

SGLT2 INHIBITORS AND BAXDROSTAT FOR TREATING CHRONIC KIDNEY DISEASE AND HYPERTENSION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 63/610,570, filed December 15, 2023, the disclosure of which is incorporated by reference herein.

TECHNICAL FIELD

[0002] The disclosure provides compounds and methods of treating chronic kidney disease and hypertension.

BACKGROUND

[0003] Estimates of global incidence, prevalence, and mortality of chronic kidney disease (CKD) have all increased dramatically since 1990; an effect driven by population growth, ageing, and increased prevalence of diabetes and hypertension (HTN) (Xie et al Kidney Int. 2018;94(3):567-81). An estimated 843.6 million people worldwide live with CKD. Chronic kidney disease was number 10 of the global most common causes of death in 2019 (Kovesdy Kidney international supplements. 2022;12(1):7-11) with predictions suggesting that it will become the fifth highest cause of years of life lost globally by 2040 (Foreman et al Lancet (London, England). 2018;392(10159):2052-90).

[0004] Effective management of HTN in patients with CKD lowers the risk of cardiovascular (CV) events and delays CKD progression (Ku et al American journal of kidney diseases : the official journal of the National Kidney Foundation. 2019;74(1):120-31). The Kidney Disease Improving Global Outcomes (KDIGO) guideline 2021 recommends treating patients with high blood pressure and CKD to a target systolic blood pressure (SBP) of < 120 mmHg, however this is not achieved in many patients despite currently available therapies. Renin-angiotensin system inhibitors (ACE inhibitors or ARBs) are recommended for patients with high blood pressure (BP) and proteinuric CKD. Independent of BP control, CKD guidelines recommend the use of ACE inhibitors or ARBs to treat CKD in patients with severely increased albuminuria. There remains an unmet need for novel treatments to improve BP control in patients with CKD and HTN, because many CKD patients do not reach target BP despite currently available therapies.

[0005] Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been demonstrated to reduce the risk of sustained kidney function decline, kidney failure, and CV death in patients with CKD and diabetes (canagliflozin, CREDENCE trial; (Perkovic et al The New England journal of medicine. 2019;380(24):2295-306) and with and without diabetes (dapagliflozin, DAPA-CKD trial (Heerspink et al The New England journal of medicine. 2020;383(15):1436-46); empagliflozin, EMPA Kidney trial (Herrington et al The New England journal of medicine. 2023;388(2):117-27). The updated KDIGO guidelines provide a 1A recommendation for the use of SGLT2 inhibitors in CKD with eGFR ≥ 20 mL/min/1.73 m² and UACR ≥ 200 mg/g (KDIGO 2023). Additionally, SGLT2 inhibitors are associated with decreased risk of hyperkalaemia, especially in the setting of treatment with agents that are known to increase hyperkalaemia risk (Agarwal et al 2022, Neuen et al 2022, Provenzano et al 2022). Despite the demonstrated kidney protective benefits of SGLT2 inhibitors, a residual risk of CKD progression to End-stage kidney disease (ESKD, also known as End-stage renal disease (ESRD)) as well as risk of cardiovascular disease (CVD) and mortality remain, highlighting the need for new therapies with complementary mechanisms of action.

[0006] In humans, persistently elevated serum aldosterone concentrations are detrimental to the kidney, while mineralocorticoid receptor antagonism has been shown efficacious. Extremely high serum aldosterone concentrations observed in patients with primary aldosteronism are known to associate with functional and structural kidney damage, manifesting in increased albuminuria and urinary markers of kidney injury (Halimi and Mimran Journal of hypertension. 1995;13(12 Pt 2):1801-2; Wu et al Journal of hypertension. 2011;29(9):1778-86; Wu et al Journal of the American Heart Association. 2023;12(4):e028146), as well as histopathological lesions such as segmental glomerulosclerosis and interstitial fibrosis (Ogata et al Hypertension 2021;78(2):411-21). Observational studies showed increased serum aldosterone concentrations in patients with CKD. Moreover, baseline serum aldosterone concentrations correlated inversely with kidney function and high aldosterone was associated with the composite endpoint of 50% eGFR decline and end-stage kidney disease in the Chronic Renal Insufficiency Cohort (CRIC) study (Verma et al European heart journal. 2022;43(38):3781-91), as well as eGFR slope (Minakuchi et al Sci Rep. 2020;10(1):16626).

[0007] Baxdrostat is a highly selective aldosterone synthase inhibitor that can significantly reduce aldosterone levels, offering the potential to not only improve BP in

patients with CKD, but also ameliorate the negative impacts of elevated aldosterone on kidney function.

[0008] Baxdrostat and dapagliflozin have different and complementary mechanisms of actions, and therefore their combination may provide particular benefits in slowing the progression of CKD in patients with CKD and HTN.

SUMMARY

[0009] The disclosure provides methods of treating chronic kidney disease (CKD) and hypertension in a patient in need thereof, the method comprising administering to the patient a combination comprising a first amount of baxdrostat or a pharmaceutically acceptable salt thereof and a second amount of a sodium-glucose co-transporter 2 (SGLT2) inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount.

[0010] Also provided is baxdrostat or a pharmaceutically acceptable salt thereof for use in any of the methods described herein.

[0011] Also provided is an SGLT2 inhibitor for use in any of the methods described herein.

[0012] Also provided is the use of baxdrostat or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in any of the methods described herein.

[0013] Also provided is the use of an SGLT2 inhibitor in the manufacture of a medicament for use in any of the methods described herein.

[0014] Also provided is a kit comprising: (a) baxdrostat or a pharmaceutically acceptable salt thereof and/or an SGLT2 inhibitor, and (b) instructions for use of the baxdrostat or a pharmaceutically acceptable salt thereof and/or an SGLT2 inhibitor in any of the methods described herein.

[0015] Further aspects of the disclosure will be apparent to one skilled in the art from reading this specification.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Figure 1 depicts the UACR change from baseline of patients in Study 1 (A Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension, Clinicaltrials.gov ID: NCT04519658).

[0017] Figure 2 depicts the study design of Study 2 (A Study in Patients with Uncontrolled Hypertension and Chronic Kidney Disease, Clinicaltrials.gov ID: NCT05432167).

[0018] Figure 3 depicts the study design of Study 3 (A Phase III, Randomised, Double Blind, Active-controlled Study to Assess the Efficacy, Safety and Tolerability of Baxdrostat in Combination with Dapagliflozin Compared with Dapagliflozin Alone on Chronic Kidney Disease (CKD) Progression in Participants with CKD and High Blood Pressure, as described herein).

[0019] Figure 4 depicts the study design of Study 4 (A Phase III, Randomised, Double-blind, Placebo-controlled, Event-driven Study to Assess the Efficacy, Safety and Tolerability of Baxdrostat in Combination with Dapagliflozin Compared with Dapagliflozin Alone on Renal Outcomes and Cardiovascular Mortality in Participants with Chronic Kidney Disease and High Blood Pressure, as described herein).

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0020] The disclosure may be more fully appreciated by reference to the following description, including the following definitions and examples. Certain features of the disclosed compositions and methods which are described herein in the context of separate aspects, may also be provided in combination in a single aspect. Alternatively, various features of the disclosed compositions and methods that are, for brevity, described in the context of a single aspect, may also be provided separately or in any sub combination. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure pertains. The terminology used in the description is for describing particular embodiments only and is not intended to be limiting of the disclosure.

[0021] In the disclosure, the singular forms “a,” “an,” and “the” include the plural reference, and reference to a particular numerical value includes at least that particular value, unless the context clearly indicates otherwise.

