication that block angiotensin I from being converted to angiotensin II, thereby dilating blood vessels and lowering blood pressure. Exemplary ACE inhibitors include benazepril, zofenopril, perindopril, trandolapril, captopril, enalapril, lisinopril, and ramipril.

[0120] An “angiotensin receptor blocker”, “ARB”, or “angiotensin II inhibitor” refers to a hypertension medication that blocks the receptor binding of angiotensin II, thereby dilating blood vessels and lowering blood pressure. Exemplary angiotensin receptor blockers include eprosartan, olmesartan, valsartan, candesartan, losartan, telmisartan, irbesartan, valsartan, and azilsartan medoxomil.

[0121] A “normal circadian rhythm” for aldosterone level follows a diurnal pattern wherein the nadir is in the late evening and the peak is in the early morning, pre-arousal. In an embodiment, the subject’s aldosterone level follows a substantially normal circadian rhythm. In one example of such an embodiment, the CYP 11 β 2 beta hydroxylase inhibitor of the invention, when dosed once daily in the morning after waking, suppresses the abnormally elevated production of Aldosterone during waking hours. In the early evening suppression of Aldosterone production starts to wane and the normal increase in serum Aldosterone returns towards normal by dawn, as it would under normal circumstances. The circadian rhythm of aldosterone in normal subjects and subjects with primary aldosteronism is described in Kem, David C., et al. “Circadian rhythm of plasma aldosterone concentration in patients with primary aldosteronism.” *The Journal of clinical investigation* 52.9 (1973): 2272-2277, the contents of which are specifically incorporated by reference herein.

[0122] This invention provides methods that reduce a subject’s systolic blood pressure “during sleep”. In this context, “during sleep” refers to the period of sleep in the subject’s normal sleep/wake cycle. In other words, “during sleep” refers to the subject’s approximately seven to nine hours of sleep (typically at night) that occurs daily in between their approximately 15 to 17 hours of wakefulness and not to any short period of sleep that may occur outside of the sleep phase of the subject’s normal sleep/wake cycle (i.e. naps). The blood pressure of individuals typically dips during sleep, with approximately 10% to 15% lower blood pressure values during sleep relative to during wakefulness. In contrast, hypertensive subjects may experience a smaller dip in blood pressure during sleep or may not experience any dip in blood pressure at all. Thus, methods of the invention help hypertensive subjects restore the dip in blood pressure that normal, non-hypertensive subjects experience during sleep.

[0123] A subject's "pre-drug level" of serum aldosterone refers to the subject's level of serum aldosterone, at the same time of day, in the absence of being treated with the recited drug. As discussed above, aldosterone level follows a diurnal pattern where the nadir is in the late evening and the peak is in the early morning, pre-arousal. Therefore, in embodiments where the dose of CYP 11 β 2 beta hydroxylase inhibitor reduces the serum aldosterone level of the subject by a certain percentage relative to their "pre-drug level", the reduction in serum aldosterone is measured relative to the same subject's serum aldosterone level in the absence of administration of the CYP 11 β 2 beta hydroxylase inhibitor at the same time of day. For example, the subject's serum aldosterone level at 11 AM when administered a CYP 11 β 2 beta hydroxylase inhibitor would be measured relative to that same subject's serum aldosterone level at 11 AM prior to any administration of the CYP 11 β 2 beta hydroxylase inhibitor.

General

[0124] For the foregoing embodiments, each embodiment disclosed herein is contemplated as being applicable to each of the other disclosed embodiment.

[0125] As used herein, all headings are simply for organization and are not intended to limit the disclosure in any manner. The content of any individual section may be equally applicable to all sections. All combinations of the various elements disclosed herein are within the scope of the invention.

[0126] Additional objects, advantages, and novel features of the present invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below finds experimental support in the following examples.

[0127] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

[0128] Examples are provided below to facilitate a more complete understanding of the invention. The following examples illustrate the exemplary modes of making and practicing the invention. However, the scope of the invention is not limited to specific embodiments disclosed in these Examples, which are for purposes of illustration only.

EXAMPLES

Example 1

[0129] A randomized, double-blinded, placebo-controlled study was conducted in which 116 patients were randomized and 87 received lorundrostat HBr.

[0130] A single ascending dose (SAD) study was conducted with the following dosing amounts tested:

- (a) 5mg
- (b) 10mg
- (c) 20mg
- (d) 50mg
- (e) 100mg
- (f) 200mg
- (g) 400mg
- (h) 800mg.

[0131] The IC₅₀ of inhibition of CYP 11 β 2 beta hydroxylase by lorundrostat HBr and the time above IC₅₀ for each dosing amount were estimated based on PKPD modeling of data from the SAD study. The estimated number of hours above IC₅₀ and the proportion of a 24 hour period above IC₅₀ for proposed dosing in the phase two, proof-of-concept study were extrapolated and are shown in the table below and in **Figure 1**.

Table 1

Lorundrostat HBr	Aldosterone	
Cohort	Hours above IC ₅₀	% 24hr
12.5 mg QD	2	8
50 mg QD	9	38
100 mg QD	13.5	56

12.5 mg BID	6	25
25 mg BID	12.5	52

[0132] Time above IC₅₀ was closely correlated with the duration of aldosterone suppression in the SAD study.

[0133] In a Multiple Ascending Dose (MAD) Study, little drug accumulation was observed at 40 mg, 120 mg and 360 mg QD doses.

Example 2

Introduction

[0134] Chronic kidney disease (CKD) is an increasingly prevalent condition globally and is strongly associated with incident cardiovascular disease (CVD, Pugh 2019). Hypertension is both a cause and effect of CKD and affects many CKD patients (Pugh 2019). Control of hypertension is important in those with CKD as it leads to slowing of disease progression as well as reduced CVD risk (Fay 2020). Existing guidelines do not offer a consensus on optimal blood pressure (BP) targets, while the clinical practice guidelines for CKD recommend that for stages 1-4, treatment should focus on comorbid conditions (e.g., hypertension, metabolic acidosis, and hyperkalemia) as opposed to correcting and reversing the damaged kidney function itself (Levin 2013). As CKD advances, it becomes harder to delay its progression (Pugh 2019). Therefore, it is vital to develop effective therapeutic treatments aimed at slowing not only the development of CKD, but to target its progression as early as possible. Although patients with hypertension and CKD require a combination of medications to achieve BP and estimated glomerular filtration rate (eGFR) targets, medication is often suboptimal leaving the conditions inadequately treated (Fay 2020). Together, these issues highlight an unmet need in the treatment of hypertension and CKD.

[0135] Lorundrostat, a selective aldosterone synthase inhibitor (ASI), is being developed for the treatment of hypertension in chronic kidney disease (CKD) with persistent albuminuria despite treatment by upstream renin-angiotensin-aldosterone system (RAAS) system inhibitors including angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB).

[0136] While the existing class of mineralocorticoid receptor antagonists (MRAs) address the dysregulated biology associated with hypertension, the new ASI class has the potential for a more favorable benefit/risk profile due to the differentiated mechanism of action, which

results in a profound decrease in circulating and local aldosterone production, rather than the marked increase seen with the MRA class. In addition, unlike spironolactone, the most commonly prescribed MRA, and other ASIs in development, lorundrostat, because of its short half-life, has the potential to be rapidly reversible should adverse events (AEs) such as hyperkalemia or hypotension be encountered. In CKD, there is increasing evidence to support the role of sodium-glucose cotransporter 2 inhibitor (SGLT2i) therapy in patients with CKD (Mende, 2022).

[0137] These therapies do not increase the risks of serious hyperkalemia or severe hypokalemia (Neuen et al, 2022) suggesting that there may also exist a potential synergistic effect of combination therapy with SGLT2 inhibitors and selective ASIs such as lorundrostat to decrease the occurrence of hyperkalemia and slow the progression of kidney disease.

[0138] This study will evaluate the safety, efficacy, and tolerability of lorundrostat in addition to a SGLT2i in subjects with hypertension and CKD with albuminuria despite treatment with ACEi or ARB.

Discussion

[0139] Hypertension is a leading risk factor for the development of CVD and its prevalence is increasing (Forouzanfar 2017). Despite increases in awareness and treatment, hypertension continues to be responsible for more years lived with disability and more combined years of life lost than any other cause of morbidity and mortality (Murray 2013). Reduction in BP reduces the risk for end-organ damage, and patients who do not reach BP goals, despite multidrug therapy, are designated as having resistant hypertension (RH, Carey 2018). Resistant hypertension is common in individuals with CKD and becomes more prevalent with declining kidney function (Tanner 2013). An analysis of more than 3,300 patients in the Chronic Renal Insufficiency Cohort (CRIC) study, a multicenter prospective observational study of adults with eGFRs of 20 to 70 mL/min/1.73 m², found the prevalence of RH among hypertensive patients to be 40.4%.

[0140] CKD affects more than 10% of the global population and is one of the leading causes of mortality worldwide (Kovesdy, 2022). According to the United States (US) Center for Disease Control and Prevention (CDC), an estimated 1 in 7 US adults have CKD (CDC, 2021). CKD is characterized by the gradual loss of kidney function and can be classified into 5 stages (Levin 2012). Stage 1 is normal or high functioning (eGFR $\geq$ 90 mL/min/1.73 m²), Stage 2 is mildly decreased (eGFR 60-89 mL/min/1.73 m²). Stage 3 is divided into 2 additional

stages, namely, Stage 3a and 3b. Stage 3a is mildly to moderately decreased (eGFR 45-59 mL/min/1.73 m²), while Stage 3b is moderately to severely decreased (eGFR 30-44 mL/min/1.73 m²). Stage 4 is severely decreased (eGFR 15-29 mL/min/1.73 m²), and the final stage, Stage 5, is kidney failure (eGFR <15 mL/min/1.73 m²). There is no cure for CKD, and despite multiple treatment options the risk of AEs and disease progression remains high, emphasizing an unmet need in CKD treatment.

[0141] Although hypertension is an important cause of CKD (Hanratty 2011), CKD itself increases BP through several mechanisms, including impaired sodium excretion and premature vascular ageing, which subsequently reduce baroreceptor sensitivity, increase sympathetic nervous tone, and activate the RAAS (Pugh 2019). Aldosterone contributes to the development of kidney disease (Vaidya 2018), by activating the mineralocorticoid receptor (MR) in kidney cells leading to podocytopathy, tubulointerstitial inflammation, and tubulointerstitial fibrosis (Epstein, 2021). Serum aldosterone concentrations are inversely correlated with the eGFR, positively associated with 24-hour urine protein, and independently associated with progression of CKD and incident end stage renal disease (ESRD) (Verma 2022). This suggests pathogenic aldosteronism has a role in CKD progression.

[0142] A strategy for lowering the aldosterone-related risk for fibrotic kidney disease is the use of ASIs (Weldon and Brown 2019; Brown 2020). ASIs could work more effectively than MR blockade as aldosterone not only confers the MR mediated genomic effects but also the nongenomic and MR independent effects leading to kidney fibrosis (Chen 2013). Clinical development of ASIs has been complicated by difficulties in obtaining sufficient selectivity blocking aldosterone synthase, but not cortisol synthase. The use of ASIs such as lorundrostat to inhibit aldosterone production in the adrenal gland as opposed to blockade of aldosterone activity at the receptor is a promising alternative approach for the treatment of CKD.

[0143] A review of trials conducted in patients with CKD showed that there are currently five classes of treatments available to slow CKD progression or reduce eGFR decline (Mende, 2022). These treatments include ACE inhibitors, ARBs, SGLT2 inhibitors, Glucagon-like peptide-1 receptor agonists (GLP1-RAs), and the MRA finerenone (Mende, 2022).

[0144] RAAS inhibitors, such as ACEi and ARBs, are commonly used to reduce albuminuria and slow down disease progression in patients with CKD (Mukoyama and Kuwabara, 2022). These therapies have beneficial clinical effects in patients with CKD with and without diabetes (Xie 2016). Although current guidelines recommend the use of RAAS

inhibitors (ACEi or ARB) to delay or prevent CKD progression (Mukoyama and Kuwabara, 2022), aldosterone levels often return to pre-treatment levels. This resulting failure of aldosterone suppression is referred to as “aldosterone breakthrough” and can contribute to the development of RH, hyperkalemia, and progression of cardiovascular and renal diseases (Mogi, 2022; Ando 2023). Patients are often advised to reduce dosage or even discontinue their treatment (Mukoyama and Kuwabara, 2022). One way to reduce the effect of “aldosterone breakthrough” is by lowering aldosterone production by inhibiting the enzyme aldosterone synthase (Weldon and Brown, 2019; Ando 2023). Short-term studies in patients with CKD and Type 2 diabetes mellitus (T2DM) have demonstrated promising reductions in albuminuria when MRAs were used as an add-on to an ACEi or ARB. However, these studies also showed an increased incidence of hyperkalemia-related discontinuation in patients treated with MRAs (Bakris 2020). Finerenone, a selective oral, non-steroidal MRA, has been shown to lower the risk of CKD progression and cardiovascular events in patients with CKD and T2DM (Bakris 2020).

[0145] The standard of care in the treatment of albuminuria has changed recently with many guidelines recommending the addition of an SGLT2i to an ACEi or ARB (Mende, 2022). A review of SGLT2i showed that they can reduce the risk of ESRD in patients with T2DM and CKD (Braunwald, 2022). Data from large, randomized, placebo-controlled kidney outcome trials in patients with T2DM (CREDENCE) and in patients with or without T2DM (DAPA-CKD) showed a reduction in the risk of CKD progression with the use of SGLT2i (Perkovic 2019; Heerspink 2020). Improvement in the kidney outcomes was also observed in the EMPA-KIDNEY trial in patients with CKD with or without diabetes with the trial being stopped early by the data monitoring committee (DMC) because of positive efficacy (Herrington 2023). Data from the CREDENCE, DAPA-CKD, and FIDELIO-DKD trials suggest that adding an appropriate SGLT2i or MRA to standard of care RAAS inhibition can improve a range of both kidney and cardiovascular outcomes in patients with or without T2DM (Garcia Sanchez 2022). SGLT2i do not increase the risk of serious hyperkalemia or severe hypokalemia (Neuen 2022) suggesting that there may also exist a potential synergistic effect of combination therapy with SGLT2i and selective ASIs such as lorundrostat. Such combination therapy could decrease the occurrence of hyperkalemia and potentially slow the progression of kidney disease and therefore warrants further investigation.

[0146] While the existing class of MRAs address the “aldosterone breakthrough”, the new ASI class has the potential for a more favorable benefit/risk profile due to the differentiated

mechanism of action, which results in a decrease in circulating and local aldosterone production, rather than the marked increase seen with the MRA class. Lorundrostat, a selective ASI, is an inhibitor of cytochrome P450 11B2 (CYP11B2; aldosterone synthase), which is a rate-limiting enzyme for aldosterone production. The results of a series of pharmacology studies demonstrate that lorundrostat is a selective inhibitor of CYP11B2 and is not associated with adverse effects upon the central nervous, respiratory, or cardiovascular systems. Unlike spironolactone, the most commonly prescribed MRA, and other ASIs in development, lorundrostat, because of its short half-life of approximately 9-12 hours as shown in Example 1, has the potential to be rapidly reversible should adverse events (AEs) such as hyperkalemia or hypotension be encountered. Without intending to be limited to a particular theory, the short half-life of lorundrostat relative to MRAs and other ASIs provides additional benefits, in particular when used to treat CKD. For example, aldosterone levels normally follow a diurnal pattern wherein the nadir is in the late evening and the peak is in the early morning, pre-arousal. When lorundrostat is dosed once daily in the morning after waking, it may suppress abnormally elevated production of aldosterone during waking hours. In the early evening, because of the half-life of lorundrostat, suppression of aldosterone production starts to wane and the subject's normal increase in serum aldosterone returns to normal by dawn, as it would under normal circumstances. Further, allowing some aldosterone production when suppression wanes reduces the accumulation of aldosterone precursors, which will provide additional benefits. Data from both a Phase 1 study in healthy subjects (NCT02953132) and a Phase 2 study in patients with uncontrolled hypertension, Target-HTN (NCT05001945), have shown lorundrostat to have acceptable safety profile and be well tolerated.

Benefit/Risk Assessment

Benefit and Risk Assessment for Lorundrostat

[0147] Clinical data obtained from healthy volunteers as well as patients with uncontrolled hypertension and RH have shown that lorundrostat has been well tolerated and has an acceptable safety profile.

Risk of Hyperkalemia

[0148] Increased potassium levels have been observed in nonclinical studies of lorundrostat and are a known risk of MRAs, in general.

[0149] Early healthy volunteer studies with lorundrostat revealed a trend of mild increase in serum potassium, although none of these increases were assessed as clinically significant. In

the Phase 2 study in 200 subjects with uncontrolled hypertension (MLS-101-201), hyperkalemic events were the most frequently reported AEs. Adjusting the event rate to censor values that failed quality control criteria designed to rule out non-reproducible and factitious hyperkalemia (e.g., elevated lactate dehydrogenase (LDH), with the failure to reproduce in a second blood sample drawn as soon as possible while the subject was on the same dose of lorundrostat), the number of events and subjects, presented as n events (N individuals) deemed as mild, moderate and severe laboratory abnormalities were: 42 (21), 28 (12), and 4 (3), respectively. In all cases, an electrocardiogram (ECG) was obtained and in no case were clinically significant abnormalities identified.

[0150] In this study, to mitigate potential risks associated with hyperkalemia, subjects will be required to have a serum potassium of ≤ 4.8 mmol/L prior to starting investigational drug and return to the clinic regularly to assess potassium levels locally at each in-clinic visit following initiation of treatment with lorundrostat. Clinical monitoring will allow early detection of potential AEs or trends that may be concerning, particularly those associated with increasing potassium levels.