[0022] When a value is expressed as an approximation by use of the descriptor “about” it will be understood that the particular value forms another embodiment. In general, use of the term “about” indicates approximations that can vary depending on the desired properties sought to be obtained by the disclosed subject matter and is to be interpreted in the specific context in which it is used, based on its function. The person skilled in the art will be

able to interpret this as a matter of routine. In some cases, the number of significant figures used for a particular value may be one non-limiting method of determining the extent of the word “about.” In other cases, the gradations used in a series of values may be used to determine the intended range available to the term “about” for each value. Where present, all ranges are inclusive and combinable. That is, references to values stated in ranges include every value within that range.

[0023] When a list is presented, unless stated otherwise, it is to be understood that each individual element of that list and every combination of that list is to be interpreted as a separate embodiment. For example, a list of embodiments presented as “A, B, or C” is to be interpreted as including the embodiments, “A,” “B,” “C,” “A or B,” “A or C,” “B or C,” or “A, B, or C.”

[0024] It is to be appreciated that certain features of the invention which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. That is, unless obviously incompatible or excluded, each individual embodiment is deemed to be combinable with any other embodiment(s) and such a combination is considered to be another embodiment. Conversely, various features of the invention that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any sub-combination. It is further noted that the claims may be drafted to exclude an optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as “only” and the like in connection with the recitation of claim elements, or use of a “negative” limitation.

[0025] The effectiveness of the compounds of the present disclosure in treating CKD and hypertension can readily be determined by a person of ordinary skill in the relevant art. Determining and adjusting an appropriate dosing regimen (*e.g.*, adjusting the amount of compound per dose and/or number of doses and frequency of dosing) can also readily be performed by a person of ordinary skill in the relevant art. One or any combination of diagnostic methods, including physical examination, assessment and monitoring of clinical symptoms, and performance of analytical tests and methods described herein, may be used for monitoring the health status of the patient.

[0026] An effective amount or therapeutically effective amount refers to an amount of one or more compounds of the present disclosure that, when administered to a patient, either as a single dose or as part of a series of doses, is effective to produce at least one therapeutic effect. The dose may depend upon the body mass, weight, and/or blood volume of

the patient. Patients may generally be monitored for therapeutic effectiveness using assays suitable for the disease, disorder, and/or condition being treated or prevented. The level of a compound that is administered to a patient may be monitored by determining the level of the compound (or a metabolite of the compound) in a biological fluid, for example, in the blood, blood fraction (*e.g.*, serum), and/or in the urine, and/or other biological sample from the patient. Any method practiced in the art to detect the compound, or metabolite thereof, may be used to measure the level of the compound during the course of a therapeutic regimen.

[0027] The dose of a compound described herein may depend upon the patient's condition, that is, stage of the disease, severity of symptoms caused by the disease, general health status, as well as age, gender, and weight, and other factors apparent to a person of ordinary skill in the medical art.

[0028] The terms "treating" or "treatment" or "to treat" refer to therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic disease, disorder, or condition. Treatment need not result in a complete cure of the condition; partial inhibition or reduction of the condition being treated is encompassed by this term.

[0029] The terms "subject" and "patient" are used interchangeably and typically refer to mammals. In some embodiments, the patient or subject is a human. In some embodiments, the subject or patient is at least 18 years of age, *i.e.*, an adult.

[0030] The term "combination" as used herein with respect to baxdrostat or a pharmaceutically acceptable salt thereof and an SGLT2 inhibitor, *e.g.* dapagliflozin, may include, for example, fixed and non-fixed (*e.g.* free) forms (including kits or other administration or dosage forms) and uses, such as the simultaneous, sequential or separate use of baxdrostat or a pharmaceutically acceptable salt thereof and an SGLT2 inhibitor, *e.g.* dapagliflozin.

[0031] The disclosure is directed to methods of treating chronic kidney disease (CKD) and hypertension in a patient in need thereof, the method comprising administering to the patient a combination comprising a first amount of baxdrostat or a pharmaceutically acceptable salt thereof and a second amount of a sodium-glucose co-transporter 2 (SGLT2) inhibitor, *e.g.* dapagliflozin, wherein the first amount and the second amount together comprise a therapeutically effective amount.

[0032] Also disclosed is a method of reducing the rate of decline in kidney function of a patient with CKD and hypertension, comprising administering to the patient a combination comprising a first amount of baxdrostat or a pharmaceutically acceptable salt thereof and a second amount of a SGLT2 inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount. In some embodiments, the rate of decline in kidney function of the patient is reduced to a greater extent than a method wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo. In some embodiments, the rate of decline in eGFR of the patient is reduced by 0.5 mL/min/1.73 m²/year or more, such as 0.75 mL/min/1.73 m²/year or more or 1.0 mL/min/1.73 m²/year or more, than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.

[0033] Also disclosed is a method of reducing the rate of decline in estimated glomerular filtration rate (eGFR) of a patient with CKD and hypertension, comprising administering to the patient a combination comprising a first amount of baxdrostat or a pharmaceutically acceptable salt thereof and a second amount of a SGLT2 inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount. In some embodiments, the rate of decline in eGFR of the patient is reduced to a greater extent than a method wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo. In some embodiments, the rate of decline in eGFR of the patient is reduced by 0.5 mL/min/1.73 m²/year or more, such as 0.75 mL/min/1.73 m²/year or more or 1.0 mL/min/1.73 m²/year or more, than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.

[0034] Also disclosed is a method of reducing the risk of sustained eGFR decline of $\geq 50\%$ from baseline in a patient with CKD and hypertension, comprising administering to the patient a combination comprising a first amount of baxdrostat or a pharmaceutically acceptable salt thereof and a second amount of a SGLT2 inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount. In some embodiments, the method reduces the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline to a greater extent than a method wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0035] Also disclosed is a method of reducing the risk of sustained eGFR decline of $\geq 57\%$ from baseline in a patient with CKD and hypertension, comprising administering to the patient a combination comprising a first amount of baxdrostat or a pharmaceutically

acceptable salt thereof and a second amount of a SGLT2 inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount. In some embodiments, the method reduces the patient's risk of sustained eGFR decline of $\geq 57\%$ from baseline to a greater extent than a method wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0036] Also disclosed is a method of reducing the risk of end-stage kidney disease (ESKD) in a patient with CKD and hypertension, comprising administering to the patient a combination comprising a first amount of baxdrostat or a pharmaceutically acceptable salt thereof and a second amount of a SGLT2 inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount. In some embodiments, the method reduces the patient's risk of ESKD to a greater extent than a method wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0037] Also disclosed is a method of reducing the risk of sustained eGFR decline of $\geq 50\%$ from baseline, reaching ESKD, or cardiovascular (CV) death in a patient with CKD and hypertension, comprising administering to the patient a combination comprising a first amount of baxdrostat or a pharmaceutically acceptable salt thereof and a second amount of a SGLT2 inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount. In some embodiments, the method reduces the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline, reaching ESKD, or CV death to a greater extent than a method wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0038] Also disclosed is a method of reducing the risk of sustained eGFR decline of $\geq 50\%$ from baseline or ESKD in a patient with CKD and hypertension, comprising administering to the patient a combination comprising a first amount of baxdrostat or a pharmaceutically acceptable salt thereof and a second amount of a SGLT2 inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount. In some embodiments, the method reduces the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline or ESKD to a greater extent than a method wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0039] Also disclosed is a method of reducing the risk of CV death, heart failure event, myocardial infarction or stroke in a patient with CKD and hypertension, comprising