Risk of Hyponatremia

[0151] A clinically insignificant decrease in serum sodium was observed in early healthy volunteer studies with lorundrostat. In the completed Phase 2 study of lorundrostat (MLS-101-201), there were 2 episodes of hyponatremia reported. One episode of severe hyponatremia occurred in a subject randomized to the lorundrostat 100 mg QD dose cohort. The subject had a past history of chronic mild hyponatremia, with serum sodium values of 132 mmol/L, 140 mmol/L and 142 mmol/L in the two weeks prior to Randomization. One week after Randomization, serum sodium was 135 mmol/L and after two weeks it was 113 mmol/L. There were no symptoms or abnormal physical findings. After discontinuation of study medication, serum sodium levels returned to a maximum value of 137 mmol/L and remained between 134 and 137 mmol/L over the subsequent five weeks of observation with no active treatment measures or hospitalization required. The other event was an episode of moderate hyponatremia in a subject dosed with 100 mg QD and a baseline sodium level of 136 mmol/L which declined to a value of 128 mmol/L at week 4 of treatment and increased to 137 mmol/L over the following four weeks after dose reduction to lorundrostat 50 mg QD. Muscle cramps were the only symptom reported, responding to brief treatment with ropinirole.

[0152] To mitigate potential risks associated with hyponatremia, subjects with a history of clinically significant hyponatremia within 1 year prior to Screening will be excluded. Frequent monitoring of serum electrolytes, including serum sodium with Medical Monitor oversight will occur throughout the study.

Risk of Hypotension and Dizziness

[0153] In healthy subjects, the incidence of dizziness/postural dizziness was slightly higher among lorundrostat treated subjects compared to placebo subjects.

[0154] Furthermore, hypotension with symptoms was seen in 3 subjects (1.8%) who received lorundrostat in the Phase 2 study of subjects with uncontrolled hypertension (MLS-101-201). These events were reversible with treatment cessation as expected based on the mechanism of action of lorundrostat. In addition, 3 subjects developed orthostatic hypotension in the absence of seated hypotension, defined as a fall of 20 mmHg in systolic BP (SBP) or 10 mmHg in diastolic BP (DBP) when going from sitting to standing position. In each case, the hypotensive episode resolved spontaneously and did not recur for the remainder of the treatment period. Two of these events were assessed by the Investigator as unlikely to be related to study medication; 1 event was assessed as possibly related.

[0155] Subject BP, in both seated and standing positions, will be regularly assessed throughout the course of this study. Investigators will be instructed to treat hypotensive episodes in accordance with the standard of care at the site/institution and medical guidelines.

Risk of Cortisol Suppression or Overproduction

[0156] No events of clinically significant serum cortisol reduction or impaired adrenocorticotrophic hormone (ACTH) stimulated cortisol production have been observed in completed clinical trials to date.

[0157] In the Phase 2 trial in subjects with uncontrolled hypertension, a small increase in morning serum cortisol following 8 weeks of treatment was observed in most active drug cohorts, as well as in placebo treated subjects. Three subjects in the 100 mg once daily (QD) cohorts had a morning serum cortisol value above the normal range. These increases were modest and not associated with symptoms or signs of clinical hypercortisolism.

[0158] In this present trial, all subjects will be monitored for signs and symptoms of hypercortisolism. In addition, subjects will have their serum cortisol measured regularly, with the blood draw performed as close to 8 a.m. as possible, but before 10 a.m. If necessary, a 24-

hour urinary free cortisol assessment and unscheduled ACTH stimulation test will be performed.

[0159] Specific entry and dose modification criteria have been added to the protocol to minimize potential risk for subjects.

Benefit and Risk Assessment for Dapagliflozin

[0160] The full benefits and risks associated with dapagliflozin are available in the current package inserts for the product.

Risk of Hypotension

[0161] Symptomatic hypotension may occur after initiating dapagliflozin particularly in subjects with impaired renal function (eGFR <60 mL/min/1.73 m²), elderly subjects (≥65 years), in subjects with low SBP, and in subjects on diuretics. Before initiating dapagliflozin, volume status will be assessed and corrected if indicated. Subjects will be educated on the symptoms of hypotension and volume depletion and will be monitored at least every 3 weeks (and more frequently if indicated) for signs and symptoms of hypotension after initiating therapy, as indicated above for lorundrostat.

Risk of Ketoacidosis

[0162] Ketoacidosis has been reported infrequently (estimated to be no greater than 0.1%) in diabetic subjects taking SGLT2i, including rare fatal cases. Subjects with a history of at least 1 severe hypoglycemic event or severe diabetic ketoacidosis event in the 12 months prior to Screening will be excluded from the trial. Subjects will be monitored for signs and symptoms of ketoacidosis, as well as predisposing conditions such as volume depletion.

Risk of Acute Kidney Injury and Impairment in Renal Function

[0163] There have been post marketing reports of acute kidney injury, some requiring hospitalization and dialysis in patients receiving SGLT2i. Otherwise, small clinically insignificant and reversible decreases in eGFR are commonly observed following the initiation of SGLT2i and are likely related to mild volume depletion. Many of these episodes may have been related to volume depletion, congestive heart failure (CHF) and ketoacidosis. Subjects with severe CHF, ketoacidosis and need for renal replacement therapy will be excluded. Subjects will be monitored for signs and symptoms of acute kidney injury.

Risk of Hypoglycemia

[0164] Hypoglycemia is a rare finding in non-diabetic subjects. A recent systematic review of SGLT2i (Teo 2021) found the incidence of hypoglycemia in non-diabetics was <0.5%. Adding SGLT2i to the T2DM treatment regimen is expected to lower blood glucose level and may cause hypoglycemia. All subjects will be monitored for signs and symptoms of hypoglycemia. Subjects with T2DM may be instructed to monitor their blood glucose level more closely upon initiation of study drug. Baseline treatment for T2DM will be adjusted, as needed, to avoid hypoglycemia.

Risk of Urosepsis and Pyelonephritis, Lower Limb Amputation, Genital Mycotic Infections, Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

[0165] All these conditions were observed rarely in clinical trials of SGLT2i. Subjects with a history of these conditions will be excluded from this study. All subjects will be monitored for the signs and symptoms of these conditions.

Other Risks

- [0166] Additional risks for study subjects may include but are not limited to:
- (a) Complications arising from study assessments (e.g., drawing blood may cause temporary discomfort from the needle stick, bruising, bleeding, and rarely, infection),
 - (b) Increased risk of exposure to pathogens causing infectious diseases from regular clinic visits, including coronavirus disease 2019 (COVID-19),
 - (c) A risk of loss of confidentiality.

Potential Benefits

- [0167] Benefits for study subjects may include but are not limited to:
- (a) Potential benefit of receiving study treatment,
 - (b) Contribution to the process of developing/improving the therapies for an unmet medical need,
 - (c) Medical evaluations/assessments (e.g., physical exam, ECG, laboratory assessments).

Overall Benefit-Risk Conclusion

[0168] Considering the measures taken to minimize risk to subjects participating in this study, the potential risks are justified by the anticipated benefits that may be afforded to subjects with hypertension and CKD.

Study Objectives and Endpoints*Study Objectives*ObjectivesPrimary Objective

[0169] To assess the effect of lorundrostat 25 mg once daily (QD), in addition to a sodium-glucose cotransporter-2 inhibitor (SGLT2i) on systolic blood pressure (SBP) in subjects with hypertension and chronic kidney disease (CKD) with albuminuria on stable treatment with an ACEi or an ARB.

Exploratory Objectives

[0170] To explore the effect of lorundrostat, in addition to a SGLT2i on albuminuria in subjects with hypertension and CKD with albuminuria on stable treatment with an ACEi/ARB.

[0171] To explore the effect of lorundrostat, in addition to a SGLT2i, on DBP in subjects with hypertension and CKD with albuminuria on stable treatment with an ACEi/ARB.

[0172] To explore the effect of lorundrostat, in addition to a SGLT2i, on biomarkers in subjects with hypertension and CKD with albuminuria on stable treatment with an ACEi/ARB.

[0173] To explore changes in kidney function in subjects with hypertension and CKD with albuminuria on a stable treatment with an ACEi/ARB treated lorundrostat in addition to a SGLT2i.

Safety Objectives

[0174] To investigate the safety and tolerability of lorundrostat, in addition to a SGLT2i, in subjects with hypertension and CKD with albuminuria on stable treatment with an ACEi/ARB.

Pharmacokinetic Objectives

[0175] To determine the plasma concentrations of lorundrostat and its major metabolite.

*Study Endpoints*EndpointsPrimary Endpoint

[0176] Placebo-adjusted change from baseline in automated office blood pressure (AOBP) SBP at Study Week 4.

Exploratory Endpoints

[0177] Placebo-adjusted change from baseline in 24-hour urine albumin at Study Week 4.

[0178] Placebo-adjusted change from baseline in AOBP DBP at Study Week 4

[0179] Change from baseline in AOBP SBP at Study Week 4 in lorundrostat treatment periods.

[0180] Percent change from baseline in 24-hour urine albumin at Study Week 4 in lorundrostat treatment periods.

[0181] Placebo-adjusted percent change from baseline in 24-hour urine protein at Study Week 4.

[0182] Placebo-adjusted percent change from baseline in urine albumin to creatinine ratio (UACR) at Study Week 4.

[0183] Change in biomarkers from baseline to Study Week 4 in lorundrostat treatment periods.

[0184] Placebo-adjusted change in estimated glomerular filtration rate (eGFR) from baseline to Study Week 4.

[0185] Percent change in eGFR from Study Week 4 to Study Week 8.

Safety Endpoints

[0186] Incidence and severity of AEs

[0187] Clinically significant changes in vital signs (body temperature, heart rate, and respiratory rate), physical examination and electrocardiogram (ECG) parameters.

[0188] Clinically significant changes in clinical laboratory assessments (hematology, chemistry and urinalysis).

[0189] Incidence of AEs of special interest (AESIs)

- (a) Modification of study drug dose due to hyperkalemia (e.g., dose reduction, dose hold, or permanent dose discontinuation)
- (b) Modification of study drug dose due to hyponatremia (e.g., dose reduction, dose hold, or permanent dose discontinuation)
- (c) Hypotension with symptoms (e.g., light-headedness, dizziness, presyncope, or syncope)
- (d) Severely elevated BP (AOBP SBP >180 mmHg or AOBP DBP >110 mmHg)
- (e) Modification of study drug dose due to hypercortisolism (morning serum cortisol >35 µg/dL, confirmed by 24-hour urinary free cortisol)
- (f) Discontinuation of study drug due to hypocortisolism confirmed by ACTH (Cosyntropin) stimulation test
- (g) Overdose of study drug
- (h) Modification of study drug dose due to reduction in kidney function (e.g., dose reduction, dose hold, or permanent dose discontinuation)

Pharmacokinetic Endpoints

[0190] Plasma concentration of lorundrostat and its major metabolite.

Study Design

Overall Study Design

[0191] This is a randomized, double-blind (DB), placebo controlled, crossover study with a two-period, two-sequence (2x2) design, evaluating the efficacy and safety of 25 mg QD lorundrostat (an ASI) in addition to a SGLT2i for the treatment of hypertension in subjects with CKD and albuminuria despite receiving stable treatment with an ACEi or an ARB.

[0192] The Subjects will be at least 18 years old with hypertension (AOBP SBP 135-180 mmHg inclusive at Randomization), and mild to severe CKD (eGFR ≥ 30 mL/min/1.73 m²) with albuminuria (UACR 200-5000 mg/g, inclusive) at the Screening Visit. The study consists of a 2-week screening period, a 2-week run-in period where subjects will either begin study provided dapagliflozin 10 mg or continue on their regularly prescribed SGLT2i, and two DB 4-week treatment periods separated by a 4-week washout period (Figure 2). Subjects will be randomized (1:1) to two treatment sequences: lorundrostat-placebo (LP) and placebo-lorundrostat (PL).

[0193] Treatment allocation will be organized as follows:

- (a) Treatment Period 1 (DB Study Week 0 to Study Week 4): Subjects will receive a lorundrostat 25 mg (sequence LP) or one matching lorundrostat-placebo tablet (sequence PL) dosed orally QD.
- (b) Washout (Study Week 4 to Study Week 8): All subjects will receive matching placebo dosed orally QD.
- (c) Treatment Period 2 (DB Study Week 0 to Study Week 4): Subjects will receive one matching lorundrostat-placebo tablet (sequence LP) or a lorundrostat 25 mg (sequence PL) dosed orally QD.

[0194] During the DB and Washout periods, subjects will continue their background therapy including ACEi/ARB and SGLT2i.

[0195] If at any time during DB eGFR drops by $\geq 30\%$ from Randomization, a decision on dose reduction, dose hold or dose discontinuation will be made in consultation between the Investigator and the Medical Monitor.

[0196] Following the completion of the study, subjects will be offered the opportunity to participate in a separate open label extension (OLE) study. If subjects do not enter the OLE, a final End-of-Study (EoS) safety visit will take place 2 weeks after the last dose of study drug.

Scientific Rationale for Study Design

[0197] Although there is widespread availability of inexpensive and effective oral BP-lowering medications, rates of hypertension control are poor irrespective of age, race, or sex (Virani 2021). There is currently no cure for CKD and despite multiple treatment options, the risk of AEs and CKD progression remains high (Bakris 2020). Together, these issues highlight an unmet need in the treatment of hypertension and CKD.

[0198] Lorundrostat is an inhibitor of CYP11B2 (aldosterone synthase), which is a rate-limiting enzyme for aldosterone production. In the Phase 2 Target-HTN (MLS-101-201) study, patients with uncontrolled hypertension demonstrated clinically relevant reductions in SBP following 8 weeks of treatment with lorundrostat when compared to placebo leading to a beneficial, reversible, dose-dependent reduction in eGFR (Mineralys Therapeutics, NCT05001945). The selectivity of lorundrostat for aldosterone inhibition was confirmed as cortisol levels were not inhibited across the range of doses.

[0199] This Phase 2 study will evaluate the efficacy, safety, and tolerability of lorundrostat in addition to SGLT2i in subjects with hypertension and CKD with persistent albuminuria despite treatment with an ACEi or ARB.

[0200] The study is designed as a DB randomized crossover study. A crossover design is selected as more efficient due to avoidance of between-subject variation and consequent lower total sample size requirement. Available data suggest reversibility of BP after short-term treatment with lorundrostat. Reversibility, combined with a 4-week single-blind placebo washout period minimize possibility of carryover effect to treatment Period 2. Use of placebo control period is justified with short duration of the trial and clinical equipoise. Placebo control allows for an unbiased assessment of treatment efficacy.

Number of Subjects / Number of Centers

[0201] Approximately 60 subjects will be enrolled in 30-40 investigational centers in the US.

Study Duration

[0202] The expected duration of the study for each subject from Screening to end of study visit is expected to be approximately 18 weeks.

Justification for Dose

[0203] This study will evaluate the safety, hypertension, and albuminuria-lowering effect of lorundrostat HBr dosed orally to a maximum of 25 mg QD.

[0204] The dose is based on the results of a Phase 1 first-in-man study (MT-4129-E01) and a Phase 1 study in subjects with normal renal function and subjects with severe renal impairment (MLS-101-005), and a phase 2 dose ranging trial in subjects with uncontrolled hypertension (MLS-101-201).

[0205] In MT-4129-E01 single doses of lorundrostat up to 800 mg, and multiple doses of lorundrostat up to 360 mg/day, taken orally once daily for 7 days, were evaluated in healthy subjects. No dose-limiting toxicities were observed. Dizziness/dizziness postural was reported by 9 out of 87 (10.3%) of lorundrostat-treated subjects compared to 1 out of 29 (3.4%) placebo subjects across all cohorts with no apparent dose relationship.

[0206] Post-dose serum potassium concentrations > 5.0 mmol/L were observed in 13 subjects (14.9%) who received lorundrostat (6 subjects in the single ascending dose cohort and 7 subjects in the multiple ascending dose cohort) across all cohorts. Only 2 of these 13 subjects

had post-dose serum potassium concentration > 5.5 mmol/L (one subject with a post-dose serum potassium concentration > 6.0 mmol/L). None of the serum potassium elevations were considered clinically significant, and there was no dose-dependent trend. There were no clinically significant findings with respect to vital signs, ECGs, or physical examinations.

[0207] In MLS-101-005, single oral doses of 100 mg lorundrostat were safe and well tolerated by subjects with severe renal impairment (n = 8, eGFR < 30 mL/min) and subjects with normal renal function (n = 9, eGFR ≥ 90 mL/min). There was no statistically significant effect of renal impairment on the pharmacokinetics (PK) of lorundrostat or its major metabolite, based on area under the curves (AUCs) and maximum observed plasma concentration (C_{max}). There were no deaths, serious adverse events (SAEs) or significant treatment-emergent adverse events (TEAEs) reported in the MLS 101 005 study.

[0208] In the MLS-101-201 Phase 2 study, a statistically significant placebo-adjusted reduction in SBP at Week 8, as measured by AOBP, of 9.6 mmHg (p = 0.0114) and 7.8 mmHg (p = 0.042) was observed in the once daily 50 mg and once daily 100 mg cohorts, respectively.

[0209] Treatment-emergent SAEs were reported in three subjects, one of which was deemed to be possibly related to lorundrostat in a subject with worsening of pre-existing hyponatremia, which reversed after treatment discontinuation. The two active, once-daily doses saw modest increases in potassium levels across the cohorts of 0.25 mmol/L with the 50 mg once daily and 0.29 mmol/L with the 100 mg once daily dose. Six subjects experienced transient elevated serum potassium greater than 6.0 mmol/L, none of which were considered an SAE, and all rapidly resolved after discontinuation or dose adjustment, which is consistent with the short half-life of lorundrostat. One of the events was assessed as erroneous due to sample misprocessing. As anticipated, and in a manner similar to ACEis and ARBs, the BP lowering effect of lorundrostat led to a beneficial, reversible dose-dependent reduction in eGFR, a measure of kidney function. Finally, the selectivity of lorundrostat for aldosterone inhibition was confirmed as cortisol levels were not observed to be inhibited across the range of doses. There were no notable findings in terms of vital signs, physical examination, or ECG parameters.

[0210] This study may also provide commercially available dapagliflozin 10mg QD for subjects naïve to SGLT2i or who elect to take study provided dapagliflozin in lieu of their regularly prescribed SGLT2i. Dapagliflozin 10 mg has been chosen because it is the dose that is Food and Drug Administration (FDA)-approved to reduce the risk of sustained eGFR

decline, end stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression in patients with $\text{eGFR} \geq 25$ mL/min/1.73 m². This dose has also been demonstrated to reduce albuminuria in diabetic and non-diabetic patients with CKD in the DAPA-CKD trial (Jongs et al., 2021).

End of Study Definition

[0211] The end of study is defined as the date of the last visit of the last subject in the study. A subject is considered to have completed the study if they have completed all periods of the study from Screening up to and including the EoS visit for those subjects not who will not participate in the OLE. Subjects who withdraw prematurely from the study will attend an EoS visit and will not be eligible to progress to the OLE study.

[0212] At the time of study completion or EoS visit, subjects will be queried regarding any AEs, concomitant medications, and concurrent procedures, which will be recorded on the appropriate page(s) of the source documents and electronic case report form (eCRF). At the final study visit, subjects with ongoing AEs that are considered by the investigator to be serious, study drug-related, or associated with the target condition will be requested to continue to follow-up with the Investigator until the AE resolves, is stable, or follow-up is no longer possible/necessary. Any death or pregnancy that occurs while on study (or, for subjects not participating in the OLE study, within 28 days after the subject's last dose of study drug) must be reported to the sponsor/designee for the study within 24 hours after the center becomes aware of the event.

Study Conduct

[0213] A schedule of study assessments is presented in the Schedule of Assessments (Table 3).

Study Population

[0214] Subjects not meeting all inclusion criteria, or meeting at least one exclusion criterion, may be re-screened if there is a reasonable probability of reversal. Retesting of laboratory samples, and a repeat AOBP assessment is allowed in the event of technical failure. Inclusion in the study of any subject who meets all eligibility criteria on re-screening will be at the discretion of the Investigator and the Medical Monitor.

Inclusion criteria

[0215] Subjects eligible for inclusion in this study must meet **all** of the following criteria:

- (a) Written informed consent, obtained before any study related assessment is performed;
- (b) At least 18 years of age at the time of signing the informed consent form (ICF);
- (c) At Screening, UACR of 200-5000 mg/g inclusive, in first morning urine void;
- (d) At Screening visit, eGFRs of: ≥ 30 mL/min/1.73 m²;
- (e) At Randomization, AOBP SBP of 135-180 mmHg, inclusive;
- (f) On a stable treatment with an ACEi or ARB for at least 4 weeks prior to Screening;
- (g) At Screening, serum cortisol (morning measurement, blood draw as close to 8 AM as possible) between 3 and 22 µg/dL, inclusive;
- (h) At Screening, body mass index (BMI) of ≥ 18 kg/m²;
- (i) Fertile male subjects and female subjects of childbearing potential, must agree to use an acceptable method of contraception from the Screening Visits to 28 days after the last dose of study drug in each study part; and
- (j) Willing and able to comply with the study instructions and attend all scheduled study visits, and are capable of providing informed consent.

Exclusion criteria

[0216] Subjects meeting any of the following criteria are **not** eligible for inclusion in this study:

- (a) Women who are pregnant, plan to become pregnant, or are breast-feeding;
- (b) Subjects with known hypersensitivity to lorundrostat or any of its respective excipients;
- (c) Subjects with known hypersensitivity to dapagliflozin or any of its respective excipients (subjects beginning dapagliflozin only);
- (d) Treatment, or anticipated treatment, with any prohibited medication within the timeframes described herein;
- (e) Treatment, or anticipated treatment, with triamterene and amiloride;
- (f) Participation in a trial involving an investigational device or drug within 4 weeks or 5 half-lives (whichever is longer) prior to the Screening Visit;
- (g) Previous treatment with lorundrostat or other ASI within 4 weeks prior to the Screening Visit;

- (h) At Screening, serum potassium > 5.0 mmol/L
- (i) At Randomization, serum potassium > 5.0 mmol/L (prior to first dosing of study drug)
- (j) At Screening, serum sodium < 135 mmol/L (corrected for hyperglycemia using the Katz formula. Rescreening of subjects with an exclusionary serum sodium is only allowed if two consecutive measurements at least one week apart are ≥ 135 mmol/L);
- (k) Total bilirubin >2x upper limit of normal (ULN) except for those with a diagnosis of Gilbert's syndrome, unless approved by Medical Monitor;
- (l) History of clinically significant hyponatremia within 1 year prior to Screening;
- (m) History of adrenal insufficiency or an abnormal ACTH stimulation test within 1 year prior to Screening;
- (n) Hospitalization for the treatment of urgent or emergent hypertension within 1 year prior to Screening;
- (o) Current, known or presumed white coat hypertension/significant white coat effect;
- (p) Current, known or presumed orthostatic hypotension (as defined in the SRM);
- (q) Current, known or presumed autonomic dysfunction;
- (r) Arm circumference >55 centimeters at Screening;
- (s) Subjects with a previously proven secondary cause of hypertension are excluded with the following exceptions:
 - (i) Subjects with documented sleep apnea are eligible to participate
 - (ii) Subjects with documented primary hyperaldosteronism are eligible to participate if they discontinue use of a MRA. They should have <20 mmHg increase in AOBP SBP, and AOBP SBP <150 mmHg at Randomization. MRA treatment may be tapered over a one-week period.
- (t) Use of epithelial sodium channel (ENaC) inhibitors or MRAs, including but not limited to amiloride, triamterene, spironolactone, eplerenone or finerenone within 4 weeks prior to Screening Visits and during study participation. With the exception of MRAs in primary aldosteronism;

- (u) Medical history of kidney disease related to autoimmune diseases (lupus, anti-neutrophil cytoplasmic antibody [ANCA] vasculitis), multiple myeloma or other known paraproteins, infiltrative diseases of the kidney, obstructive nephropathy, cystic kidney diseases, and renal transplantation;
- (v) Medical history of advanced liver disease, including cirrhosis ;
- (w) Medical history of active autoimmune disease or recent or anticipated need for immunosuppressive therapy;
- (x) Subjects with a medical history of urosepsis and pyelonephritis, lower limb amputation, genital mycotic infections, necrotizing fasciitis of the perineum (Fournier's Gangrene);
- (y) History of heart failure, myocardial infarction, stroke, or transient ischemic attack within 6 months prior to Screening. Heart failure of New York Heart Association (NYHA) Class II or more requires approval by the Medical Monitor;
- (z) Diabetes mellitus with a glycosylated hemoglobin (HbA_{1c}) >10% (>86 mmol/mol) at Screening;
- (aa) Planned major surgery requiring hospitalization during the study period or performed within 4 weeks prior to the Screening Visit;
- (bb) History of malignant neoplasms within the 5 years prior to Screening except for known history of basal and squamous cell skin cancer and any carcinoma *in-situ*;
- (cc) Known or suspected abuse of illicit drugs or alcohol within 1 year prior to the Screening Visit;
- (dd) In the opinion of the Principal Investigator, any other condition that will preclude participation in the study.

Modification of Diet and Glucose Control

[0217] Brief dietary counseling reflecting the current standard of care will be provided to all subjects including low potassium diet in patients with CKD.

[0218] For subjects with T2DM entering the study, the Principle Investigator (PI) will evaluate the subject's current diet, diabetes treatment regimen and glucose monitoring regimen with the subject prior to randomization to determine whether modification of any of these are required in view of the potential initiation of dapagliflozin.

[0219] For subjects who are on insulin treatment and/or metformin and are prone to hypoglycemic events based on the subject's medical history, additional glucose monitoring should be incorporated into their standard of care as determined by the PI and if clinically indicated.

Lifestyle Considerations

Caffeine, Alcohol, and Tobacco

[0220] Subjects will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for at least 30 minutes before the start of any study-related BP measurements.

[0221] Subjects will abstain from alcohol for at least 30 minutes before the start of any study-related BP measurement.

[0222] Subjects will abstain from smoking and the use of cannabis-derived or nicotine-containing products (including nicotine patches, gums, and e-cigarettes) for at least 30 minutes before the start of any study-related BP measurement.

Activity/Exercise

[0223] Subjects will abstain from strenuous exercise for at least 30 minutes before the start of any study-related BP measurement and for 24 hours before each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities (e.g., watching television, reading).

Study Drug Administration and Management

[0224] The study drug products for this study are lorundrostat as well as the matching placebo. Additionally, commercially available dapagliflozin will be provided to SGLT2i naïve subjects or those that wish to switch to study provided SGLT2i. Subjects may also choose to stay on their currently prescribed SGLT2i.

[0225] The formulation and the manufacturing of study drug follows generally accepted standard procedures.

Description of Study Drug

[0226] The study drug product lorundrostat is an immediate release formulation containing standard excipients generally recognized as safe including bulking agent, disintegrant, glidant, and lubricant that are compressed into a tablet.

[0227] A tabulated summary of lorundrostat characteristics as well as matching placebo are shown below.

Table 2: Summary of Lorundrostat and Matching Placebo Characteristics

Name of IMP	Lorundrostat	Lorundrostat placebo
Active substance(s):	HBr salt form: C ₂₄ H ₃₃ N ₇ O ₂ HBr	None
Inactive substance(s):	Standard excipients generally recognized as safe including bulking agent, disintegrant, glidant, and lubricant	The same as lorundrostat
Appearance:	Round, white, film-coated tablets with no identifying marks	Tablet matching the appearance of lorundrostat but without active substance, administered analogously to lorundrostat.
Strength:	12.5 mg, 25 mg (equivalent to 14.74 mg and 29.48 mg of lorundrostat HBr). The daily dose of lorundrostat will not exceed 25 mg.	Not Applicable
Dosage:	25 mg tablets taken orally QD at approximately the same time each morning for 4 weeks	Subjects will receive one matching lorundrostat-placebo tablet dosed orally QD for 4 weeks
Route of administration:	Oral	Oral
Manufacturer:	Patheon	Patheon
Packaging and labeling:	30 count 60 cc white round high density polyethylene bottles with a child-resistant cap	The same as lorundrostat

[0228] All packaged tablets will be assigned a unique identifying number, used by the randomization and trial supply management (RTSM) system to identify the content but maintaining the blind of the subject and site. The test materials will be identified by the lot, batch numbers, retest date, and certificate of analysis.

Dosing and Administration

[0229] During the study all subjects will take the same number of tablets, regardless of treatment allocation, to maintain the blind. Subjects will be instructed to take the tablets orally QD at approximately the same time each morning.

*Preparation, Handling, Storage, Accountability*Study Drug Packaging and Labeling

[0230] Study drug will be labelled, packed, and released in accordance with all applicable laws, regulations, and administrative provisions relating to the implementation of good manufacturing practice and good clinical practice in the conduct of clinical trials on medicinal products for human use.

[0231] Lorundrostat, dapagliflozin, and matching placebo tablets/capsules are packaged in 30 count 60 cc white round high density polyethylene bottles with a child-resistant cap. As the study is a DB study, labeling of the lorundrostat and matching placebo tablets/capsules packaging will not show the treatment allocation. All other information required by regulation will appear on the label.

Study Drug Handling and Disposal

[0232] All study drug supplies are to be used only for this clinical study and not for any other purpose. Authorized study personnel must maintain a full record of study drug disposition (i.e., a log by date received, dispensation date and subject, date of return from the subject, and detailed study drug usage by each study subject).

[0233] After reconciliation, used study drug will be handled according to instructions provided by the Sponsor. At study conclusion, all remaining unused supplies will be similarly handled. Authorized study personnel will record any unaccounted supplies in the final accountability records.

Study Drug Storage

[0234] The study drugs should be stored at room temperature (59°F to 77°F [15°C to 25°C]) in an approved storage area with access limited to authorized study personnel.

Study Drug Accountability

[0235] Study drugs (including placebo) will be maintained under adequate security by appropriate site personnel (eg, pharmacist) and in accordance with applicable regulatory requirements. Study drugs remaining at the end of the study will be returned to the sponsor or their representative or destroyed on behalf of the sponsor.

[0236] The investigator or designee must maintain adequate records of receipt and distribution of all study drug, using appropriate accountability records.

Randomization and Blinding

[0237] Subjects will be randomized (1:1) to two treatment sequences: LP and PL. Randomization numbers and study drug supplies will be assigned using RTSM. Access to the randomization codes will be controlled and documented.

[0238] The identity of study drug assignments (lorundrostat or placebo) during the DB treatment periods will be concealed from the investigator, the subject, research center staff, and all personnel involved in the conduct of the study, with the exception of the unblinded sponsor drug management staff who will oversee the study drug allocations and RTSM/dispensing compliance at the study centers.

[0239] Except when it is essential for the medical management of the subject, unblinding the treatment assignment will be considered a protocol deviation. Emergency treatment allocation information will be available by secured access to the RTSM system. If possible, the investigator should contact the sponsor before unblinding any subject's treatment assignment. In the event that this is not possible, the sponsor should be notified within 24 h after the unblinding event. After unblinding, the subject will be discontinued from study drug treatment, but will continue participation in the study, including participation in all remaining visits and assessments, until the EoS visit. The reason for unblinding must be documented in the eCRF.

Study Drug Compliance

[0240] Compliance with study drug dosing will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets during the site visits, use of medication adherence monitoring platform and will be documented in the source documents and relevant case report form. Deviation(s) from the dosage regimen should be recorded.

[0241] A record of the quantity of study drug dispensed to and administered by each subject must be maintained and reconciled with study intervention and compliance records. Study drug start and stop dates, including dates for study drug holds and/or dose reductions will also be recorded.

[0242] Study drug compliance will be defined by the treatment compliance ratio: the number of doses taken by the subject divided by the number of doses dispensed. Compliance is defined as taking between 75% and 125% of the study drug provided.

[0243] This study may use a medication adherence monitoring platform. The platform will be provided on a smartphone application. Built-in reminders and a communication system

allow real-time intervention in case of missed doses, reinforce the proper dosing schedule and improve data integrity.

Dose Modification

[0244] If an unscheduled dose adjustment of lorundrostat or SGLT2i occurs at any time during the study, an unscheduled visit to assess safety will be conducted no more than 2 weeks after the dose adjustment occurs (See Table 3 for details). Please note, the SGLT2i dose should remain stable during the study. Subjects who have an unscheduled adjustment of lorundrostat dose, or who temporarily discontinue study drug (i.e., study drug is not permanently discontinued) are eligible for participation in the OLE study.

Safety Criteria for Dose Adjustment or Discontinuation of Study Drug

[0245] If, at any time during the study, a subject experiences a clinically significant laboratory or medical assessment (e.g., hyperkalemia, hyponatremia, symptomatic hypotension, severely elevated BP, hypercortisolemia, hypocortisolemia, reduction in kidney function), laboratory test results will be confirmed using a local laboratory and AOBP measurements will be repeated. At the discretion of the Investigator, in consultation with the Medical Monitor, the dose of the study drug may be modified, or temporarily or permanently discontinued. The Investigator may temporarily interrupt study drug without prior consultation with the Medical Monitor at their discretion, and discuss their decision and whether the interruption should be converted to a discontinuation with the Medical Monitor within 24 hours. A subject with modification of their study drug will not be withdrawn from the study.

Concomitant Therapy

[0246] Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the subject is taking at screening or takes during the study will be recorded along with:

- (a) Reason for use
- (b) Dates of administration including start and end dates
- (c) Dosage information including dose and frequency

Prohibited Treatments

[0247] The following medications are prohibited from the Screening Visits until the End of Treatment (EOT), unless otherwise stated:

- (a) Previous treatment with lorundrostat or other ASI within 4 weeks or 5 half-lives (whichever is longer) prior to the Screening Visit.
- (b) Use of ENaC inhibitors or MRAs, including, but not limited to amiloride, triamterene, spironolactone, eplerenone or finerenone, from 4 weeks prior to the Screening Visits and during study participation. With the exception of MRAs in primary aldosteronism.
- (c) Use of anti-hypertensive medications (AHT) medications other than lorundrostat and those already prescribed at the Screening Visit, for the duration of study participation, require approval of the Investigator, followed by reporting to the Medical Monitor. Consultation with the Medical Monitor is recommended.
- (d) Chronically administered oral corticosteroids from 3 months prior to the Screening Visit and during study participation. Short-term (ie, ≤ 2 weeks) use of topical corticosteroids is allowed if taken ≥ 1 month prior to Randomization.
- (e) Sympathomimetic decongestants on the morning of any study-related BP assessment.
- (f) Intramuscular steroids from 3 months prior to the Screening Visit until completion of study participation. Inhaled and intra-ocular corticosteroids are allowed.
- (g) Short-acting nitrates taken for angina or for underlying cardiac disease during study participation are allowed but should be monitored and study drug discontinued if symptoms of hypotension or orthostatic hypertension occur or SBP < 110 mmHg is documented. Chronic, long-acting doses of nitrates are acceptable.
- (h) Use of digoxin is allowed but levels should be monitored.
- (i) Enrollment of subjects requiring treatment with strong CYP3A and CYP3A4 inducers (e.g., apalutamide, carbamazepine, enzalutamide, fosphenytoin, lumacaftor, mitotane, phenobarbital, phenytoin, primidone, rifampin, St. John's Wort) must be approved by the Medical Monitor. Moderate inducers of CYP3A and CYP3A4 are acceptable.
- (j) Use of Proton Pump Inhibitors (PPIs) for more than 3 days per week. These must be abstained for at least 5 days prior to a scheduled visit.
- (k) Use of digoxin is allowed, but levels should be monitored.

[0248] The decision to administer a prohibited medication/treatment during the study period is done with the safety of the subject as the primary consideration.

Discontinuation/Withdrawal Criteria

Discontinuation of Study Drug

[0249] Subjects who wish to stop treatment for any reason may stop at any time during the study.