administering to the patient a combination comprising a first amount of baxdrostat or a pharmaceutically acceptable salt thereof and a second amount of a SGLT2 inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount. In some embodiments, the method reduces the patient's risk of CV death, heart failure event, myocardial infarction or stroke to a greater extent than a method wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0040] Also disclosed is a method of reducing the risk of CV death or heart failure event in a patient with CKD and hypertension, comprising administering to the patient a combination comprising a first amount of baxdrostat or a pharmaceutically acceptable salt thereof and a second amount of a SGLT2 inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount. In some embodiments, the method reduces the patient's risk of CV death or heart failure event to a greater extent than a method wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0041] Also disclosed is a method of reducing the risk of CV death in a patient with CKD and hypertension, comprising administering to the patient a combination comprising a first amount of baxdrostat or a pharmaceutically acceptable salt thereof and a second amount of a SGLT2 inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount. In some embodiments, the method reduces the patient's risk of CV death to a greater extent than a method wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0042] Also disclosed is a method of reducing the risk of death in a patient with CKD and hypertension, comprising administering to the patient a combination comprising a first amount of baxdrostat or a pharmaceutically acceptable salt thereof and a second amount of a SGLT2 inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount. In some embodiments, the method reduces the patient's risk of death to a greater extent than a method wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0043] The severity of hypertension may be classified into categories, as shown in the table below:

American Heart Association (AHA) Categories of Blood Pressure for Adults	
Blood Pressure Category	Definition
Normal	SBP <120 mmHg and DBP <80 mmHg
Elevated	SBP 120-129 mmHg and DBP <80 mmHg
Stage 1 hypertension	SBP 130-139 mmHg or DBP 80-89 mmHg
Stage 2 hypertension	SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg
Hypertensive crisis	SBP >180 mmHg or DBP >120 mmHg

SBP = Systolic blood pressure; DBP = Diastolic blood pressure

[0044] In some embodiments, the hypertension is Stage 1 hypertension or Stage 2 hypertension. In some embodiments, the hypertension is Stage 1 hypertension. In some embodiments, the hypertension is Stage 2 hypertension. In some embodiments, the hypertension is not hypertensive crisis.

[0045] In some embodiments, the hypertension is uncontrolled hypertension (uHTN). In some embodiments, uHTN is hypertension that is being unsuccessfully treated with 1 or 2 antihypertensive agents.

[0046] In some embodiments, the patient has a systolic blood pressure (SBP) $\geq$ 120 mmHg. In some embodiments, the patient has a SBP $\geq$ 130 mmHg. In some embodiments, the patient has a SBP $\geq$ 140 mmHg.

[0047] In some embodiments, the patient has a SBP $\leq$ 180 mmHg. In some embodiments, the patient has a systolic blood pressure (SBP) $\geq$ 120 mmHg and $\leq$ 180 mmHg. In some embodiments, the patient has a SBP $\geq$ 130 mmHg and $\leq$ 180 mmHg. In some embodiments, the patient has a SBP $\geq$ 140 mmHg and $\leq$ 180 mmHg.

[0048] In some embodiments, the SBP is mean seated SBP.

[0049] In some embodiments, the patient has a diastolic blood pressure (DBP) $\geq$ 80 mmHg. In some embodiments, the patient has a diastolic blood pressure (DBP) $\geq$ 90 mmHg. In some embodiments, the patient has a diastolic blood pressure (DBP) $\leq$ 110 mmHg. In some embodiments, the patient has a diastolic blood pressure (DBP) $\leq$ 120 mmHg. In some embodiments, the DBP is mean seated DBP.

[0050] The severity of CKD may be classified into the stages described below:

[0051] Stage 1: Kidney damage with $\text{eGFR} \geq 90 \text{ mL/min/1.73 m}^2$ for 3 months or more.

[0052] Stage 2: Kidney damage with $\text{eGFR} 60\text{-}89 \text{ mL/min/1.73 m}^2$ for 3 months or more.

[0053] Stage 3a: Mild to moderate loss of kidney function ($\text{eGFR} 45\text{-}59 \text{ mL/min/1.73 m}^2$) for 3 months or more.

[0054] Stage 3b: Moderate to severe loss of kidney function ($\text{eGFR} 30\text{-}44 \text{ mL/min/1.73 m}^2$) for 3 months or more.

[0055] Stage 4: Severe loss of kidney function ($\text{eGFR} 15\text{-}29 \text{ mL/min/1.73 m}^2$) for 3 months or more.

[0056] Stage 5: Kidney failure ($\text{eGFR} < 15 \text{ mL/min/1.73 m}^2$) for 3 months or more or dialysis.

[0057] “End stage kidney disease (ESKD)” as used herein refers to (i) having a sustained $\text{eGFR} < 15 \text{ mL/min/1.73 m}^2$, (ii) receiving chronic dialysis treatment, or (iii) receiving a renal transplant.

[0058] In some embodiments, the CKD is Stage 1 CKD, Stage 2 CKD, Stage 3a CKD, Stage 3b CKD or Stage 4 CKD. In some embodiments, the CKD is Stage 1 CKD, Stage 2 CKD, Stage 3a CKD, or Stage 3b CKD. In some embodiments, the CKD is Stage 1 CKD, Stage 2 CKD, or Stage 3a CKD. In some embodiments, the CKD is Stage 2 CKD, Stage 3a CKD, Stage 3b CKD or Stage 4 CKD. In some embodiments, the CKD is Stage 2 CKD, Stage 3a CKD, or Stage 3b CKD. In some embodiments, the CKD is Stage 2 CKD, or Stage 3a CKD.

[0059] In some embodiments, the patient has an estimated glomerular filtration rate (eGFR) ≥ 15 and $< 90 \text{ mL/min/1.73 m}^2$. In some embodiments, the patient has an $\text{eGFR} \geq 30$ and $< 90 \text{ mL/min/1.73 m}^2$. In some embodiments, the patient has an $\text{eGFR} \geq 15$ and $< 60 \text{ mL/min/1.73 m}^2$. In some embodiments, the patient has an $\text{eGFR} \geq 30$ and $< 60 \text{ mL/min/1.73 m}^2$. In some embodiments, the patient has an $\text{eGFR} \geq 25$ and $\leq 75 \text{ mL/min/1.73 m}^2$.

[0060] In some embodiments, the patient has CKD at risk of progression. In some embodiments, the patient has CKD at high risk of progression. In some embodiments, the patient has or is at risk of an eGFR decline at a rate of $> 3 \text{ mL/min/1.73 m}^2/\text{year}$.

[0061] In some embodiments, the patient has a urine albumin creatinine ratio (UACR) $\geq 100 \text{ mg/g}$. In some embodiments, the patient has a UACR $\geq 200 \text{ mg/g}$. In some

embodiments, the patient has a UACR ≥ 200 mg/g and ≤ 5000 mg/g. In some embodiments, the patient has a UACR > 200 mg/g and < 5000 mg/g. In some embodiments, the patient has albuminuria.

[0062] In some embodiments, the patient has normal serum potassium. In some embodiments, the patient does not have hyperkalemia. In some embodiments, the patient has serum potassium of < 5.5 mmol/L. In some embodiments, the patient has serum potassium of < 5.0 mmol/L. In some embodiments, the patient has serum potassium of ≤ 4.8 mmol/L. In some embodiments, the patient has serum potassium of 3.5 to 4.8 mmol/L. In some embodiments, the patient has serum potassium of 3.5 to 4.8 mmol/L and an eGFR of ≥ 45 mL/min/1.73 m². In some embodiments, the patient has serum potassium of 3.5 to 4.5 mmol/L and an eGFR of < 45 mL/min/1.73 m².