[0250] Reasons for discontinuing study drug may include:

- (a) Unavoidable use of prohibited/excluded medications
- (b) Administrative decision by the investigator or the sponsor
- (c) Chronic or repeated Subject noncompliance with the study drug dosing schedule
- (d) Development of an AEs/SAEs/AESI at the discretion of the site Investigator, in consultation with the Medical Monitor. If the site Investigator deems the event urgent, then study drug should be held and consultation with the Medical Monitor regarding potential restart of study medication at the assigned or a reduced dose should be performed
- (e) Unblinding of subject's study drug treatment assignment
- (f) Subject becomes pregnant (or wishes to discontinue birth control measures)
- (g) Any other reason that, in the opinion of the Investigator, precludes the subject's further participation in the trial

[0251] Subjects who permanently discontinue study drug will continue participation in the study, including participation in all remaining visits and assessments until the EoS visit. Subjects who have permanently discontinued study drug will NOT progress to the OLE study.

[0252] Details regarding subjects who discontinue study drug will be recorded on the appropriate page(s) of the eCRF. If a subject discontinues study drug because of an AE, the Investigator may be requested to schedule follow-up visits until the event has resolved or stabilized.

Withdrawal of a Subject from the Study

[0253] Subjects have the right to withdraw participation in the study at any time and for any reason or for no reason and will be removed from the study upon request. The Investigator will encourage subjects who wish to withdraw from the study to return for subsequent

observations up to and including the Safety Follow-Up/EW visit. Subjects who withdraw prematurely from the study for any reason will not be eligible to participate in the OLE study. These subjects will be followed up as per standard of care. If a subject is unable or unwilling to return to the study center, the reason for withdrawal will be recorded. Each subject's right to withdraw will be honored; subjects who desire no further follow-up contact will be asked to declare so in writing. Details regarding subjects who choose to discontinue study participation will be recorded on the appropriate page(s) of the eCRF.

[0254] Reasons for withdrawing, or being withdrawn, from study may include but are not limited to:

- (a) Subject withdraws consent
- (b) Withdrawal from participation due to subject convenience (ie, due to a change in the subject's willingness or ability to attend study visits, eg, resulting from new job, work schedule change, or move to another geographical area)
- (c) Lost to follow-up (ie, the investigator has exhausted all reasonable methods of contacting the subject, which should be documented by at least 3 unsuccessful attempts to contact the subject)
- (d) Chronic or recurrent non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or the Sponsor
- (e) Death
- (f) Other

[0255] If a subject withdraws consent, data collected before such a withdrawal of consent may be retained and used.

Lost to Follow Up

[0256] A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

[0257] The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- (a) The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

- (b) The investigator or designee must make every effort to regain contact with the subject. Three telephone calls, and if necessary, a certified letter should be sent to the subject's last known mailing address or local equivalent methods. These contact attempts should be documented in the subject's medical record.
- (c) Should the subject continue to be unreachable, the site will continue efforts to contact the subject at each study visit per schedule and document their effort. No subject will be considered a true lost to follow up until the end of the trial.
- (d) At the end of the trial, vital status can be verified by the study site by contacting the subject's primary care physician or other sources according to local rules and regulations.

Study Assessment and Procedures

[0258] Table 3 and the Study Design section outline the Schedule of Assessments and study conduct details, respectively, for all subjects and all study periods. Protocol waivers or exemptions are not allowed

Table 3

Study Period	Screening ¹	Run-in	Randomization ²	Treatment Period 1 (4 weeks)		Wash Out (4 weeks)	Treatment Period 2 (4 weeks)		EoS ³	Unscheduled Visit ⁴
Weeks ⁵	-4	-2	0	2	4	8	10	EOT 12	14	UNS
Study Visit#	1	2	3	4	5	6	7	8	9	
Informed Consent ⁶	X									
Randomization			X							
Demographics	X									
Medical history	X									
Eligibility confirmed	X		X							
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Physical exam, body weight, height ⁷	X		X	X	X	X	X	X	X	X
Vital signs,	X	X	X	X	X	X	X	X	X	X
AOBP, seated and standing	X		X	X	X	X	X	X	X	X
12-lead ECG	X		X						X	X
Serum chemistry (including eGFR, excluding potassium) (central lab)	X		X	X	X	X	X	X	X	X
Cystatic-C (Central lab)	X		X	X	X	X	X	X	X	X
Serum potassium (local lab)	X		X ⁸	X	X	X	X	X	X	X
HbA _{1c} (central lab)	X				X			X	X	X
Hematology (central lab)			X		X			X	X	X
Urinalysis, spot urine (central lab)	X				X			X	X	X
Dispense kit for first morning urine void	X	X		X			X			X
Subject collects first morning urine void, midstream ⁹	X		X		X	X		X		X
Dispense kit, for 24-hour urine ¹⁰	X	X		X	X		X			X
Subject collects 24-hour urine ¹¹		X	X			X		X		X
Pregnancy test ¹²	X		X		X	X		X	X	X
Adverse events ¹³	X	X	X	X	X	X	X	X	X	X
Study drug dispensed		X ¹⁴	X		X	X				X
In-clinic dosing			X	X	X	X	X	X		X
Study drug compliance			X	X	X	X	X	X	X	X
Biomarkers (central lab) ¹⁵			X		X	X		X	X	X
Morning serum cortisol ¹⁶	X			X	X		X	X		X
PK (sampling) ¹⁷				X	X		X	X		
ACTH stimulation test ¹⁸										X

¹ Screening will be 2 weeks. However, if required, the screening window may be extended to 4 weeks without approval from the Medical Monitor.

² Only subjects who continue to meet all eligibility criteria will be randomized.

³ Visit for subjects not participating in the open label extension study only. Study visit window is ± 5 days.

⁴ Assessments performed during an unscheduled visit will be done on an as needed basis.

⁵ Study visit windows are ± 3 days.

⁶ Written informed consent must be obtained prior to conducting any study procedures.

⁷ At the Screening Visit a physical examination will be performed and should include an evaluation of the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Height will be measured at Screening only. At other visits, a limited, symptom-directed physical examination should be performed. Any abnormality identified should be recorded either as medical history or AE accordingly.

⁸ Serum potassium must be collected 3 days prior to Randomization and values must be reviewed by the Investigator for Randomization eligibility.

⁹ During Screening, one first morning urine void to be brought in, in the first week after Screening to determine eligibility. An unscheduled visit during Screening period for subjects to return first morning void must take

Abbreviations: ACTH, adrenocorticotrophic hormone; AE, adverse event; AESIs, adverse events of special interest; AOBP, automated office blood pressure; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EoS, End of study; EOT, end of treatment; EW, early withdrawal; HbA_{1C}, glycosylated hemoglobin; SAE, serious adverse event; UNS, unscheduled visit.

place a minimum of 7 days prior to the Run-in visit so that the result is available for eligibility review. The sample needs to be 200-5000 mg/g inclusive to meet eligibility criteria. Samples will be assessed for albumin, protein, and creatinine.

¹⁰ Subjects will be given a 24-hour urine collection kit to take home at preceding visits. An aliquot of urine will be retained for future biomarker assessments.

¹¹ Subjects must start urine collection on Day-1 and return the collected 24-hour urine on Week 0

Randomization visit. 24-hour urine samples will be utilized for assessment of albumin, protein, creatinine, sodium, potassium, cortisol, and aldosterone. An aliquot of urine will be retained for future assessments.

¹² Women of childbearing potential only. A sample for serum pregnancy test will be collected at Screening. Follicle stimulating hormone must be used to confirm postmenopausal status in all postmenopausal women at Screening. Urine pregnancy tests will be done at other visits. If urine pregnancy test is positive, a serum pregnancy test will be collected to confirm results at the local lab.

¹³ All AEs and SAEs will be collected from signing of informed consent form until the subject has completed the EoS/EW visit or transitioned to the open label extension study. All AESIs will be collected upon initiation of treatment until the subject has completed the EoS/EW visit or transitioned to the open label extension study.

¹⁴ Only for SGLT2i naïve patient or patient switching to sponsor provided SGLT2i.

¹⁵ An aliquot of serum will be retained for future biomarker assessments. A sample of whole blood will be collected at Randomization and retained for future proteomic and genomic assessments. A mid-stream urine sample will also be collected for future biomarker analyses. Blood and urine samples will be processed and stored as described in the laboratory manual.

¹⁶ Blood draw for cortisol assessment should occur as close to 8 AM and before 10 AM on the morning of the study visit.

¹⁷ Subjects should have a blood sample drawn just prior to dosing and another blood sample taken 1-2 hrs. post-dose

¹⁸ ACTH (Cosyntropin) stimulation testing to be performed at unscheduled visits if clinically indicated by signs, including serum cortisol below 3 µg/dL, or below 10 µg/dL accompanied by symptoms of hypocortisolism.

- [0259] Informed consent must be obtained before any trial related activity.
- [0260] At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact details of relevant trial site staff.
- [0261] Adherence to the study design requirements is essential and required for study conduct.
- [0262] All subjects should attend study visits after at least 8 h of fasting unless there is a medical reason not to fast as determined by the investigator.
- [0263] Any deviation from study conduct as outlined in the Protocol and/or SRM will be captured and recorded as a Protocol Deviation.
- [0264] Acute safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject requires dose modification or discontinuation of study drug.
- [0265] All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- [0266] Source data of clinical assessments performed and recorded in the eCRF must be available and will usually be the subject's medical records. Additional recordings to be considered source data include but are not limited to laboratory reports, AOBP, and ECG assessments.
- [0267] Assessments should be carried out according to the institution's standard of practice unless otherwise specified in the current section. Efforts should be made to limit the bias between assessments.
- [0268] Phone calls may be conducted between study visits to follow up on study drug compliance, and/or as a general follow-up for any questions or clarifications that the subject may have.

Clinical Laboratory Tests

- [0269] Clinical safety laboratory tests will be conducted by a central laboratory according to the time points specified in the Schedule of Assessments (Table 3). Analytes for clinical safety laboratory tests are listed in Table 4. The investigator must review the laboratory report,

document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. All laboratory tests with values considered clinically significantly abnormal during participation in the study or after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Medical Monitor. If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

Table 4: Clinical Laboratory Analytes

Chemistry	Urine	Other Laboratory Measurements
Sodium Potassium (local lab) Chloride Bicarbonate Magnesium Phosphate Total protein Albumin Calcium Glucose BUN Creatinine eGFR CKD-EPI w/o race Total bilirubin Direct bilirubin AST ALT Alkaline phosphatase Serum aldosterone PRA Serum cortisol Cystatin-C	First Morning Urine Void: Creatinine Albumin Protein Urinalysis, spot urine (central lab): RBC Glucose Protein Urine pH Ketones Bilirubin Urine specific gravity Blood 24-hour urine*: Albumin Protein Free cortisol Aldosterone Sodium Potassium Creatinine	Hematology - CBC auto differential panel (central lab): Hematocrit Hemoglobin RBC count WBC count Platelet count MCH MCHC MCV Mean platelet volume Red cell distribution width CBC, nucleated red blood cell WBC differential (basophils, eosinophils, immature granulocytes, lymphocytes, monocytes, neutrophils [% absolute count]) Pregnancy Testing: Serum or Urine Pregnancy (for WOCBP only) FSH (postmenopausal women only) Biomarkers** (central lab): hsCRP NTproBNP NGAL KIM-1 exploratory biomarkers Other: HbA1c ACTH Stimulation testing

Refer to the Schedule of Assessments (Table 3) for collection time points.

* An aliquot of urine will be retained for future assessments. **A serum aliquot, a sample of whole blood for proteomic and genomic assessments, and a mid-stream urine sample

will be collected and retained for future biomarker analyses. Abbreviations: ACTH, adrenocorticotrophic hormone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FSH, follicle-stimulating hormone; HbA1c, glycosylated hemoglobin; hsCRP, high-sensitivity C-reactive protein; KIM-1, kidney injury molecule-1; NTproBNP, N-terminal (NT)-pro hormone BNP; NGAL, Neutrophil gelatinase-associated lipocalin; PRA, plasma renin activity; RBCs, red blood cells; WBC, White blood cell; w/o, without.

Demographics and Other Baseline Characteristics

Medical History

[0270] Medical history data are to be collected at the Screening Visit. For female subjects of childbearing potential, the date of the last menstrual period should be noted. Data will be updated at subsequent visits as appropriate.

Concomitant Medications

[0271] A detailed history of medications and procedures will be documented for each subject at the Screening Visits. Concurrent medications (especially changes in medication) will be documented for each patient at each scheduled visit.

[0272] Any medication that in the opinion of the investigator will interfere with the study drugs is prohibited (see “Prohibited Treatments”).

Demographic Data

[0273] Subject demographic data will be collected at the Screening Visits. These data include the year of birth, age, gender, race, and other relevant baseline characteristics.

Efficacy Assessments

First Morning Urine Void Measurements

[0274] First morning urine void collection will be performed as per the schedule of assessments (Table 3) and outlined in the SRM. Subjects will be given first morning void collection kits to take home. A mid-stream sample of the first morning urine will be collected in the morning when they wake up and prior to dosing with study drug. The date and time of urine collection should be recorded. A detailed description for urine collection and storage will be provided in the laboratory manual and instructions will be provided to the subjects. During Screening, one first morning urine void is to be brought in, in the first week after Screening Visit to determine eligibility. An unscheduled visit during Screening for subjects to return first morning void must take place a minimum of 7 days prior to the Week 0 visit so that the result

is available for eligibility review. The sample needs to be ≥ 300 mg/g to meet eligibility criteria. Samples will be assessed for albumin, protein, and creatinine. 24-hour urine Measurements

[0275] 24-hour urine collection will be performed as per the schedule of assessment (Table 3).

[0276] Subjects will be provided with a 24-hour urine collection kit to take home for collection of urine preceding the analysis days outlined in the schedule of assessment (Table 3). The 24-hour urine collection starts after the first morning urine and is collected for 24 hours with the last urine added the morning of the second day. The date and time of the start and end of the urine collection should be recorded.

[0277] 24-hour urine samples will be used to measure 24-hour albumin, protein, sodium, potassium, cortisol, and aldosterone. An aliquot of urine will be retained for future assessments.

Blood Pressure Measurements

[0278] Measurement of BP will be done as per the Schedules of Assessments (Table 3). This is essential to classify individuals and record study treatment effect; consequently, BP should be measured using an automatic BP device at the site provided by the Sponsor that is identical for all participating sites and managed by qualified personnel. Deviations from this must be approved by the Sponsor prior to implementation. Subjects should be seated when performing the AOBP assessment. In addition, the same person should use the BP device for a given subject at each visit whenever possible, and the measurement should be performed using the same arm of the subject and the appropriate cuff size, as determined during the Screening visit.

[0279] Details on BP procedure (measurement and transfer of data) including subject preparation (e.g., arm selection, arm position, cuff size) will be provided.

[0280] Heart rate will also be recorded and collected with all AOBP measurements. Sitting and standing SBPs and DBPs will be recorded and collected along with corresponding heart rates. Orthostatic BP change will be calculated and recorded.

Biomarker Analysis

[0281] For the efficacy and safety assessments of the study, biomarkers are measured at a central laboratory to allow estimation of change from Baseline. These measurements will be performed as per the schedule of assessment (Table 3).

Population Pharmacokinetic Assessments

[0282] At the Week 2, 4, 10 and 12 visits (Table 3), subjects will have blood drawn for popPK analysis at trough (i.e., just before dosing) and 1-2 hours after the dose. For visits when PK samples are to be drawn, subjects should arrive at the clinic before taking that day's dose of study drug. The time of each blood draw and the time of study drug dosing on the day of the PK blood draws will be noted on the respective eCRF page. Instructions for collection, preparation, handling, and shipping PK specimens are provided in the Laboratory Manual.

Safety Assessments

Physical Examination

[0283] A thorough physical examination will be performed by trained medical personnel at Screening and should include an evaluation of the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. Height will be measured at Screening only. On other visits, a limited, symptom-directed physical examination should be performed. Changes from baseline abnormalities should be recorded in source documents. New or worsened clinically significant abnormalities should be recorded as AEs on the AE eCRF.

Vital Signs

[0284] In addition to BP and heart rate, body temperature, and respiratory rate will be assessed with the subjects in a seated position. Subjects should be seated for at least 5 min before taking the measurement.

Electrocardiogram

[0285] Single 12-lead ECGs will be recorded as per the Schedule of Assessments (Table 3). Clinically significant abnormal ECG findings should be reported as AEs and treated as clinically appropriate. In addition, a 12-lead ECG assessment will be performed on subjects with a re-check serum potassium as outlined below.

Clinical Safety Laboratory Tests

[0286] Blood and urine samples will be collected and clinical safety laboratory tests will be conducted by a central or local laboratory as per the Schedule of Assessments (Table 3). Serum sodium, potassium, and creatinine concentrations will be collected as per local guidelines and assessed at a local laboratory. Instructions for collection, preparation, handling,

and shipping of central clinical laboratory specimens are provided in the Laboratory Manual for the study. Analytes for clinical safety labs are listed in Table 4.

[0287] Subjects will be given a 24-hour urine collection kit to take home for collection of urine as outlined in the Schedule of Assessments (Table 3). Urine will be analyzed for albumin, total protein, free cortisol, aldosterone, sodium, potassium and creatinine levels. Subjects with a morning serum cortisol assessment $>35 \mu\text{g/dL}$ will perform an unscheduled 24-hour urine collection for assessment of 24-hour urinary free cortisol.

Adrenocorticotrophic Hormone Stimulation Test

[0288] An unscheduled ACTH (cosyntropin)-stimulation test is to be performed if morning serum cortisol is $<3 \mu\text{g/dL}$, or if morning serum cortisol is $<10 \mu\text{g/dL}$ AND accompanied by symptoms of hypocortisolism such as weakness, loss of appetite, unintentional weight loss, hyponatremia, hypoglycemia, PLUS clinical findings of orthostatic hypotension, pre-syncope or syncope. Instructions on implementing the test, including administration of cosyntropin and timing, processing, storage, and transport of samples for central laboratory testing are provided in the Laboratory Manual.

Pregnancy Testing

[0289] Pregnancy tests are required for women of childbearing potential (WOCBP) only. A serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed at other visits as per Schedule of Assessments (Table 3). If a urine pregnancy test is positive, a serum pregnancy test will be collected to confirm results at the local laboratory.

Adverse Events, Serious Adverse Events, and Other Safety Reporting

[0290] The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE, and remain responsible for following up on all AEs and SAEs.

Time Period and Frequency for Collecting AE and SAE Information

[0291] For subjects rolling over into the OLE, all AEs and SAEs will be collected from signing of the study ICF until just before the first assessment in the OLE study. All AESIs will be collected from Randomization until just before the first assessment in the OLE study. For subjects not participating in the OLE, all AEs and SAEs will be collected from signing of the ICF to 28 days post the last dose of study drug. All AESIs will be collected from Randomization until the EOS visit.

[0292] Adverse events that begin before the start of study drug (lorundrostat or placebo) at Randomization, but after obtaining informed consent will not be considered TEAEs. Under no circumstance should the reporting of SAEs and AESI exceed 24 hours. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

[0293] Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of study participation (i.e., after the completion of the EoS/EW visit). However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must notify the Sponsor promptly.

[0294] In the event that study drug is interrupted, AEs and SAEs will be collected throughout the interruption. If study drug is permanently discontinued for any reason, the reason will be recorded and the subject should be encouraged to remain in the study so that important safety information can be obtained. All AEs and SAEs leading to discontinuation of study drug or discontinuation of study will be collected. Once a subject withdraws consent to participate in the study, no further information can be collected from the subject.

Method of Detecting AEs and SAEs

[0295] Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

[0296] Investigators will seek information on AEs at each subject contact. All AEs, whether reported by the subject or noted by study personnel, will be recorded.

[0297] A consistent, nondirective questioning methodology should be adopted for eliciting AE information at all subject evaluation time points. Examples of nondirective questions include the following:

- (a) “How have you felt since your last study visit?”
- (b) “Have you had any new or changed health problems since you were last here?”

Follow-up of AEs and SAEs

[0298] After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and AESIs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

Regulatory Reporting Requirements for SAEs

[0299] Prompt notification (within 24 h) by the investigator to the sponsor/designee of an SAE is essential so that regulatory obligations and ethical responsibilities towards the safety of subject and the safety of a study intervention under clinical investigation are met.

[0300] The sponsor has a responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and investigators.

[0301] An investigator who receives an Investigational new drug (IND) safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local and institutional requirements.

[0302] IND safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators.

Pregnancy

[0303] Details of all pregnancies in female subjects and female partners of male subjects will be collected from Screening until either just prior to the start of the OLE study, or until 28 days after the last subject visit (for those not participating in the OLE study).

[0304] If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 h of learning of the female subject or female partner of male subject (after obtaining the necessary signed informed consent from the female partner) pregnancy.

[0305] While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

[0306] Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and will be reported as such.

[0307] The subject/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject/pregnant female partner and the neonate and the information will be forwarded to the sponsor/designee.

[0308] Any post study pregnancy-related SAE considered reasonably related to the study drug by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former study subject/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Death Events

[0309] Any AE resulting in death that occurs for subjects rolling over into the OLE will be collected from signing of the study ICF until just before the first assessment in the OLE study. For subjects not participating in the OLE, any AE resulting in death will be collected from signing of the ICF up to 28 days after the last dose of the study drug. All AEs resulting in death are considered SAEs and must be reported to the Sponsor (or designee) and/or the study Medical Monitor within 24 hours of awareness of the event.

[0310] All deaths that occur during the protocol-specified AE reporting period regardless of attribution, will be recorded on an eCRF and reported in a safety event report form and expeditiously sent to the sponsor/designee.

[0311] When recording a death on an eCRF or safety event report form, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept whenever possible. When reporting SAEs, "death" should not be reported as an SAE term, but rather as the outcome of a specific SAE unless the event preceding the death is unknown. If the death is due to overall disease progression and cannot be attributed to another medical concept, disease progression should be reported as the event term. If an autopsy was performed, the autopsy report should be provided.

Adverse Events of Special Interest

[0312] Adverse events of special interest are required to be reported by the investigator to the sponsor/designee immediately (ie, no more than 24 h after learning of the event) regardless of their causality to the study drug treatment. The most appropriate diagnosis should be recorded, or if a diagnosis cannot be established, the abnormal laboratory values should be recorded on the safety event report form and reported to the sponsor/designee immediately, either as an AESI or and/or a SAE.

[0313] NOTE: If any of the following events are reported as SAEs then there is no need to complete a separate AESI form.

[0314] The AESIs for all study drugs (lorundrostat and placebo) include the following:

- (a) Modification of study drug dose due to hyperkalemia (e.g., dose reduction, dose hold, or permanent dose discontinuation)
- (b) Modification of study drug dose due to hyponatremia (e.g., dose reduction, dose hold, or permanent dose discontinuation)
- (c) Hypotension with symptoms (e.g., light-headedness, dizziness, presyncope, or syncope)
- (d) Severely elevated BP (AOBP SBP >180 mmHg or AOBP DBP >110 mmHg)
- (e) Modification of study drug dose due to hypercortisolism (morning serum cortisol >35 µg/dL, confirmed by 24-hour urinary free cortisol)
- (f) Discontinuation of study drug due to hypocortisolism confirmed by ACTH (Cosyntropin) stimulation test
- (g) Overdose of study drug or dapagliflozin
- (h) Modification of study drug dose due to reduction in kidney function (e.g., dose reduction, dose hold, or permanent dose discontinuation).

Hyperkalemia

[0315] All subjects will be regularly monitored for the occurrence of hyperkalemia. This includes baseline screening, and regular intervals (as noted in the Schedule of Assessments [Table 3]). The investigator can perform a re-test at any time if they consider it necessary to confirm the serum potassium or sodium concentration.

[0316] If hyperkalemia is felt to be spurious in the opinion of the PI (such as from hemolysis), then a repeat value should be obtained within 48 hours and the Medical Monitor should be contacted to discuss potentially holding study drug while confirmatory results are pending. Treatment for hyperkalemia, including potassium binders, is allowed. If a new treatment for hyperkalemia is initiated on study, please notify the Medical Monitor.

[0317] In any instance when an ECG is performed, if the ECG shows new signs consistent with hyperkalemia, refer the subject to an urgent care center or other appropriate care facility for further evaluation and intervention, and consult the Medical Monitor.

[0318] Any subject with serum potassium < 5.5 mmol/L will remain on study drug treatment.

[0319] Any subject with a serum potassium > 5.5 mmol/L but ≤ 6.0 mmol/L will continue on study drug and have a repeat test (re-check) performed within 72 h of the initial local lab result.

- (a) If upon re-check serum potassium < 5.5 mmol/L, continue on study drug at the same dose.
- (b) If upon re-check serum potassium is > 5.5 mmol/L and ≤ 6.0 mmol/L, reduce study drug dose and re-check serum potassium at the next study visit (or within 2 weeks, whichever is sooner)

[0320] Any subject with a serum potassium > 6.0 mmol/L but ≤ 6.5 mmol/L will have study drug held immediately and will have a repeat serum potassium and a 12-lead ECG performed within 24 hours of the initial local laboratory result. Continue to hold study drug until the result of the repeat serum potassium and ECG are assessed.

- (a) If upon re-check serum potassium is ≤ 5.5 mmol/L, restart study drug at same dose and repeat serum potassium at the next scheduled study visit.
- (b) If upon re-check serum potassium is > 5.5 mmol/L but ≤ 6.0 mmol/L and the ECG is normal, restart the study drug at a reduced dose and re-check serum potassium within 72 h. If re-check potassium remains > 6.0 mmol/L, follow bullet below.
- (c) If serum potassium remains > 6.0 mmol/L, permanently discontinue study drug, and repeat serum potassium and ECG within 48 h of the most recent assessment and continue to monitor serum potassium until value ≤ 5.1 mmol/L. Consult with Medical Monitor.

[0321] Any subject with a serum potassium > 6.5 mmol/L will have study drug held immediately and should be referred to urgent care center or other appropriate care facility for further evaluation (including repeat potassium and ECG) and intervention. Continue to hold study drug until the result of the repeat serum potassium and ECG within the emergency setting are known and assessed. Consult with Medical Monitor.

- (a) If upon re-check serum potassium is ≤ 5.5 mmol/L, re-start study drug at same dose and repeat serum potassium at next scheduled study visit.
- (b) If upon re-check serum potassium is > 5.5 and ≤ 6.0 mmol/L and the ECG is normal, re-start study drug at a reduced dose and re-check serum

potassium within 72 hours. If re-check potassium is >6.0 mmol/L, follow the below.

- (c) If serum potassium remains > 6.0 mmol/L, permanently discontinue study drug, repeat serum potassium and ECG within 48 h of the most recent assessment, and continue to monitor serum potassium until value ≤ 5.1 mmol/L. Consult with Medical Monitor.

Hyponatremia

[0322] All subjects will be regularly monitored for the occurrence of hyponatremia. This includes baseline Screening and regular intervals as noted in Table 3. The Investigator can perform a re-test at any time if they consider it necessary to confirm the serum potassium concentration.

[0323] Any subject with a serum sodium of < 135 mmol/L (corrected for hyperglycemia) will be asked to return to the clinic for a repeat test (re-check) of their serum sodium processed at a local laboratory as follows:

- (a) If a subject experiences mild hyponatremia, defined as a corrected serum sodium <135 and ≥ 130 mmol/L), and remains asymptomatic, sodium levels should be rechecked within the next 72 – 96 hours. Based on the opinion of the PI (in conjunction with Medical Monitor if needed) study drug may be continued or held until re-checked.
 - (i) If upon re-check, the corrected serum sodium returns to normal (i.e., ≥ 135 mmol/L), restart or continue study drug at the same dose prior to event onset.
 - (ii) If upon re-check, the corrected serum sodium remains <135 and ≥ 130 mmol/L, the results should be discussed with the Medical Monitor and a decision made if study drug should be continued, held, or dose reduced
- (b) If a subject experiences moderate or severe hyponatremia, defined as a corrected serum sodium <130 study drug should be held, sodium levels should be rechecked within the next 48 hours.
 - (i) If upon re-check, the corrected serum sodium returns to normal (i.e., ≥ 135 mmol/L), restart study drug at a lower dose. The Investigator should consult with the Medical Monitor to discuss the underlying etiology of hyponatremia.

- (ii) If upon re-check, the corrected sodium level remains <135 mmol/L, continue to hold study drug and retest serum sodium levels at least weekly until values return to normal (i.e., ≥ 135 mmol/L).
- (c) If a subject experiences severe hyponatremia, defined as a corrected serum sodium level <125 mmol/L, in associations with signs and symptoms (e.g., nausea, vomiting, confusion, headache, loss of energy and fatigue, muscle weakness), the subject should be asked to visit the emergency room for re-check, follow-up, examination and hospitalization (if clinically warranted). The Medical Monitor should be contacted to discuss the appropriateness of ongoing study participation based on etiology, treatment in the emergency room, and repeat sodium levels. If there is no explanation for the occurrence of severe hyponatremia, study drug should be permanently discontinued. If upon re-check, corrected sodium levels return to moderate or mild hyponatremia levels, the actions outlined above should be followed.

Symptomatic and Asymptomatic Hypotension

[0324] If subjects experience symptoms of hypotension (e.g., light-headedness, dizziness, presyncope, or syncope) during the study, it will be medically managed by the investigator in communication with the Medical Monitor. Dose reduction of study drug according to the instructions in the SRM may be considered.

[0325] In cases of hypotension without symptoms (AOBP DBP <65 mmHg, or DBP between ≥ 65 and <85 mmHg plus AOBP SBP <100 mmHg), the lorundrostat dose should be reduced first. If a subject experiences symptoms of hypotension (e.g., frequent light headedness, pre-syncope, dizziness) but does not meet the above defined BP threshold for hypotension, the study drug dose should be reduced. Dose reduction of the study drug is the first step. If symptoms and/or BP thresholds persist following dose reduction, the subject may be discontinued from study drug in consultation with the Medical Monitor.

Severely Elevated Blood Pressure

[0326] Subjects with systolic AOBP of >180 mmHg or diastolic AOBP of >110 mmHg will have any prescribed AHT regimen adjusted as described in the SRM. If additional medications are needed, doxazosin 1 mg is recommended, but medication additions are performed at the Investigator's discretion in consultation with the Medical Monitor.

Hypercortisolism

[0327] All subjects will be monitored for signs and symptoms of hypercortisolism (ie, new onset or unexplained worsening of: hyperglycemia, hypertension, weight gain, abdominal striae, round facies).

[0328] Any subject with serum cortisol >35 $\mu\text{g/dL}$ (morning measurement) will perform an unscheduled 24-hour urine collection for assessment of 24-hour urinary free cortisol. The subject will continue the study drug with no dose adjustment.

- (a) Any subject with a 24-hour urinary free cortisol level >40 $\mu\text{g/24h}$ and ≤ 50 $\mu\text{g/24h}$ will perform a repeat test 4 weeks later.
- (b) Any subject with a 24-hour urinary free cortisol level >50 $\mu\text{g/24h}$ will have their study drug dose reduced by 50% and will perform a repeat test 4 weeks later.

Hypocortisolism

[0329] Subjects will have their serum cortisol measured as per the schedule of assessments, with the blood draw performed as close to 8 am as possible, and before 10 am.

- (a) Any subject with a morning serum cortisol <3 $\mu\text{g/dL}$ will undergo an ACTH stimulation test within 1 week of the result being known.
- (b) Any subject with morning serum cortisol <10 $\mu\text{g/dL}$ accompanied by ≥ 2 signs and symptoms of adrenal insufficiency (ie, weakness, loss of appetite, unintentional weight loss, hyponatremia, hypoglycemia) plus clinical findings of orthostatic hypotension, pre-syncope or syncope, will undergo an ACTH stimulation test within 48 h of the result being known.
 - (i) If associated with a concurrent acute illness, including coronavirus disease 2019 (COVID-19), the ACTH stimulation test timing will be at the discretion of investigator but may be delayed for no more than 5 days from the morning serum cortisol result being known.
- (c) Any subject with morning serum cortisol <10 $\mu\text{g/dL}$ accompanied by ≥ 2 signs and symptoms of adrenal insufficiency but no BP or laboratory abnormalities will undergo an ACTH stimulation test within 1 week of the result being known.
- (d) Any subject with morning serum cortisol <10 $\mu\text{g/dL}$ accompanied by asymptomatic orthostatic hypotension with hypoglycemia or hyponatremia

will undergo an ACTH stimulation test within 1 week of the result being known.

- (e) Any subject with an ACTH test result diagnostic of adrenal insufficiency will immediately discontinue study drug and will be referred to specialized care (eg, endocrinologist/urgent care) for further management. The subject is not required to withdraw from the study in such cases.

Safety Monitoring Considerations

[0330] A DMC will meet periodically to monitor the study. The primary function of this committee is safety monitoring. As part of these reviews, the DMC will receive summaries of study conduct measures as well as unblinded safety and efficacy data. The DMC may recommend discontinuing enrollment for safety.

[0331] The full scope and responsibilities of the DMC will be described in the DMC Charter per the Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees.

Statistical Considerations

[0332] This is a randomized, placebo controlled, crossover study with a two-period, two-sequence (2x2) design. Details of the statistical analysis, including the handling of missing values will be described in the statistical analysis plan (SAP). This section provides key elements of the statistical approaches foreseen at the time of planning the study.

Analysis Sets

[0333] The Intent-to-treat (ITT) Analysis Set includes all subjects, regardless of whether or not treatment was received.

[0334] The Full Analysis Set (FAS) will include all subjects who receive at least one dose of study drug. Subjects will be categorized according to the treatment assignment.

[0335] The Safety Analysis Set (SAF) will include all subjects who receive at least one dose of study drug. Subjects will be categorized according to the treatment actually received.

[0336] The popPK analysis set will include all subjects who received at least one dose of lorundrostat and had at least one evaluable popPK sample taken. Subjects in this analysis set will be categorized according to the treatment received.

Statistical Analyses

[0337] Unless otherwise specified, demographic and baseline characteristics will be summarized for ITT analysis set by the treatment arm. Efficacy outcomes will be analyzed using the FAS, unless otherwise specified. Safety outcome analyses will be performed on the SAF.

[0338] For continuous variables, the descriptive statistics of n, mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum will be summarized. The frequency and percentage of observed levels will be reported for all categorical variables.

[0339] The primary analysis of the primary efficacy estimand will assess the superiority of lorundrostat treatment compared to placebo in change from baseline in AOBP SBP at Study Week 4. Each subject contributes two pairs of treatment observations (change at Study Week 4 from Study Week 0 and, change at Study Week 12 from Study Week 8). A mixed model for repeated measures (MMRM) including treatment arm (Lorundrostat and Placebo), sequence (LP and PL) and Treatment Period (Period 1 and Period 2) as fixed effects, subject (sequence), as random (repeated) effect, and baseline (Study Week 0 and Study Week 8) AOBP SBP as a covariate will be used in the analysis. An estimate of the least square means, and the associated standard errors and 90% confidence intervals (CIs) of change from baseline at Study Week 4 will be reported for each arm. The primary analysis will be based on the evaluation of the least square estimate for the treatment arm effect which represents placebo-adjusted effect in lorundrostat treatment periods. Prior to the main estimation, a general linear model with effects of sequence, subject (sequence), period and treatment will be fitted to evaluate the existence of possible carryover/sequence effect.

[0340] Statistical approaches for the secondary and exploratory endpoints will be described in the SAP.

Alpha Value:

[0341] The overall alpha (α) value is set to one-sided 0.05. There will be no adjustment for multiplicity.