[0063] In some embodiments, the patient has serum sodium of < 135 mmol/L.

[0064] In some embodiments, the patient does not have Type 1 diabetes mellitus. In some embodiments, the patient does not have uncontrolled Type 2 diabetes mellitus. In some embodiments, the patient does not have uncontrolled Type 2 diabetes mellitus with HbA1c $> 10.5\%$ (> 91 mmol/mol). In some embodiments, the patient has Type 2 diabetes mellitus. In some embodiments, the patient has controlled Type 2 diabetes mellitus.

[0065] In some embodiments, the patient is New York Heart Association functional HF class I, class II or class III. In some embodiments, the patient is not New York Heart Association functional HF class IV.

[0066] In some embodiments, the methods described herein reduce the rate of decline in kidney function of the patient. In some embodiments, the method reduces the rate of decline in kidney function of the patient to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.

[0067] In some embodiments, the methods described herein reduce the decline in kidney function of the patient from baseline to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo. In some embodiments, the decline in kidney function is measured at about 2 years into treatment with the combination. In some embodiments, the decline in kidney function is measured at about 26 weeks into treatment with the combination.

[0068] In some embodiments, the methods described herein reduce the rate of decline in eGFR of the patient. In some embodiments, the method reduces the rate of decline

in eGFR of the patient to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.

[0069] In some embodiments, the methods described herein reduce the rate of decline in eGFR of the patient, and the patient has an eGFR ≥ 30 and < 90 mL/min/1.73 m². In some embodiments, the method reduces the rate of decline in eGFR of the patient to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo, and the patient has an eGFR ≥ 30 and < 90 mL/min/1.73 m².

[0070] In some embodiments, the methods described herein reduce the rate of decline in eGFR of the patient by 0.5 mL/min/1.73 m²/year or more, such as 0.75 mL/min/1.73 m²/year or more or 1.0 mL/min/1.73 m²/year or more.

[0071] In some embodiments, the methods described herein reduce the rate of decline in eGFR of the patient by 0.5 mL/min/1.73 m²/year or more, such as 0.75 mL/min/1.73 m²/year or more or 1.0 mL/min/1.73 m²/year or more, than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.

[0072] In some embodiments, the methods described herein reduce the decline in eGFR of the patient from baseline to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo. In some embodiments, the decline in eGFR is measured at about 2 years into treatment with the combination. In some embodiments, the decline in eGFR is measured at about 26 weeks into treatment with the combination.

[0073] In some embodiments, the methods described herein reduce UACR of the patient from baseline. In some embodiments, the method reduces UACR of the patient from baseline to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo. In some embodiments, the UACR is measured at about 2 years into treatment with the combination. In some embodiments, the UACR is measured at about 26 weeks into treatment with the combination. In some embodiments, the UACR is measured at about 16 weeks into treatment with the combination.

[0074] In some embodiments, the methods described herein reduce UACR of the patient from baseline by 20% or more, such as 25% or more, or 30% or more. In some embodiments, the UACR is measured at about 2 years into treatment with the combination. In some embodiments, the UACR is measured at about 26 weeks into treatment with the combination. In some embodiments, the UACR is measured at about 16 weeks into treatment with the combination.

[0075] In some embodiments, the methods described herein reduce UACR of the patient from baseline by 20% or more, such as 25% or more or 30% or more, than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo. In some embodiments, the UACR is measured at about 2 years into treatment with the combination. In some embodiments, the UACR is measured at about 26 weeks into treatment with the combination. In some embodiments, the UACR is measured at about 16 weeks into treatment with the combination.

[0076] In some embodiments, the methods described herein reduce SBP of the patient from baseline. In some embodiments, the method reduces SBP of the patient from baseline to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo. In some embodiments, the SBP is measured at about 2 years into treatment with the combination. In some embodiments, the SBP is measured at about 26 weeks into treatment with the combination. In some embodiments, the SBP is measured at about 16 weeks into treatment with the combination. In some embodiments, the SBP is mean seated SBP.

[0077] In some embodiments, the methods described herein reduce SBP of the patient from baseline by 4 mmHg or more, such as 5 mmHg or more or 6 mmHg or more, than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo. In some embodiments, the SBP is measured at about 2 years into treatment with the combination. In some embodiments, the SBP is measured at about 26 weeks into treatment with the combination. In some embodiments, the SBP is measured at about 16 weeks into treatment with the combination. In some embodiments, the SBP is mean seated SBP.

[0078] In some embodiments, the methods described herein reduce SBP of the patient to <120 mmHg. In some embodiments, the methods described herein reduce SBP of the patient to <130 mmHg.

[0079] In some embodiments, the methods described herein reduce the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline. In some embodiments, the method reduces the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0080] In some embodiments, the methods described herein reduce the patient's risk of sustained eGFR decline of $\geq 57\%$ from baseline. In some embodiments, the method

reduces the patient's risk of sustained eGFR decline of $\geq 57\%$ from baseline to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0081] In some embodiments, the methods described herein reduce the patient's risk of ESKD. In some embodiments, the method reduces the patient's risk of ESKD to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0082] In some embodiments, the methods described herein reduce the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline or ESKD. In some embodiments, the method reduces the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline or ESKD to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0083] In some embodiments, the methods described herein reduce the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline or ESKD, and the patient has an eGFR ≥ 30 and < 60 mL/min/1.73 m². In some embodiments, the method reduces the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline or ESKD to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1), and the patient has an eGFR ≥ 30 and < 60 mL/min/1.73 m².

[0084] In some embodiments, the methods described herein reduce chronic eGFR slope of the patient. In some embodiments, the method reduces chronic eGFR slope of the patient to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo. In some embodiments, the chronic eGFR slope is the rate of decline in eGFR of the patient between about 8 weeks and about 2 years into treatment with the combination. In some embodiments, the rate of decline in eGFR of the patient between about 8 weeks and about 2 years into treatment with the combination is reduced by 0.5 mL/min/1.73 m²/year or more, such as 0.75 mL/min/1.73 m²/year or more or 1.0 mL/min/1.73 m²/year or more, than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.

[0085] In some embodiments, the methods described herein reduce the patient's risk of sustained eGFR decline, reaching ESKD, or CV death. In some embodiments, the method reduces the patient's risk of sustained eGFR decline, reaching ESKD, or CV death to a

greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0086] In some embodiments, the methods described herein reduce the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline, reaching ESKD, or CV death. In some embodiments, the method reduces the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline, reaching ESKD, or CV death to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0087] In some embodiments, the methods described herein reduce the patient's risk of CV death, heart failure event, myocardial infarction or stroke. In some embodiments, the methods described herein reduce the patient's risk of CV death, heart failure event, myocardial infarction or stroke to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0088] In some embodiments, the methods described herein reduce the patient's risk of CV death or heart failure event. In some embodiments, the methods described herein reduce the patient's risk of CV death or heart failure event to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0089] In some embodiments, the methods described herein reduce the patient's risk of CV death. In some embodiments, the methods described herein reduce the patient's risk of CV death to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[0090] In some embodiments, "cardiovascular (CV) death" refers to a death of a patient wherein the primary cause of death is due to acute myocardial infarction (MI), sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage, or other cardiovascular causes. "Other cardiovascular causes" refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease). In some embodiments, CV death may also include the death of a patient wherein the underlying cause of death is unknown.