Safety Analyses

[0342] AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC), preferred term (PT), as well as by severity, causality, and time to occurrence.

Sample Size Determination

[0343] Approximately 60 subjects randomized in a 1:1 ratio to the two sequences (LP and PL) will provide 85% power to detect a placebo-adjusted change in AOBP SBP of at least 5.5 mmHg, assuming a 14 mmHg as a standard deviation of change, and 1-sided alpha of 0.05.

Handling of Missing Data

[0344] Missing values imputation will be described in SAP.

Planned Subgroup Analyses

[0345] Analyses of subgroups by age, sex, race, and BMI will be performed for the primary and selected secondary endpoints on the FAS population.

Results

[0346] Based on the study outlined above, it is determined that subjects afflicted with chronic kidney disease (CKD) are effectively treated with lorundrostat HBr.

[0347] Based on the study outlined above, it is determined that hypertension is effectively treated with lorundrostat HBr in subjects afflicted with chronic kidney disease (CKD) and hypertension.

[0348] Based on the study outlined above, it is determined that subjects who have a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 300-3500 mg/g and/or an estimated glomerular filtration rate (eGFR) of at least 30 or at least 45 mL/min/1.73m² and less than 90 mL/min/1.73m² when taking a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) are effectively treated with lorundrostat HBr.

[0349] Based on the study outlined above, it is determined that subjects who: (a) do not have Type 1 diabetes, (b) have a serum cortisol of between 3 µg/dL and 22 µg/dL in the morning, (c) have a body mass index (BMI) of 18-40 kg/m²; (d) have a serum potassium of less than 4.8 mmol/L; and/or (e) have a serum sodium of greater than 135 mmol/L, are effectively treated with lorundrostat HBr.

[0350] Based on the study outlined above, it is determined that subjects afflicted with chronic kidney disease (CKD) who are being treated with an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB) are effectively treated with lorundrostat HBr.

[0351] Based on the study outlined above, it is determined that subjects afflicted with chronic kidney disease (CKD) who are being treated with a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB) are effectively treated with lorundrostat HBr.

[0352] Based on the study outlined above it is determined that:

- (a) the amount of the ACEi or ARB when administered with the lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the ACEi or ARB inhibitor that is effective to treat CKD when the ACEi or ARB inhibitor is administered alone;
- (b) the amount of the ACEi or ARB when administered with the lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the ACEi or ARB that is effective to treat CKD when the ACEi or ARB inhibitor is administered in the absence of administration of the lorundrostat or a pharmaceutically acceptable salt thereof; and/or
- (c) the amount of the ACEi or ARB that is effective to treat CKD when administered in the absence of administration of the lorundrostat or pharmaceutically acceptable salt thereof causes one or more adverse effects in the subject, wherein the one or more adverse effects are not caused by the amounts of the ACEi or ARB, and lorundrostat or pharmaceutically acceptable salt thereof that are effective to treat CKD when administered together.

[0353] Based on the study outlined above it is determined that the amount of lorundrostat or pharmaceutically acceptable salt thereof when administered together with the ACEi or ARB are more effective to treat the subject than when each agent at the same amount is administered alone.

[0354] Based on the study outlined above it is determined that the effective amount of lorundrostat or pharmaceutically acceptable salt thereof is:

- (a) 10-15 mg per day;
- (b) 12.5 mg per day;
- (c) 20-30 mg per day;
- (d) 25 mg per day;
- (e) 40-60 mg per day; or
- (f) 50 mg per day.

[0355] Based on the study outlined above it is determined that the method is effective when the amount of lorundrostat HBr is administered in the morning.

[0356] Based on the study outlined above it is determined that administering to a subject afflicted with chronic kidney disease (CKD) an amount of lorundrostat or a pharmaceutically acceptable salt thereof once per day, and an amount of a dapagliflozin once per day, together are sufficient to treat CKD in the subject.

[0357] Based on the study outlined above, it is determined that subjects who have a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-3500 mg/g and/or an estimated glomerular filtration rate (eGFR) of at least 30 or at least 45 mL/min/1.73m² and less than 90 mL/min/1.73m² when taking a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) are effectively treated with a combination of lorundrostat HBr and dapagliflozin.

[0358] Based on the study outlined above, it is determined that subjects who: (a) do not have Type 1 diabetes, (b) have a serum cortisol of between 3 µg/dL and 22 µg/dL in the morning, (c) have a body mass index (BMI) of 18-40 kg/m²; (d) have a serum potassium of less than 4.8 mmol/L; and/or (e) have a serum sodium of greater than 135 mmol/L, are effectively treated with a combination of lorundrostat HBr and dapagliflozin.

[0359] Based on the study outlined above, it is determined that subjects afflicted with chronic kidney disease (CKD) who are being treated with an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB) are effectively treated with a combination of lorundrostat HBr and dapagliflozin.

[0360] Based on the study outlined above, it is determined that that hypertension is effectively treated with a combination of lorundrostat HBr and dapagliflozin in subjects afflicted with hypertension and chronic kidney disease (CKD) who are being treated with an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB).

[0361] Based on the study outlined above, it is determined that subjects afflicted with chronic kidney disease (CKD) who are being treated with a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB) are effectively treated with a combination of lorundrostat HBr and dapagliflozin.

[0362] Based on the study outlined above, it is determined that hypertension is effectively treated with a combination of lorundrostat HBr and dapagliflozin in subjects afflicted with hypertension and chronic kidney disease (CKD) who are being treated with a maximally

tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB).

[0363] Based on the study outlined above, it is determined that:

- (a) the amount of the ACEi or ARB when administered with lorundrostat HBr and dapagliflozin is lower than the amount of the ACEi or ARB inhibitor that is effective to treat CKD when the ACEi or ARB inhibitor is administered alone;
- (b) the amount of the ACEi or ARB when administered with lorundrostat HBr and dapagliflozin is lower than the amount of the ACEi or ARB that is effective to treat CKD when the ACEi or ARB inhibitor is administered in the absence of administration of lorundrostat HBr and/or dapagliflozin; and/or
- (c) the amount of the ACEi or ARB that is effective to treat CKD when administered in the absence of administration of the lorundrostat HBr and/or dapagliflozin causes one or more adverse effects in the subject, wherein the one or more adverse effects are not caused by the amounts of the ACEi or ARB, lorundrostat HBr and dapagliflozin that are effective to treat CKD when administered together.

[0364] Based on the study outlined above, it is determined that:

- (a) the amounts of the lorundrostat HBr and dapagliflozin when taken together are effective to achieve a greater than additive therapeutic result in treating the subject;
- (b) the amount of the dapagliflozin is lower than the amount of the dapagliflozin that is effective to treat CKD when the dapagliflozin is administered alone;
- (c) the amount of lorundrostat HBr is lower than the amount of the lorundrostat HBr that is effective to treat CKD when lorundrostat HBr is administered alone;
- (d) the amount of the dapagliflozin is lower than the amount of the dapagliflozin that is effective to treat CKD when the dapagliflozin is administered in the absence of administration of lorundrostat HBr; and/or
- (e) the amount of the dapagliflozin that is effective to treat CKD when administered in the absence of administration of lorundrostat HBr causes one or more adverse effects in the subject, wherein the one or more adverse

effects are not caused by the amounts of the dapagliflozin and lorundrostat HBr that are effective to treat CKD when administered together.

[0365] Based on the study outlined above it is determined that the effective amount of dapagliflozin is 8-12 mg per day or 10 mg per day.

[0366] Based on the study outlined above it is determined that the method is effective when the amount of dapagliflozin is administered in the morning.

[0367] Based on the study outlined above it is determined that the method comprising administering to the subject an amount of lorundrostat HBr once per day is effective to:

- (a) treat proteinuria in the subject;
- (b) treat albuminuria in the subject; and/or
- (c) attenuate progression of nephropathy.

[0368] Based on the study outlined above it is determined that:

- (a) the subject's 24-hour or first morning urine void urine albumin-to-creatinine ratio (UACR) is reduced relative to the subject's 24-hour or first morning urine void UACR prior to receiving the lorundrostat HBr;
- (b) the subject's 24-hour total urine albumin (TUA) is reduced relative to the subject's TUA prior to receiving the lorundrostat HBr;
- (c) the subject's 24-hour urinary protein to creatinine ratio (UPCR) is reduced relative to the subject's UPCR prior to receiving the lorundrostat HBr; and/or
- (d) the subject's 24-hour urine protein is reduced relative to the subject's 24-hour urine protein prior to receiving the lorundrostat HBr.

[0369] Based on the study outlined above it is determined that the subject's aldosterone level follows a substantially normal circadian rhythm when they are administered the amount of lorundrostat HBr.

[0370] Based on the study outlined above it is determined that:

- a) the amount of the lorundrostat HBr inhibits CYP 11 β 2 beta hydroxylase activity for a duration that is sufficient to maintain a state of sodium and volume depletion in the subject;
- a) the method does not produce a persistent state of hyperkalemia or mild non-anion gap metabolic acidosis in the subject;

- b) the lorundrostat HBr does not substantially accumulate in the subject, preferably wherein the lack of substantial accumulation of the lorundrostat HBr in the subject allows for the subject's aldosterone levels to return to pre-drug baseline within 24-48 hours of the lorundrostat or pharmaceutically acceptable salt thereof being administered, more preferably within 16-24 hours of the lorundrostat HBr being administered;
- c) the subject's potassium levels are generally maintained in a clinically normal range;
- d) the subject's potassium levels are mildly elevated relative to the subject's potassium levels prior to administration of the lorundrostat HBr;
- e) the subject's potassium levels are elevated by 0.35 mmol/L or less,
- f) the subject's potassium levels are maintained below a level of 5.5 mmol/L,
- g) the subject's potassium levels are maintained between 3.5 mEq/l to 5.1 mEq/l; and/or
- h) the lorundrostat HBr is administered to the subject in an amount which:
 - i) suppresses aldosterone production in the subject;
 - ii) increases serum and/or plasma potassium levels in the subject; and/or
 - iii) increases plasma renin activity (PRA) in the subject;

[0371] Based on the study outlined above it is determined that:

- (a) serum and/or plasma aldosterone AUC-24 is reduced in the subject by at least 25% relative to the aldosterone levels in the subject prior to administration of the lorundrostat HBr;
- (b) serum and/or plasma potassium levels in the subject are increased by at least 0.2 mMol/L relative to the serum and/or plasma potassium levels in the subject prior to administration of the lorundrostat HBr; and/or
- (c) PRA in the subject is increased by at least 5 ng/ml/hr relative to the PRA in the subject prior to administration of the lorundrostat HBr.

[0372] Based on the study outlined above it is determined that the method comprising administering to the subject an amount of lorundrostat HBr and an amount of dapagliflozin once per day is effective to:

- (a) hypertension in the subject;
- (b) treat proteinuria in the subject;
- (c) treat albuminuria in the subject; and/or

- (d) attenuate progression of nephropathy.

[0373] Based on the study outlined above it is determined that:

- (a) the subject's 24-hour or first morning urine void urine albumin-to-creatinine ratio (UACR) is reduced relative to the subject's 24-hour or first morning urine void UACR prior to receiving the lorundrostat HBr and dapagliflozin;
- (b) the subject's 24-hour total urine albumin (TUA) is reduced relative to the subject's TUA prior to receiving the lorundrostat HBr and dapagliflozin;
- (c) the subject's 24-hour urinary protein to creatinine ratio (UPCR) is reduced relative to the subject's UPCR prior to receiving the lorundrostat HBr and dapagliflozin; and/or
- (d) the subject's 24-hour urine protein is reduced relative to the subject's 24-hour urine protein prior to receiving the lorundrostat HBr and dapagliflozin.

[0374] Based on the study outlined above it is determined that:

- (a) the subject's 24-hour or first morning urine void urine albumin-to-creatinine ratio (UACR) is reduced by at least 30%, by at least 40%, by between 30% and 70%, by between 30% and 60%, by between 30% and 50%, by between 40% and 80%, by between 40% and 70%, by between 40% and 60%, relative to the subject's 24-hour or first morning urine void UACR prior to receiving the lorundrostat HBr and dapagliflozin, if administered;
- (b) the subject's 24-hour total urine albumin (TUA) is reduced at least 30, by at least 40%, by between 30% and 70%, by between 30% and 60%, by between 30% and 50%, by between 40% and 80%, by between 40% and 70%, by between 40% and 60%, relative to the subject's TUA prior to receiving the lorundrostat HBr and dapagliflozin, if administered;
- (c) the subject's 24-hour urinary protein to creatinine ratio (UPCR) is reduced by at least 30%, by at least 40%, by between 30% and 70%, by between 30% and 60%, by between 30% and 50%, by between 40% and 80%, by between 40% and 70%, by between 40% and 60%, relative to the subject's UPCR prior to receiving the lorundrostat HBr and dapagliflozin, if administered; and/or
- (d) the subject's 24-hour urine protein is reduced at least 30%, by at least 40%, by between 30% and 70%, by between 30% and 60%, by between 30% and 50%, by between 40% and 80%, by between 40% and 70%, by between

40% and 60%, relative to the subject's 24-hour urine protein prior to receiving the lorundrostat HBr and dapagliflozin, if administered.

[0375] Based on the study outlined above it is determined that the methods tested are effective to treat hypertension and/or CKD in subjects who are afflicted with both CKD and hypertension. Based on the study outlined above it is determined that the methods tested are effective to treat hypertension in subjects who are afflicted with both CKD and hypertension. Based on the study outlined above it is determined that the methods tested are effective to treat subjects who are afflicted with hypertension, where the subject has systolic blood pressure of at least 135 mmHg and a systolic blood pressure of at least 80 mmHg.

[0376] Based on the study outlined above it is determined that the method comprising administering to the subject an amount of lorundrostat HBr is effective to:

- (a) reduce the subject's systolic blood pressure by at least 10 mmHg, by 10-55 mmHg, by 10-50 mmHg, by 10-45 mmHg, by 10-40 mmHg, by 10-35 mmHg, by 10-30 mmHg, by 10-25 mmHg, by 10-20 mmHg, or by 10-15 mmHg, relative to the subject's systolic blood pressure prior to administration of the lorundrostat HBr for a period of at least eight weeks; and/or
- (b) reduce the subject's diastolic blood by at least 5 mmHg, by 5-25 mmHg, by 5-20 mmHg, or by 5-15 mmHg relative to the subject's diastolic blood pressure prior to administration of lorundrostat HBr for a period of at least eight weeks;
- (c) reduce the subject's average systolic blood pressure during sleep relative to:
 - (i) the subject's average systolic blood pressure during sleep prior to receiving the lorundrostat HBr for a period of at least eight weeks;
 - (ii) the subject's average systolic blood pressure during sleep prior to receiving the lorundrostat HBr for a period of at least eight weeks; and/or
 - (iii) the subject's average daytime systolic blood pressure;
- (d) reduce the subject's average systolic blood pressure during sleep by at least 10%, by between 10% and 40%, by between 10% and 30%, or by between 10% and 20% relative to the subject's average daytime systolic blood pressure;

- (e) reduce the subject's average systolic blood pressure during sleep by at least 8 mmHg, by at least 10mmHg, by between 8 and 55 mmHg, by between 10 and 45 mmHg, or by between 10 and 25 mmHg, relative to the subject's average systolic blood pressure during sleep prior to receiving the lorundrostat HBr for a period of at least eight weeks; and/or
- (f) reduce the subject's average systolic blood pressure during sleep by at least 8 mmHg, by at least 10mmHg, by between 8 and 55 mmHg, by between 10 and 45 mmHg, or by between 10 and 25 mmHg, relative to the subject's average systolic blood pressure during sleep prior to receiving the lorundrostat HBr for a period of at least eight weeks.

[0377] Based on the study outlined above it is determined that the method comprising administering to the subject an amount of lorundrostat HBr and an amount of dapagliflozin is effective to:

- (a) reduce the subject's systolic blood pressure by at least 10 mmHg, by 10-55 mmHg, by 10-50 mmHg, by 10-45 mmHg, by 10-40 mmHg, by 10-35 mmHg, by 10-30 mmHg, by 10-25 mmHg, by 10-20 mmHg, or by 10-15 mmHg, relative to the subject's systolic blood pressure prior to administration of the lorundrostat HBr and dapagliflozin for a period of at least eight weeks; and/or
- (b) reduce the subject's diastolic blood by at least 5 mmHg, by 5-25 mmHg, by 5-20 mmHg, or by 5-15 mmHg relative to the subject's diastolic blood pressure prior to administration of lorundrostat HBr and dapagliflozin for a period of at least eight weeks;
- (c) reduce the subject's average systolic blood pressure during sleep relative to:
 - (i) the subject's average systolic blood pressure during sleep prior to receiving the lorundrostat HBr and dapagliflozin for a period of at least eight weeks;
 - (ii) the subject's average systolic blood pressure during sleep prior to receiving the lorundrostat HBr for a period of at least eight weeks; and/or
 - (iii) the subject's average daytime systolic blood pressure.
- (d) reduce the subject's average systolic blood pressure during sleep by at least 10%, by between 10% and 40%, by between 10% and 30%, or by between

10% and 20% relative to the subject's average daytime systolic blood pressure;

- (e) reduce the subject's average systolic blood pressure during sleep by at least 8 mmHg, by at least 10mmHg, by between 8 and 55 mmHg, by between 10 and 45 mmHg, or by between 10 and 25 mmHg, relative to the subject's average systolic blood pressure during sleep prior to receiving the lorundrostat HBr and dapagliflozin for a period of at least eight weeks; and/or
- (f) reduce the subject's average systolic blood pressure during sleep by at least 8 mmHg, by at least 10mmHg, by between 8 and 55 mmHg, by between 10 and 45 mmHg, or by between 10 and 25 mmHg, relative to the subject's average systolic blood pressure during sleep prior to receiving the lorundrostat HBr for a period of at least eight weeks.

[0378] Based on the study outlined above, it is determined that subjects who have a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-5000 mg/g or 300-3500 mg/g and/or an estimated glomerular filtration rate (eGFR) of at least 30 or at least 45 mL/min/1.73m² and less than 90 mL/min/1.73m² when taking a stable dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) are effectively treated for hypertension, or both CKD and hypertension with lorundrostat HBr.

[0379] Based on the study outlined above, it is determined that subjects who: (a) do not have Type 1 diabetes, (b) have a serum cortisol of between 3 µg/dL and 22 µg/dL in the morning, (c) have a body mass index (BMI) of 18-40 kg/m²; (d) have a serum potassium of less than 4.8 mmol/L; and/or (e) have a serum sodium of greater than 135 mmol/L, are effectively treated for both CKD and hypertension with lorundrostat HBr.

[0380] Based on the study outlined above, it is determined that subjects afflicted with chronic kidney disease (CKD) and hypertension who are being treated with an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB) are effectively treated with lorundrostat HBr.

[0381] Based on the study outlined above, it is determined that subjects afflicted with chronic kidney disease (CKD) and hypertension who are being treated with a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB) are effectively treated with lorundrostat HBr.

[0382] Based on the study outlined above it is determined that:

- (a) the amount of the ACEi or ARB when administered with the lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the ACEi or ARB inhibitor that is effective to treat CKD and/or hypertension when the ACEi or ARB inhibitor is administered alone;
- (b) the amount of the ACEi or ARB when administered with the lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the ACEi or ARB that is effective to treat CKD and/or hypertension when the ACEi or ARB inhibitor is administered in the absence of administration of the lorundrostat or a pharmaceutically acceptable salt thereof; and/or
- (c) the amount of the ACEi or ARB that is effective to treat CKD and hypertension when administered in the absence of administration of the lorundrostat or pharmaceutically acceptable salt thereof causes one or more adverse effects in the subject, wherein the one or more adverse effects are not caused by the amounts of the ACEi or ARB, and lorundrostat or pharmaceutically acceptable salt thereof that are effective to treat CKD and/or hypertension when administered together.

[0383] Based on the study outlined above it is determined that the amount of lorundrostat or pharmaceutically acceptable salt thereof when administered together with the ACEi or ARB are more effective to treat CKD and/or hypertension the subject than when each agent at the same amount is administered alone.

[0384] Based on the study outlined above it is determined that the effective amount of lorundrostat or pharmaceutically acceptable salt thereof is:

- (a) 10-15 mg per day;
- (b) 12.5 mg per day;
- (c) 20-30 mg per day;
- (d) 25 mg per day;
- (e) 40-60 mg per day; or
- (f) 50 mg per day.

[0385] Based on the study outlined above it is determined that the method is effective to treat CKD and/or hypertension when the amount of lorundrostat HBr is administered in the morning.

[0386] Based on the study outlined above it is determined that administering to a subject afflicted with CKD and/or hypertension an amount of lorundrostat or a pharmaceutically acceptable salt thereof once per day, and an amount of a dapagliflozin once per day, together are sufficient to treat CKD and/or hypertension in the subject.

[0387] Based on the study outlined above, it is determined that subjects who have a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-5000 mg/g or 300-3500 mg/g and/or an estimated glomerular filtration rate (eGFR) of at least 30 or at least 45 mL/min/1.73m² and less than 90 mL/min/1.73m² when taking a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) are effectively treated for CKD and/or hypertension with a combination of lorundrostat HBr and dapagliflozin.

[0388] Based on the study outlined above, it is determined that subjects who: (a) do not have Type 1 diabetes, (b) have a serum cortisol of between 3 µg/dL and 22 µg/dL in the morning, (c) have a body mass index (BMI) of 18-40 kg/m²; (d) have a serum potassium of less than 4.8 mmol/L; and/or (e) have a serum sodium of greater than 135 mmol/L, are effectively treated for CKD and/or hypertension with a combination of lorundrostat HBr and dapagliflozin.

[0389] Based on the study outlined above, it is determined that subjects afflicted with chronic kidney disease (CKD) and hypertension who are being treated with an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB) are effectively treated for CKD and/or hypertension with a combination of lorundrostat HBr and dapagliflozin.

[0390] Based on the study outlined above, it is determined that subjects afflicted with chronic kidney disease (CKD) and hypertension who are being treated with a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) and/or angiotensin receptor blocker (ARB) are effectively treated for CKD and/or hypertension with a combination of lorundrostat HBr and dapagliflozin.

[0391] Based on the study outlined above, it is determined that:

- (a) the amount of the ACEi or ARB when administered with lorundrostat HBr and dapagliflozin is lower than the amount of the ACEi or ARB inhibitor that is effective to treat CKD and/or hypertension when the ACEi or ARB inhibitor is administered alone;

- (b) the amount of the ACEi or ARB when administered with lorundrostat HBr and dapagliflozin is lower than the amount of the ACEi or ARB that is effective to treat CKD and/or hypertension when the ACEi or ARB inhibitor is administered in the absence of administration of lorundrostat HBr and/or dapagliflozin; and/or
- (c) the amount of the ACEi or ARB that is effective to treat CKD and/or hypertension when administered in the absence of administration of the lorundrostat HBr and/or dapagliflozin causes one or more adverse effects in the subject, wherein the one or more adverse effects are not caused by the amounts of the ACEi or ARB, lorundrostat HBr and dapagliflozin that are effective to treat CKD and/or hypertension when administered together.

[0392] Based on the study outlined above, it is determined that:

- (a) the amounts of the lorundrostat HBr and dapagliflozin when taken together are effective to achieve a greater than additive therapeutic result in treating the subject;
- (b) the amount of the dapagliflozin is lower than the amount of the dapagliflozin that is effective to treat CKD when the dapagliflozin is administered alone;
- (c) the amount of lorundrostat HBr is lower than the amount of the lorundrostat HBr that is effective to treat CKD and/or hypertension when lorundrostat HBr is administered alone;
- (d) the amount of the dapagliflozin is lower than the amount of the dapagliflozin that is effective to treat CKD when the dapagliflozin is administered in the absence of administration of lorundrostat HBr; and/or
- (e) the amount of the dapagliflozin that is effective to treat CKD when administered in the absence of administration of lorundrostat HBr causes one or more adverse effects in the subject, wherein the one or more adverse effects are not caused by the amounts of the dapagliflozin and lorundrostat HBr that are effective to treat CKD when administered together.

[0393] Based on the study outlined above it is determined that the method is effective to treat a subject who is also afflicted with Type 2 diabetes mellitus (T2DM).

[0394] Based on the study outlined above it is determined that the method is effective to treat a subject who is not afflicted with Type 2 diabetes mellitus (T2DM).

[0395] Based on the study outlined above it is determined that the method is effective to treat a subject who is not afflicted with Type 1 diabetes.

[0396] Based on the study outlined above it is determined that the method is effective to treat a subject who does not have primary aldosteronism.

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CLAIMS

What is claimed is:

1. A method of treating chronic kidney disease (CKD) in a subject afflicted with CKD, the method comprising administering to the subject an amount of lorundrostat or a pharmaceutically acceptable salt thereof once per day, wherein the amount is effective to treat CKD in the subject.
2. A method of treating chronic kidney disease (CKD) in a subject afflicted with CKD, the method comprising
 - a) receiving an identification of the subject as having:
 - i) CKD, characterized by the following when stable dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably a maximally tolerated dose of an ACEi or ARB:
 - (1) a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-3500 mg/g or 200-5000mg/g; and/or
 - (2) an estimated glomerular filtration rate (eGFR) of at least 30 or mL/min/1.73m² at least 45 mL/min/1.73m² and preferably less than 90 mL/min/1.73m²;
 - ii) mild to moderate CKD, characterized by the following when taking a stable dose of an ACEi or ARB, preferably a maximally tolerated dose of an ACEi or ARB:
 - (1) albuminuria, characterized by a 24-hour or first morning urine void UACR of 300-3500 mg/g; and
 - (2) an estimated glomerular filtration rate (eGFR) of at least 45 mL/min/1.73m² and less than 90 mL/min/1.73m²; or
 - iii) moderate to severe CKD, characterized by the following when taking a stable dose of an ACEi or ARB, preferably a maximally tolerated dose of an ACEi or ARB:
 - (1) albuminuria, characterized by a 24-hour or first morning urine void UACR of 300-3500 mg/g; and

- (2) an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73m² and less than 45 mL/min/1.73m²; and
 - b) administering to said subject an effective amount of lorundrostat or a pharmaceutically acceptable salt thereof once per day, wherein the amount is effective to treat CKD in the subject.
- 3. The method of claim 2, wherein step a) comprises receiving an identification of the subject as:
 - a) having hypertension, preferably characterized by a systolic blood pressure of between 135-180 mmHg, inclusive;
 - b) not having Type 1 diabetes;
 - c) having a serum cortisol of between 3 µg/dL and 22 µg/dL, inclusive, in the morning;
 - d) having a body mass index (BMI) of 18-40 kg/m² or 18-45 kg/m²;
 - e) having a serum potassium of less than 4.8 mmol/L; and/or
 - f) having a serum sodium of greater than 135 mmol/L, preferably wherein said serum sodium measurement is corrected for hyperglycemia, if present.
- 4. The method of any one of claims 1 to 3, wherein the subject afflicted with CKD is being treated with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB).
- 5. The method of claim 4, wherein the subject afflicted with CKD is being treated with a maximally tolerated dose of an ACEi or ARB.
- 6. The method of claim 4 or 5, wherein:
 - a) the amount of the ACEi or ARB when administered with the lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the ACEi or ARB inhibitor that is effective to treat CKD when the ACEi or ARB inhibitor is administered alone;
 - b) the amount of the ACEi or ARB when administered with the lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the ACEi or ARB that is effective to treat CKD when the ACEi or ARB inhibitor is administered in the absence of administration of the lorundrostat or a pharmaceutically acceptable salt thereof; and/or

- c) the amount of the ACEi or ARB that is effective to treat CKD when administered in the absence of administration of the lorundrostat or pharmaceutically acceptable salt thereof causes one or more adverse effects in the subject, wherein the one or more adverse effects are not caused by the amounts of the ACEi or ARB, and lorundrostat or pharmaceutically acceptable salt thereof that are effective to treat CKD when administered together.
- 7. The method of any one of claims 4 to 6, wherein the amount of lorundrostat or pharmaceutically acceptable salt thereof when administered together with the ACEi or ARB are more effective to treat the subject than when each agent at the same amount is administered alone.
 - 8. The method of any one of claims 1 to 7, wherein the amount of lorundrostat or pharmaceutically acceptable salt thereof is:
 - a) 10-15 mg per day, preferably 12.5 mg per day;
 - b) 20-30 mg per day, preferably 25 mg per day; or
 - c) 40-60 mg per day, preferably 50 mg per day.
 - 9. The method of any one of claims 1 to 8, wherein the lorundrostat or a pharmaceutically acceptable salt thereof is administered in the morning.
 - 10. The method of any one of claims 1 to 9, wherein the lorundrostat or a pharmaceutically acceptable salt thereof administered daily:
 - a) for at least one week;
 - b) for at least two weeks;
 - c) for at least four weeks;
 - d) for at least eight weeks; or
 - e) For at least 12 weeks.
 - 11. The method of any one of claims 1 to 10, wherein the lorundrostat or pharmaceutically acceptable salt thereof is the monohydrobromide salt of lorundrostat.
 - 12. The method of any one of claims 1 to 11, the method further comprising administering to the subject an amount of a sodium–glucose cotransporter 2 (SGLT2) inhibitor once per day, wherein the amount of the SGLT2 inhibitor and the amount of lorundrostat or

pharmaceutically acceptable salt thereof taken together are sufficient to treat CKD in the subject.

13. The method of claim 12, wherein the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof are administered in a combined pharmaceutical composition.
14. The method of claim 12, wherein the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof are administered simultaneously, contemporaneously or concomitantly.
15. The method of any one of claims 12 to 14, wherein the subject afflicted with CKD is being treated with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB).
16. The method of claim 15, wherein the subject afflicted with CKD is being treated with a maximally tolerated dose of an ACEi or ARB.
17. The method of claim 15 or 16, wherein:
 - a) the amount of the ACEi or ARB when administered with the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the ACEi or ARB inhibitor that is effective to treat CKD when the ACEi or ARB inhibitor is administered alone;
 - b) the amount of the ACEi or ARB when administered with the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the ACEi or ARB that is effective to treat CKD when the ACEi or ARB inhibitor is administered in the absence of administration of the SGLT2 inhibitor and/or lorundrostat or pharmaceutically acceptable salt thereof; and/or
 - c) the amount of the ACEi or ARB that is effective to treat CKD when administered in the absence of administration of the SGLT2 inhibitor and/or lorundrostat or pharmaceutically acceptable salt thereof causes one or more adverse effects in the subject, wherein the one or more adverse effects are not caused by the amounts of the ACEi or ARB, SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof that are effective to treat CKD when administered together.

18. The method of any one of claims 12 to 17, wherein:
- a) the amounts of the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof when taken together are effective to achieve a greater than additive therapeutic result in treating the subject;
 - b) the amount of the SGLT2 inhibitor is lower than the amount of the SGLT2 inhibitor that is effective to treat CKD when the SGLT2 inhibitor is administered alone;
 - c) the amount of lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the lorundrostat or pharmaceutically acceptable salt thereof that is effective to treat CKD when lorundrostat or pharmaceutically acceptable salt thereof is administered alone;
 - d) the amount of the SGLT2 inhibitor is lower than the amount of the SGLT2 inhibitor that is effective to treat CKD when the SGLT2 inhibitor is administered in the absence of administration of lorundrostat or pharmaceutically acceptable salt thereof; and/or
 - e) the amount of the SGLT2 inhibitor that is effective to treat CKD when administered in the absence of administration of lorundrostat or pharmaceutically acceptable salt thereof causes one or more adverse effects in the subject, wherein the one or more adverse effects are not caused by the amounts of the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof that are effective to treat CKD when administered together.
19. The method of any one of claims 12 to 18, wherein the amount of the SGLT2 inhibitor, and the amount of lorundrostat or pharmaceutically acceptable salt thereof when administered together are more effective to treat the subject than when each agent at the same amount is administered alone.
20. The method of any one of claims 12 to 19, wherein the SGLT2 inhibitor is selected from the group consisting of dapagliflozin, empagliflozin, ipragliflozin, luseogliflozin, canagliflozin, ertugliflozin and bexagliflozin.
21. The method of any one of claims 12 to 20, wherein the SGLT2 inhibitor is dapagliflozin.

22. The method of claim 21, wherein the amount of dapagliflozin is 8-12 mg per day, preferably 10 mg per day.
23. The method of any one of claims 12 to 22, wherein the SGLT2 inhibitor and the lorundrostat or pharmaceutically acceptable salt thereof are administered in the morning.
24. The method of any one of claims 12 to 23, wherein the SGLT2 inhibitor and the lorundrostat or pharmaceutically acceptable salt thereof:
- a) are administered daily for at least one week;
 - b) are administered daily for at least two weeks;
 - c) are administered daily for at least four weeks; or
 - d) are administered daily for at least eight weeks.
25. The method of any one of claims 1 to 24, wherein the method is effective to:
- a) treat proteinuria in the subject, preferably wherein the method is effective to treat albuminuria in the subject; and/or
 - b) attenuate progression of nephropathy.
26. The method of any one of claims 1 to 25, wherein:
- a) the subject's 24-hour or first morning urine void urine albumin-to-creatinine ratio (UACR) is reduced relative to the subject's 24-hour or first morning urine void UACR prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered;
 - b) the subject's 24-hour total urine albumin (TUA) is reduced relative to the subject's TUA prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered;
 - c) the subject's 24-hour urinary protein to creatinine ratio (UPCR) is reduced relative to the subject's UPCR prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered; and/or
 - d) the subject's 24-hour urine protein is reduced relative to the subject's 24-hour urine protein prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered.
27. The method of any one of claims 1 to 26, wherein:

- a) the subject's 24-hour or first morning urine void urine albumin-to-creatinine ratio (UACR) is reduced by at least 30%, by at least 40%, by between 30% and 70%, by between 30% and 60%, by between 30% and 50%, by between 40% and 80%, by between 40% and 70%, by between 40% and 60%, relative to the subject's 24-hour or first morning urine void UACR prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered;
 - b) the subject's 24-hour total urine albumin (TUA) is reduced by at least 30%, by at least 40%, by between 30% and 70%, by between 30% and 60%, by between 30% and 50%, by between 40% and 80%, by between 40% and 70%, by between 40% and 60%, relative to the subject's TUA prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered;
 - c) the subject's 24-hour urinary protein to creatinine ratio (UPCR) is reduced by at least 30%, by at least 40%, by between 30% and 70%, by between 30% and 60%, by between 30% and 50%, by between 40% and 80%, by between 40% and 70%, by between 40% and 60%, relative to the subject's UPCR prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered; and/or
 - d) the subject's 24-hour urine protein is reduced by at least 30%, by at least 40%, by between 30% and 70%, by between 30% and 60%, by between 30% and 50%, by between 40% and 80%, by between 40% and 70%, by between 40% and 60%, relative to the subject's 24-hour urine protein prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof and SGLT2 inhibitor, if administered.
28. The method of any one of claims 1 to 27, wherein the subject's aldosterone level follows a substantially normal circadian rhythm.
29. The method of any one of the claims 1 to 27, wherein:
- a) the amount of the lorundrostat or pharmaceutically acceptable salt thereof inhibits CYP 11 β 2 beta hydroxylase activity for a duration that is sufficient to maintain a state of sodium and volume depletion in the subject;