[0091] In some embodiments, a "heart failure event" (HF event) is a hospitalization for HF or HF without hospitalisation.

[0092] In some embodiments, an "HF event" is a hospitalization for HF.

[0093] In some embodiments, the hospitalization for HF comprises a hospital admission lasting at least 24 hours or as measured by a change in calendar date, and the patient has objective evidence of new or worsening HF.

[0094] In some embodiments, the hospitalization for HF meets one or more of the following criteria: (i) admission to the hospital with a primary cause of HF; and/or (ii) new or worsening symptoms due to HF exhibited by the patient; and/or (iii) objective evidence of new or worsening HF; and/or (iv) initiation or intensification of treatment specifically for HF. In some embodiments, the hospitalization for HF meets all of the above criteria. In some embodiments, new or worsening symptoms due to HF exhibited by the patient comprises at least one of the following: dyspnoea (such as dyspnoea with exertion, dyspnoea at rest, orthopnoea, and/or paroxysmal nocturnal dyspnoea); decreased exercise tolerance; fatigue; and other symptoms of worsened end-organ perfusion or volume overload. In some embodiments, objective evidence of new or worsening HF comprises physical examination findings considered to be due to HF, laboratory evidence of new or worsening HF and/or invasive evidence of new or worsening HF. In some embodiments, the physical examination findings considered to be due to HF comprises at least one of the following findings: peripheral oedema; increasing abdominal distention or ascites (such as in the absence of primary hepatic disease); pulmonary rales/crackles/crepitations; increased jugular venous pressure and/or hepatojugular reflux; third heart sound (S3) gallop; and clinically significant or rapid weight gain related to fluid retention. In some embodiments, laboratory evidence of new or worsening HF comprises at least one of the following findings: increased B-type natriuretic peptide (BNP)/NT-proBNP concentrations consistent with decompensation of heart failure; radiological, ultrasonographic, or implantable monitor evidence of pulmonary congestion; and non-invasive or implantable diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. In some embodiments, invasive evidence of new or worsening HF comprises at least one of the following findings: right heart catheterization showing elevated pulmonary capillary wedge pressure (pulmonary artery occlusion pressure), elevated central venous pressure, and/or depressed cardiac index; and left heart catheterization showing elevated left ventricular end-diastolic pressure consistent with decompensation of HF. In some embodiments, the initiation or intensification of treatment specifically for HF comprises at least one of the following: initiation of maintenance diuretic therapy; augmentation in oral diuretic therapy (such as increasing, for example doubling, diuretic dose or initiation of combination diuretic therapy);

initiation of intravenous administration of a diuretic; initiation of intravenous administration of a vasoactive agent (such as catecholamine, phosphodiesterase-3 inhibitor, or other vasopressor or vasodilator); mechanical or surgical intervention (such as mechanical circulatory support); and mechanical fluid removal (such as ultrafiltration, haemofiltration and haemodialysis).

[0095] In some embodiments, the HF without hospitalisation comprises an outpatient visit in an emergency department or ambulatory setting, and the patient has objective evidence of new or worsening HF.

[0096] In some embodiments, the HF without hospitalisation meets one or more of the following criteria: (i) new or worsening symptoms due to HF exhibited by the patient; and/or (ii) objective evidence of new or worsening HF; and/or (iii) initiation or intensification of treatment specifically for HF. In some embodiments, the HF without hospitalisation meets all of the above criteria. In some embodiments, new or worsening symptoms due to HF exhibited by the patient comprises at least one of the following: dyspnoea (such as dyspnoea with exertion, dyspnoea at rest, orthopnoea, and/or paroxysmal nocturnal dyspnoea); decreased exercise tolerance; fatigue; and other symptoms of worsened end-organ perfusion or volume overload. In some embodiments, objective evidence of new or worsening HF comprises physical examination findings considered to be due to HF, imaging evidence of structural or functional cardiac disease consistent with a diagnosis of HF, laboratory evidence of new or worsening HF and/or invasive evidence of new or worsening HF. In some embodiments, the physical examination findings considered to be due to HF comprises at least one of the following findings: peripheral oedema; increasing abdominal distention or ascites (such as in the absence of primary hepatic disease); pulmonary rales/crackles/crepitations; increased jugular venous pressure and/or hepatojugular reflux; third heart sound (S3) gallop; and clinically significant or rapid weight gain related to fluid retention. In some embodiments, imaging evidence of structural or functional cardiac disease consistent with a diagnosis of HF comprises at least one of the following findings: left ventricular systolic dysfunction; left atrial enlargement; left ventricular diastolic dysfunction; increased pulmonary pressure; and left ventricular hypertrophy. In some embodiments, laboratory evidence of new or worsening HF comprises at least one of the following findings: increased B-type natriuretic peptide (BNP)/NT-proBNP concentrations; radiological, ultrasonographic, or implantable monitor evidence of pulmonary congestion; and non-invasive or implantable diagnostic evidence of clinically significant elevated left- or right-

sided ventricular filling pressure or low cardiac output. In some embodiments, invasive evidence of new or worsening HF comprises at least one of the following findings: right heart catheterization showing elevated pulmonary capillary wedge pressure (pulmonary artery occlusion pressure), elevated central venous pressure, and/or depressed cardiac index; and left heart catheterization showing elevated left ventricular end-diastolic pressure consistent with decompensation of HF. In some embodiments, the initiation or intensification of treatment specifically for HF comprises at least one of the following: initiation of oral administration of at least one new oral diuretic therapy, SGLT2i treatment, renin-angiotensin system inhibitor, angiotensin receptor neprilysin inhibitors, beta-blocker, MRA, ivabradine, digoxin, vericiguat or hydralazine/isosorbide dinitrate prescribed as a treatment for HF; augmentation in oral diuretic therapy (such as increasing, for example doubling, diuretic dose or initiation of combination diuretic therapy); initiation of intravenous administration of a diuretic; initiation of intravenous administration of a vasoactive agent (such as catecholamine, phosphodiesterase-3 inhibitor, or other vasopressor or vasodilator); mechanical or surgical intervention (such as mechanical circulatory support); and mechanical fluid removal (such as ultrafiltration, haemofiltration and haemodialysis).

[0097] In some embodiments, HF without hospitalisation is an urgent HF medical visit.

[0098] In some embodiments, an urgent HF medical visit is an emergency room visit for a new or worsening HF but does not require hospitalization. In some embodiments, an urgent HF medical visit is an urgent unscheduled visit to a physician's office for new or worsening HF.

[0099] In some embodiments, the HF event is HF hospitalisation or worsening HF event without hospitalization, as described in Abraham et al., *Eur J Heart Fail.*, 2020;22(12):2175-86.

[00100] In some embodiments, the HF event is HF hospitalisation or an urgent outpatient visit for HF, as described in Hicks et al., *Circulation*, 2018 137(9), 961-972.

[00101] In some embodiments, the methods described herein reduce the patient's risk of death. In some embodiments, the methods described herein reduce the patient's risk of death to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo (for example, resulting in a hazard ratio < 1).

[00102] The methods described herein may refer to a clinical outcome relative to treatment or methods wherein baxdrostat or a pharmaceutically acceptable salt thereof is

replaced with placebo. As an example of such a comparison, a clinical outcome from a method comprising administering baxdrostat and dapagliflozin would be compared to the clinical outcome obtained from an otherwise identical method comprising administering placebo and dapagliflozin. As a further example, a clinical outcome from a method comprising administering baxdrostat, dapagliflozin and a standard of care agent for CKD would be compared to the clinical outcome obtained from an otherwise identical method comprising administering placebo, dapagliflozin and the standard of care agent for CKD.

[00103] The methods described herein may refer to a reduction in the risk of a clinical event (such as CV death). In some embodiments, the reduction in the risk is measured as a reduction in the time to first occurrence of the clinical event. For example, a reduction in the risk of CV death may be measured as a reduction in the time to CV death. In some embodiments, the reduction in the time to first occurrence of the clinical event may be measured relative to the time to first occurrence of the clinical event in a treatment or method wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.

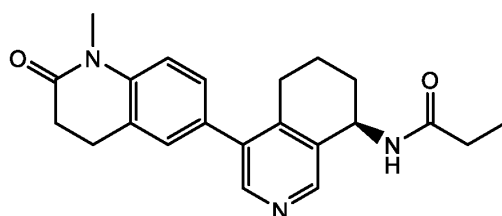
[00104] The methods described herein may refer to a reduction in the risk of a composite of clinical events (such as sustained eGFR decline of $\geq 50\%$ from baseline, reaching ESKD, or CV death). In some embodiments, the reduction in the risk is measured as a reduction in the time to first occurrence of one of the clinical events in the composite. For example, a reduction in the risk of sustained eGFR decline of $\geq 50\%$ from baseline, reaching ESKD, or CV death may be measured as a reduction in the time to the first to occur of sustained eGFR decline of $\geq 50\%$ from baseline, reaching ESKD, or CV death. In some embodiments, the reduction in the time to first occurrence of one of the clinical events in the composite may be measured relative to the time to first occurrence of one of the clinical events in the composite in a treatment or method wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.

[00105] In embodiments herein, a hazard ratio is used to indicate the risk reduction provided by the methods described herein. In some embodiments, the hazard ratio is < 1 . In some embodiments, the hazard ratio is ≤ 0.9 . In some embodiments, the hazard ratio is ≤ 0.85 . In some embodiments, the hazard ratio is ≤ 0.8 . In some embodiments, the hazard ratio is < 1 and the entirety of the 95% confidence interval (CI) of the hazard ratio is < 1 . In some embodiments, the hazard ratio is ≤ 0.9 and the entirety of the 95% CI of the hazard ratio is < 1 . In some embodiments, the hazard ratio is ≤ 0.85 and the entirety of the 95% CI of the

hazard ratio is < 1 . In some embodiments, the hazard ratio is ≤ 0.8 and the entirety of the 95% CI of the hazard ratio is < 1 .

[00106] Some embodiments described herein may refer to a change, such as a reduction, in a clinical outcome, or a change, such as a reduction, in a clinical outcome relative to other treatments or methods. In some embodiments, the change, such as a reduction, is clinically significant. In some embodiments, the change, such as a reduction, is statistically significant. In some embodiments, the change, such as a reduction, is statistically significant. In some embodiments, the change, such as a reduction, is clinically significant and statistically significant.

[00107] The chemical name of baxdrostat is N-[(8R)-4-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-5,6,7,8-tetrahydroisoquinolin-8-yl]propanamide, and the chemical structure of baxdrostat is:



[00108] Baxdrostat may be prepared by the methods disclosed in the International Patent Application published as WO2013/041591. The disclosure contemplates the use of pharmaceutically acceptable salts of baxdrostat in the methods described herein. “Pharmaceutically acceptable” refers to properties and/or substances that are acceptable to the patient from a pharmacological/toxicological vantage, and to the manufacturing pharmaceutical chemist from a physical/chemical vantage regarding composition, formulation, stability, patient acceptance, and bioavailability.

[00109] A pharmaceutically acceptable salt of baxdrostat includes salts with a pharmaceutically acceptable acid or base, *e.g.*, inorganic acids, *e.g.*, hydrochloric, sulfuric, phosphoric, diphosphoric, hydrobromic, hydroiodic, nitric, and phosphoric acid and organic acids, *i.e.*, adipic, citric, fumaric, maleic, malic, malonic, mandelic, ascorbic, oxalic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic, cyclohexylsulfamic (cyclamic), edisylate, glutaric, or p-toluenesulfonic acid. Pharmaceutically acceptable bases include alkali metal, *e.g.*, sodium or potassium, and alkali

earth metal, *e.g.*, calcium or magnesium, hydroxides, and organic bases, *e.g.*, alkyl amines, arylalkyl amines and heterocyclic amines.

[00110] In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof administered in the methods described herein is baxdrostat. In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof administered in the methods described herein is a pharmaceutically acceptable salt of baxdrostat.

[00111] In some embodiments, baxdrostat or pharmaceutically acceptable salt thereof is in a form suitable for oral administration. In some embodiments, the baxdrostat or pharmaceutically acceptable salt thereof is in the form of a tablet.

[00112] In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof is administered at a dosage of about 0.5 mg/day to about 4 mg/day. In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof is administered at a dosage of about 0.5 mg/day, about 1 mg/day or about 2 mg/day. In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof is administered at a dosage of about 1 mg/day or about 2 mg/day. In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof is administered at a dosage of about 1 mg/day. In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof is administered at a dosage of about 2 mg/day.

[00113] In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof is administered at a dosage of 0.5 mg/day to 4 mg/day. In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof is administered at a dosage of 0.5 mg/day, 1 mg/day or 2 mg/day. In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof is administered at a dosage of 1 mg/day or 2 mg/day. In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof is administered at a dosage of 1 mg/day. In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof is administered at a dosage of 2 mg/day.

[00114] In some embodiments, the dosage of baxdrostat or a pharmaceutically acceptable salt thereof is selected such that the patient does not exhibit hyperkalemia. In some embodiments, the dosage of baxdrostat or a pharmaceutically acceptable salt thereof is selected from about 0.5 mg/day, about 1 mg/day and about 2 mg/day such that the patient does not exhibit hyperkalemia. In some embodiments, the dosage of baxdrostat or a pharmaceutically acceptable salt thereof is selected from about 1 mg/day and about 2 mg/day such that the patient does not exhibit hyperkalemia.

[00115] In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof is administered initially at a dosage of about 1 mg/day and then up-titrated to about 2 mg/day. In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof is administered initially at a dosage of about 1 mg/day and then up-titrated to about 2 mg/day provided that the patient does not have hyperkalemia. In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof is administered initially at a dosage of about 1 mg/day and then up-titrated to about 2 mg/day provided that serum potassium is $\leq$ 4.8 mmol/L.

[00116] In some embodiments, the dosage of baxdrostat or a pharmaceutically acceptable salt thereof is down-titrated to about 1 mg/day if the patient has hyperkalemia. In some embodiments, the dosage of baxdrostat or a pharmaceutically acceptable salt thereof is down-titrated to about 1 mg/day if serum potassium is > 5.5 mmol/L.

[00117] Embodiments describing a mass of baxdrostat or a pharmaceutically acceptable salt thereof refer to the specified mass of baxdrostat or an equivalent molar amount of a pharmaceutically acceptable salt of baxdrostat. For example, 2 mg/day of a pharmaceutically acceptable salt of baxdrostat refers to the dosage of the pharmaceutically acceptable salt of baxdrostat required to deliver 2 mg/day of baxdrostat.

[00118] In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof is administered once daily. In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof is administered orally once daily.