- b) the method does not produce a persistent state of hyperkalemia or mild non-anion gap metabolic acidosis in the subject;
- c) the lorundrostat or pharmaceutically acceptable salt thereof does not substantially accumulate in the subject, preferably wherein the lack of substantial accumulation of the lorundrostat or pharmaceutically acceptable salt thereof in the subject allows for the subject's aldosterone levels to return to pre-drug baseline within 24-48 hours of the lorundrostat or pharmaceutically acceptable salt thereof being administered, more preferably within 16-24 hours of the lorundrostat or pharmaceutically acceptable salt thereof being administered;
- d) the subject's potassium levels are generally maintained in a clinically normal range, preferably wherein the subject's potassium levels are mildly elevated relative to the subject's potassium levels prior to administration of the lorundrostat or pharmaceutically acceptable salt thereof, more preferably wherein the subject's potassium levels are elevated by 0.35 mmol/L or less, more preferably wherein the subject's potassium levels are maintained below a level of 5.5 mmol/L, more preferably wherein the subject's potassium levels are maintained between 3.5 mEq/l to 5.1 mEq/l; and/or
- e) the lorundrostat or pharmaceutically acceptable salt thereof is administered to the subject in an amount which:
 - i) suppresses aldosterone production in the subject;
 - ii) increases serum and/or plasma potassium levels in the subject; and/or
 - iii) increases plasma renin activity (PRA) in the subject;preferably wherein:
 - i) serum and/or plasma aldosterone AUC-24 is reduced in the subject by at least 25% relative to the aldosterone levels in the subject prior to administration of the lorundrostat or pharmaceutically acceptable salt thereof;
 - ii) serum and/or plasma potassium levels in the subject are increased by at least 0.2 mMol/L relative to the serum and/or plasma potassium levels in the subject prior to administration of the lorundrostat or pharmaceutically acceptable salt thereof; and/or

- iii) PRA in the subject is increased by at least 5 ng/ml/hr relative to the PRA in the subject prior to administration of the lorundrostat or pharmaceutically acceptable salt thereof.
30. The method of any one of the claims 1 to 29, wherein:
- a) the subject is afflicted by CKD characterized by one or more or all of the following:
 - i) a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-3500 mg/g or 200-5000mg/g;
 - ii) an estimated glomerular filtration rate (eGFR) of at least 25 mL/min/1.73m² or at least 30 mL/min/1.73m² and preferably less than 90 mL/min/1.73m²;
 - iii) nephropathy;
 - iv) proteinuria such as albuminuria;
 - v) urine sediment abnormalities;
 - vi) abnormalities such as electrolyte abnormalities due to tubular disorders;
 - vii) abnormalities detected by histology; and
 - viii) structural abnormalities detected by imaging; or
 - b) the subject is afflicted by mild to moderate CKD, characterized by:
 - i) an eGFR of at least 45 mL/min/1.73 m² and less than 90 mL/min/1.73 m²; and
 - ii) albuminurea characterized by a UACR of ≥ 300 mg/g to 3500 mg/g; or
 - c) the subject is afflicted by moderate to severe CKD, characterized by:
 - i) an eGFR of at least 30 mL/min/1.73 m² and less than 45 mL/min/1.73 m²; and
 - ii) albuminurea characterized by a UACR of ≥ 300 mg/g to 3500 mg/g.
31. The method of any one of the claims 1 to 30, wherein the subject is also afflicted with hypertension, preferably wherein the subject has a systolic blood pressure of at least 120 mmHg and a systolic blood pressure of at least 80 mmHg, more preferably wherein the subject has a systolic blood pressure of between 135-180 mmHg, inclusive.
32. The method of claim 31, wherein:
- a) the method is effective to:

- i) reduce the subject's systolic blood pressure by at least 10 mmHg, by 10-55 mmHg, by 10-50 mmHg, by 10-45 mmHg, by 10-40 mmHg, by 10-35 mmHg, by 10-30 mmHg, by 10-25 mmHg, by 10-20 mmHg, or by 10-15 mmHg, relative to the subject's systolic blood pressure prior to administration of the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof for a period of at least eight weeks; and/or
- ii) reduce the subject's diastolic blood by at least 5 mmHg, by 5-25 mmHg, by 5-20 mmHg, or by 5-15 mmHg relative to the subject's diastolic blood pressure prior to administration of the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof for a period of at least eight weeks;
- iii) reduce the subject's average systolic blood pressure during sleep relative to
 - (1) the subject's average systolic blood pressure during sleep prior to receiving the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof for a period of at least eight weeks;
 - (2) the subject's average systolic blood pressure during sleep prior to receiving the lorundrostat or pharmaceutically acceptable salt thereof for a period of at least eight weeks; and/or
 - (3) the subject's average daytime systolic blood pressure.
- iv) reduce the subject's average systolic blood pressure during sleep by at least 10%, by between 10% and 40%, by between 10% and 30%, or by between 10% and 20% relative to the subject's average daytime systolic blood pressure;
- v) reduce the subject's average systolic blood pressure during sleep by at least 8 mmHg, by at least 10mmHg, by between 8 and 55 mmHg, by between 10 and 45 mmHg, or by between 10 and 25 mmHg, relative to the subject's average systolic blood pressure during sleep prior to receiving the SGLT2 inhibitor and lorundrostat or pharmaceutically acceptable salt thereof for a period of at least eight weeks; and/or
- vi) reduce the subject's average systolic blood pressure during sleep by at least 8 mmHg, by at least 10mmHg, by between 8 and 55 mmHg, by

between 10 and 45 mmHg, or by between 10 and 25 mmHg, relative to the subject's average systolic blood pressure during sleep prior to receiving lorundrostat or pharmaceutically acceptable salt thereof for a period of at least eight weeks; and/or

- b) the amount of the ACEi or ARB when administered with the lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the ACEi or ARB inhibitor that is effective to treat CKD and/or hypertension when the ACEi or ARB inhibitor is administered alone;
 - c) the amount of the ACEi or ARB when administered with the lorundrostat or pharmaceutically acceptable salt thereof is lower than the amount of the ACEi or ARB that is effective to treat CKD and/or hypertension when the ACEi or ARB inhibitor is administered in the absence of administration of the lorundrostat or a pharmaceutically acceptable salt thereof; and/or
 - d) the amount of the ACEi or ARB that is effective to treat CKD and/or hypertension when administered in the absence of administration of the lorundrostat or pharmaceutically acceptable salt thereof causes one or more adverse effects in the subject, wherein the one or more adverse effects are not caused by the amounts of the ACEi or ARB, and lorundrostat or pharmaceutically acceptable salt thereof that are effective to treat CKD and/or hypertension when administered together.
 - e) the amount of lorundrostat or pharmaceutically acceptable salt thereof when administered together with the ACEi or ARB are more effective to treat CKD and/or hypertension in the subject than when each agent at the same amount is administered alone.
33. The method of any one of the claims 1 to 31, wherein the subject is also afflicted with Type 2 diabetes mellitus (T2DM).
34. The method of any one of the claims 1 to 31, wherein the subject:
- a) is not afflicted with Type 2 diabetes mellitus (T2DM); and/or
 - b) is not afflicted with Type 1 diabetes.
35. The method of any one of the claims 1 to 34, wherein the subject does not have primary aldosteronism.

36. A method of identifying a subject for treatment with lorundrostat or pharmaceutically acceptable salt thereof, the method comprising:
- a) measuring the subject's 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) and/or an estimated glomerular filtration rate (eGFR);
 - b) selecting a subject who, when taking a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), has:
 - i) chronic kidney disease (CKD), characterized by:
 - (1) a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-3500 mg/g or 200-5000mg/g; and/or
 - (2) an estimated glomerular filtration rate (eGFR) of at least 30 or at least 45 mL/min/1.73m² and preferably less than 90 mL/min/1.73m²;
 - ii) mild to moderate CKD, characterized by:
 - (1) albuminuria, characterized by a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 300-3500 mg/g; and
 - (2) an estimated glomerular filtration rate (eGFR) of at least 45 mL/min/1.73m² and less than 90 mL/min/1.73m²; or
 - iii) moderate to severe CKD, characterized by:
 - (1) albuminuria, characterized by a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 300-3500 mg/g; and
 - (2) an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73m² and less than 45 mL/min/1.73m²;
- thereby identifying said subject for treatment with lorundrostat or pharmaceutically acceptable salt thereof.
37. The method of claim 36, wherein the subject is identified for treatment with:
- a) 10-15 mg per day of lorundrostat or a pharmaceutically acceptable salt thereof, preferably 12.5 mg per day of lorundrostat or a pharmaceutically acceptable salt thereof;

- b) 20-30 mg per day of lorundrostat or pharmaceutically acceptable salt thereof, preferably 25 mg per day of lorundrostat or a pharmaceutically acceptable salt thereof; or
 - c) 40-60 mg per day per day of lorundrostat or pharmaceutically acceptable salt thereof, preferably 50 mg per day of lorundrostat or a pharmaceutically acceptable salt thereof.
38. A method of identifying a subject for treatment with a sodium-glucose cotransporter 2 (SGLT2) inhibitor and lorundrostat or pharmaceutically acceptable salt thereof, the method comprising:
- a) measuring the subject's 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) and/or an estimated glomerular filtration rate (eGFR);
 - b) selecting a subject who, when taking a maximally tolerated dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), has:
 - i) chronic kidney disease (CKD), characterized by:
 - (1) a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 200-3500 mg/g or 200-5000mg/g; and/or
 - (2) an estimated glomerular filtration rate (eGFR) of at least 30 or at least 45 mL/min/1.73m² and preferably less than 90 mL/min/1.73m²; or
 - ii) mild to moderate CKD, characterized by:
 - (1) albuminuria, characterized by a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 300-3500 mg/g; and
 - (2) an estimated glomerular filtration rate (eGFR) of at least 45 mL/min/1.73m² and less than 90 mL/min/1.73m²; or
 - iii) moderate to severe CKD, characterized by:
 - (1) albuminuria, characterized by a 24-hour or first morning urine void urinary albumin to creatinine ratio (UACR) of 300-3500 mg/g; and
 - (2) an estimated glomerular filtration rate (eGFR) of at least 30 mL/min/1.73m² and less than 45 mL/min/1.73m²;

thereby identifying said subject for treatment with a sodium-glucose cotransporter 2 (SGLT2) and lorundrostat or pharmaceutically acceptable salt thereof.

39. The method of claim 38, wherein the SGLT2 inhibitor is selected from the group consisting of dapagliflozin, empagliflozin, ipragliflozin, luseogliflozin, canagliflozin, ertugliflozin and bexagliflozin.
40. The method of claim 39, wherein the SGLT2 inhibitor is dapagliflozin.
41. The method of claim 40, wherein the subject is identified for treatment with:
 - a) 10-15 mg per day of lorundrostat or a pharmaceutically acceptable salt thereof, preferably 12.5 mg per day of lorundrostat or a pharmaceutically acceptable salt thereof, and 8-12 mg per day of dapagliflozin, preferably 10 mg per day of dapagliflozin;
 - b) 20-30 mg per day of lorundrostat or pharmaceutically acceptable salt thereof, preferably 25 mg per day of lorundrostat or a pharmaceutically acceptable salt thereof, and 8-12 mg per day of dapagliflozin, preferably 10 mg per day of dapagliflozin;
 - c) 40-60 mg per day per day of lorundrostat or a pharmaceutically acceptable salt thereof, preferably 50 mg per day of lorundrostat or a pharmaceutically acceptable salt thereof, and 8-12 mg per day of dapagliflozin, preferably 10 mg per day of dapagliflozin.
42. The method of any one of claims 36 to 41, wherein the lorundrostat or pharmaceutically acceptable salt thereof is the monohydrobromide salt of lorundrostat.
43. The method of any one of claims 36 to 42, wherein step b) further comprises selecting a subject without Type 1 diabetes.
44. The method of any one of claims 36 to 43, wherein:
 - a) step a) further comprises measuring the subject's serum cortisol in the morning, and step b) further comprises selecting a subject with a serum cortisol of between 3 µg/dL and 22 µg/dL;
 - b) step a) further comprises determining the subject's body mass index (BMI), and step b) further comprises selecting a subject with a BMI of 18-40 kg/m²;

- c) step a) further comprises measuring the subject's serum potassium, and step b) further comprises selecting a subject with a serum potassium of less than 4.8 mmol/L;
 - d) step a) further comprises measuring the subject's serum sodium, and step b) further comprises selecting a subject with a serum sodium of greater than 135 mmol/L; and/or
 - e) step a) further comprises measuring the subject's systolic blood pressure, and step b) further comprises selecting a subject with hypertension, preferably characterized by a systolic blood pressure of at least 135 mmHg, more preferably between 135 mmHg and 180 mmHg, inclusive.
45. Lorundrostat or a pharmaceutically acceptable salt thereof for use in any one of the methods of claims 1 to 35.
46. A pharmaceutical composition comprising lorundrostat or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier for use in any one of the methods of claims 1 to 35.
47. Lorundrostat or a pharmaceutically acceptable salt thereof for use in treating chronic kidney disease (CKD) in a subject afflicted with CKD, wherein said use is in combination with a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably wherein the SGLT2 inhibitor is dapagliflozin.
48. Use of lorundrostat or pharmaceutically acceptable salt thereof for treating chronic kidney disease (CKD) in a subject afflicted with CKD in combination with a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably wherein the SGLT2 inhibitor is dapagliflozin.
49. Lorundrostat or a pharmaceutically acceptable salt thereof for use in treating chronic kidney disease (CKD) and hypertension in a subject afflicted with CKD and hypertension, wherein said use is in combination with a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably wherein the SGLT2 inhibitor is dapagliflozin.

50. Use of lorundrostat or pharmaceutically acceptable salt thereof for treating chronic kidney disease (CKD) and hypertension in a subject afflicted with CKD and hypertension in combination with a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), preferably wherein the SGLT2 inhibitor is dapagliflozin.
51. A package comprising:
- a) a first pharmaceutical composition comprising an amount of lorundrostat or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier;
 - b) a second pharmaceutical composition comprising an amount of sodium-glucose cotransporter 2 (SGLT2) inhibitor;
 - c) optionally, a third pharmaceutical composition comprising an amount of an angiotensin-converting enzyme inhibitor (ACEi);
 - d) optionally, a fourth pharmaceutical composition comprising an amount of an angiotensin receptor blocker (ARB); and
 - e) instructions for use of the first and second pharmaceutical compositions, and third and fourth pharmaceutical compositions, if present, together to treat a subject afflicted with CKD, or CKD and hypertension.
52. A package comprising:
- a) a first pharmaceutical composition comprising an amount of lorundrostat or pharmaceutically acceptable salt thereof, an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and a pharmaceutically acceptable carrier; and
 - b) optionally, a second pharmaceutical composition comprising an amount of an angiotensin-converting enzyme inhibitor (ACEi) and/or an amount of an angiotensin receptor blocker (ARB) and a pharmaceutically acceptable carrier; and
 - c) instructions for use of the pharmaceutical composition(s) to treat a subject afflicted with chronic kidney disease (CKD), or CKD and hypertension.
53. A pharmaceutical composition comprising:
- a) an amount of lorundrostat or a pharmaceutically acceptable salt thereof;

- b) an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor or a pharmaceutically acceptable salt thereof;
- c) optionally an amount of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) or a pharmaceutically acceptable salt thereof;

wherein the lorundrostat or pharmaceutically acceptable salt thereof, SGLT2 inhibitor, and ACEi or ARB, if present, are administered simultaneously, contemporaneously or concomitantly.

54. A pharmaceutical composition comprising an amount of lorundrostat or pharmaceutically acceptable salt thereof for use in treating chronic kidney disease (CKD) or CKD and hypertension in a subject afflicted with CKD or CKD and hypertension in combination with an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and optionally an amount of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB).
55. A pharmaceutical composition in unit dosage form, useful in treating a subject afflicted with chronic kidney disease (CKD) or CKD and hypertension, which comprises:
- a) an amount of lorundrostat or a pharmaceutically acceptable salt thereof;
 - b) an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor or a pharmaceutically acceptable salt thereof; and
 - c) optionally an amount of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) or a pharmaceutically acceptable salt thereof;
- wherein the respective amounts of said lorundrostat or pharmaceutically acceptable salt thereof, said SGLT2 inhibitor, and said ACEi or ARB, if present, in said composition are effective, upon concomitant administration to said subject of one or more of said unit dosage forms of said composition, to treat the subject.
56. A therapeutic package for dispensing to, or for use in dispensing to, a subject afflicted with chronic kidney disease (CKD) or CKD and hypertension, which comprises:
- a) one or more unit doses, each such unit dose comprising:
 - i) an amount of lorundrostat or a pharmaceutically acceptable salt thereof;
 - ii) an amount of a sodium-glucose cotransporter 2 (SGLT2) inhibitor or a pharmaceutically acceptable salt thereof; and

- iii) optionally an amount of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) or a pharmaceutically acceptable salt thereof;
wherein the respective amounts of said lorundrostat or pharmaceutically acceptable salt thereof, said SGLT2 inhibitor, and said ACEi or ARB, if present, in said unit doses are effective, upon concomitant administration to said subject, to treat CKD or CKD and hypertension in the subject, and
 - b) a finished pharmaceutical container therefor, said container containing said unit dose or unit doses, said container further containing or comprising labeling directing the use of said package in the treatment of said subject.
57. The package of any one of claims 51 to 52, the pharmaceutical composition of any one of claims 53 to 55, or the therapeutic package of claim 56, wherein the SGLT2 inhibitor is dapagliflozin.
58. The package of any one of claims 51 to 52, the pharmaceutical composition of any one of claims 53 to 55, or the therapeutic package of claim 56, wherein the lorundrostat or pharmaceutically acceptable salt thereof is the monohydrobromide salt of lorundrostat.
59. The package, pharmaceutical composition, or therapeutic package of claim 57 or 58, wherein the pharmaceutical composition, unit dose, or unit dosage form comprises 10-15 mg, 20-30 mg, or 40-60 mg of lorundrostat or pharmaceutically acceptable salt thereof, preferably 12.5 mg, 25 mg, or 50 mg of lorundrostat or pharmaceutically acceptable salt thereof, and 8-12 mg of dapagliflozin, preferably 10 mg of dapagliflozin.