[00119] In some embodiments, the SGLT2 inhibitor is chosen from those disclosed in U.S. Pat. No. 6,515,177, WO/2003/099836, U.S. PG Pub. No. 2006/0194809, U.S. PG Pub. No. 2006/0063722 A1, WO/2002/083066, U.S. PG Pub. No. 2003/0064935, U.S. Pat. No. 6,774,112, U.S. PG Pub. No. 2005/0209166, U.S. PG Pub. No. 2006/0074031, U.S. PG Pub. No. 2006/0035841, U.S. PG Pub. No. 2006/0009400, U.S. PG Pub. No. 2006/0025349, U.S. PG Pub. No. 2006/0122126, U.S. PG Pub. No. 2006/0019948, U.S. PG Pub. No. 2006/0194809, U.S. Pat. No. 6,908,905, U.S. Pat. No. 6,815,428, U.S. Pat. No. 6,555,519, U.S. Pat. No. 6,683,056, EP 598359 A1, JP 035988, U.S. Pat. No. 5,731,292, EP 0850948 A1, U.S. Pat. No. 6,048,842, JP 09188625 A, JP 09124685 A, JP 09124684, EP 773226 A1, U.S. Pat. No. 5,767,094, JP 08027006 A, EP 684254 A1, JP 10245391 (Dainippon), U.S. PG Pub. No. 2005/0233982 (Boehringer Ingelheim Corp.), U.S. PG Pub. No. 2005/0119192 (Kissei Pharmaceutical Co.), WO/2006/035796 (Kissei Pharmaceutical Co.), JP 2006/117651

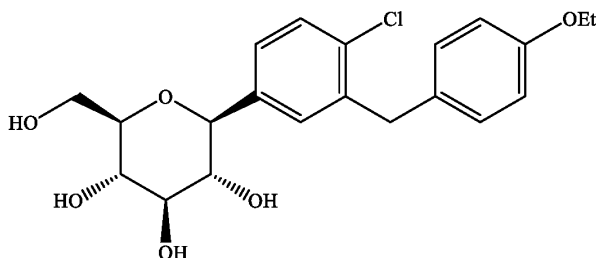
(Taisho Pharmaceutical Co.), JP 2004/4359630 (Yamanouchi Pharmaceutical Co.), WO/2006/080421 (Chugai Seiyaku Kabushiki Kaishi), U.S. PG Pub. No. 2005/0233988 (Tanabe Seiyaku Co.), WO/2005/012321 (Tanabe Seiyaku Co.), U.S. Pat. No. 7,015,201 (Ajinomoto Co.), WO 2006/058597 (Merck Patent GmbH), WO 2006/011469 (Chugai Seiyaku Kabushiki Kaisha), U.S. PG Pub. No. 2003/0195235 (Johnson & Johnson), and WO 2006/037537 (Boehringer Ingelheim).

[00120] In some embodiments, the SGLT2 inhibitor is chosen from those disclosed in Tsujihara, K. et al., Chem. Pharm. Bull., 44:1174-1180 (1996); Hongu, M. et al., Chem. Pharm. Bull., 46:22-33 (1998); Hongu, M. et al., Chem. Pharm. Bull., 46:1545-1555 (1998); and Oku, A. et al., Diabetes, 48:1794-1800 (1999).

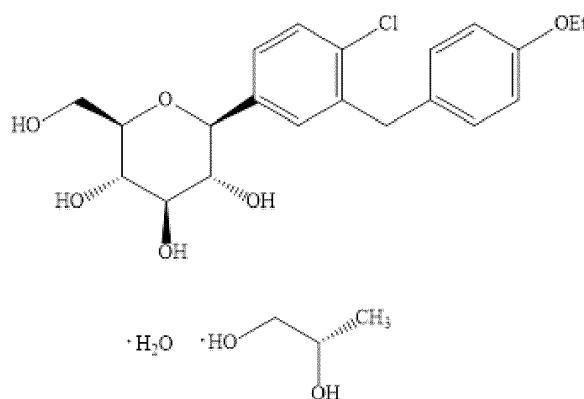
[00121] In some embodiments, the SGLT2 inhibitor may be dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, sotagliflozin, ipragliflozin, tofogliflozin, or luseogliflozin, or a pharmaceutically acceptable salt thereof.

[00122] In some embodiments, the SGLT2 inhibitor is dapagliflozin such as described in U.S. Patent Nos. 6,414,126 and 6,515,117, which are incorporated by reference in their entireties.

[00123] The chemical name of dapagliflozin is (1S)-1,5-anhydro-1-C-{4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl}-D-glucitol and the chemical structure of dapagliflozin is:



[00124] In some embodiments, dapagliflozin is in the form of a (S)-propylene glycol ((S)-PG) solvate, which has the structure:



[00125] Methods for preparing a (S)-PG solvate of dapagliflozin, including a crystalline (S)-PG solvate, are provided in U.S. Pat. No. 7,919,598.

[00126] In some embodiments, the SGLT2 inhibitor, such as dapagliflozin, is in a form suitable for oral administration. In some embodiments, the SGLT2 inhibitor, such as dapagliflozin, is in the form of a tablet.

[00127] In some embodiments, the dapagliflozin is administered at a dosage of about 10 mg/day. In some embodiments, the dapagliflozin is administered at a dosage of 10 mg/day.

[00128] In some embodiments, the dapagliflozin is administered once daily. In some embodiments, the dapagliflozin is administered orally once daily.

[00129] In some embodiments, about 0.5 mg, about 1 mg or about 2 mg of baxdrostat or a pharmaceutically acceptable salt thereof is administered to the patient once daily, and about 10 mg of dapagliflozin is administered to the patient once daily. In some embodiments, about 1 mg or about 2 mg of baxdrostat or a pharmaceutically acceptable salt thereof is administered to the patient once daily, and about 10 mg of dapagliflozin is administered to the patient once daily. In some embodiments, about 1 mg of baxdrostat or a pharmaceutically acceptable salt thereof is administered to the patient once daily, and about 10 mg of dapagliflozin is administered to the patient once daily. In some embodiments, about 2 mg of baxdrostat or a pharmaceutically acceptable salt thereof is administered to the patient once daily, and about 10 mg of dapagliflozin is administered to the patient once daily.

[00130] In some embodiments, about 0.5 mg, about 1 mg or about 2 mg of baxdrostat is administered to the patient once daily, and about 10 mg of dapagliflozin is administered to the patient once daily. In some embodiments, about 1 mg or about 2 mg of baxdrostat is administered to the patient once daily, and about 10 mg of dapagliflozin is

administered to the patient once daily. In some embodiments, about 1 mg of baxdrostat is administered to the patient once daily, and about 10 mg of dapagliflozin is administered to the patient once daily. In some embodiments, about 2 mg of baxdrostat is administered to the patient once daily, and about 10 mg of dapagliflozin is administered to the patient once daily.

[00131] In some embodiments, about 0.5 mg, about 1 mg or about 2 mg of baxdrostat in the form of a tablet is administered to the patient orally once daily, and about 10 mg of dapagliflozin in the form of a tablet is administered to the patient orally once daily. In some embodiments, about 1 mg or about 2 mg of baxdrostat in the form of a tablet is administered to the patient orally once daily, and about 10 mg of dapagliflozin in the form of a tablet is administered to the patient orally once daily. In some embodiments, about 1 mg of baxdrostat in the form of a tablet is administered to the patient orally once daily, and about 10 mg of dapagliflozin in the form of a tablet is administered to the patient orally once daily. In some embodiments, about 2 mg of baxdrostat in the form of a tablet is administered to the patient orally once daily, and about 10 mg of dapagliflozin in the form of a tablet is administered to the patient orally once daily.

[00132] In some embodiments, the baxdrostat or pharmaceutically acceptable salt thereof is administered before, after, or concurrently with the SGLT2 inhibitor. In some embodiments, the baxdrostat or pharmaceutically acceptable salt thereof is administered concurrently with the SGLT2 inhibitor.

[00133] In some embodiments, about 0.5 mg, about 1 mg or about 2 mg of baxdrostat in the form of a tablet is administered to the patient orally once daily, and about 10 mg of dapagliflozin in the form of a tablet is administered to the patient orally once daily, wherein the baxdrostat and dapagliflozin are administered concurrently. In some embodiments, about 1 mg or about 2 mg of baxdrostat in the form of a tablet is administered to the patient orally once daily, and about 10 mg of dapagliflozin in the form of a tablet is administered to the patient orally once daily, wherein the baxdrostat and dapagliflozin are administered concurrently. In some embodiments, about 1 mg of baxdrostat in the form of a tablet is administered to the patient orally once daily, and about 10 mg of dapagliflozin in the form of a tablet is administered to the patient orally once daily, wherein the baxdrostat and dapagliflozin are administered concurrently. In some embodiments, about 2 mg of baxdrostat in the form of a tablet is administered to the patient orally once daily, and about 10 mg of dapagliflozin in the form of a tablet is administered to the patient orally once daily, wherein the baxdrostat and dapagliflozin are administered concurrently.

[00134] In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof and the SGLT2 inhibitor, e.g., dapagliflozin, are administered with standard of care agents for CKD. Exemplary standard of care agents for CKD include angiotensin-converting enzyme inhibitors (ACEis or ACE inhibitors) and angiotensin receptor blockers (ARBs). Standard of care agents for CKD and their dosages are well-known to medical practitioners who examine and treat patients with CKD. Representative examples of ACE inhibitors include captopril, enalapril, and lisinopril. Representative examples of ARBs include valsartan, losartan, and irbesartan.

[00135] The standard of care agents for CKD, as described herein, may be used prior to and/or during administration of the combination comprising baxdrostat or a pharmaceutically acceptable salt thereof and the SGLT2 inhibitor, e.g., dapagliflozin. In some embodiments, the standard of care agents for CKD and the baxdrostat or a pharmaceutically acceptable salt thereof and the SGLT2 inhibitor, e.g., dapagliflozin, are administered together, at the same or at different times. In some embodiments, the patient is receiving a stable regimen of an ACE inhibitor or an ARB at the maximum tolerated daily dose. In some embodiments, an ACE inhibitor or an ARB, the baxdrostat or a pharmaceutically acceptable salt thereof and the SGLT2 inhibitor, e.g., dapagliflozin, are administered together, at the same or at different times.

[00136] In some embodiments, the patient has not received a mineralocorticoid receptor antagonist (MRA) (such as spironolactone, eplerenone, or finerenone) in the four weeks prior to the first administration of the combination. In some embodiments, the patient is not treated with a mineralocorticoid receptor antagonist (such as spironolactone, eplerenone, or finerenone) during treatment with the combination.

[00137] In some embodiments, the patient has not received a potassium-sparing diuretic (such as triamterene or amiloride) in the four weeks prior to first administration of the combination. In some embodiments, the patient is not treated with a potassium-sparing diuretic (such as triamterene or amiloride) during treatment with the combination.

[00138] In some embodiments, the patient has not received a potassium binder (such as sodium zirconium cyclosilicate, patiomer, or sodium polystyrene sulfonate) in the four weeks prior to first administration of the combination. In some embodiments, the patient is not treated with a potassium binder (such as sodium zirconium cyclosilicate, patiomer, or sodium polystyrene sulfonate) during treatment with the combination.

[00139] In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof and the SGLT2 inhibitor, e.g., dapagliflozin, are administered with a potassium binder (such as sodium zirconium cyclosilicate, patiomer, or sodium polystyrene sulfonate). In some embodiments, the baxdrostat or a pharmaceutically acceptable salt thereof and the SGLT2 inhibitor, e.g., dapagliflozin, are administered with a potassium binder (such as sodium zirconium cyclosilicate, patiomer, or sodium polystyrene sulfonate) if the patient develops hyperkalemia.

[00140] In some embodiments, there is provided baxdrostat or a pharmaceutically acceptable salt thereof for use in any of the methods described herein. In some embodiments, there is provided baxdrostat for use in any of the methods described herein.

[00141] In some embodiments, there is provided an SGLT2 inhibitor for use in any of the methods described herein. In some embodiments, there is provided dapagliflozin for use in any of the methods described herein. In some embodiments, there is provided (S)-PG solvate of dapagliflozin for use in any of the methods described herein.

[00142] In some embodiments, there is provided a combination comprising baxdrostat or a pharmaceutically acceptable salt thereof and an SGLT2 inhibitor for use in any of the methods described herein. In some embodiments, there is provided a combination comprising baxdrostat and dapagliflozin for use in any of the methods described herein. In some embodiments, there is provided a combination comprising baxdrostat and (S)-PG solvate of dapagliflozin for use in any of the methods described herein.

[00143] In some embodiments, there is provided the use of baxdrostat or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in any of the methods described herein. In some embodiments, there is provided the use of baxdrostat in the manufacture of a medicament for use in any of the methods described herein.

[00144] In some embodiments, there is provided the use of an SGLT2 inhibitor in the manufacture of a medicament for use in any of the methods described herein. In some embodiments, there is provided the use of dapagliflozin in the manufacture of a medicament for use in any of the methods described herein. In some embodiments, there is provided the use of (S)-PG solvate of dapagliflozin in the manufacture of a medicament for use in any of the methods described herein.

[00145] In some embodiments, there is provided the use of a combination comprising baxdrostat or a pharmaceutically acceptable salt thereof and an SGLT2 inhibitor in the manufacture of a medicament for use in any of the methods described herein. In some

embodiments, there is provided the use of a combination comprising baxdrostat and dapagliflozin in the manufacture of a medicament for use in any of the methods described herein. In some embodiments, there is provided the use of a combination comprising baxdrostat and (S)-PG solvate of dapagliflozin in the manufacture of a medicament for use in any of the methods described herein.

[00146] In some embodiments, there is provided a kit comprising: (a) baxdrostat or a pharmaceutically acceptable salt thereof and/or an SGLT2 inhibitor, and (b) instructions for use of the baxdrostat or a pharmaceutically acceptable salt thereof and/or an SGLT2 inhibitor in any of the methods described herein.

[00147] In some embodiments, there is provided a kit comprising: (a) baxdrostat and/or dapagliflozin, and (b) instructions for use of the baxdrostat and/or dapagliflozin in any of the methods described herein.

[00148] In some embodiments, there is provided a kit comprising: (a) baxdrostat and/or (S)-PG solvate of dapagliflozin, and (b) instructions for use of the baxdrostat and/or (S)-PG solvate of dapagliflozin in any of the methods described herein.

[00149] All documents cited herein are each entirely incorporated by reference herein, including all data, tables, figures, and text presented in the cited documents.

ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACE	Angiotensin converting enzyme
ACEI or ACEi	Angiotensin converting enzyme inhibitor
AE	Adverse event
AESI	Adverse event of special interest
ARB	Angiotensin receptor blocker
ASI	Aldosterone synthase inhibitor
AxMP	Auxiliary medicinal product
BMI	Body mass index
BP	Blood pressure
CI(s)	Confidence interval(s)
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology

Abbreviation	Definition
CV	Cardiovascular
DAE	Discontinuation of IP due to AE
DBP	Diastolic blood pressure
DKA	Diabetic ketoacidosis
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EoS	End of study
EoT	End of treatment
ESKD	End-stage kidney disease
FDA	Food and Drug Administration
HbA1c	Glycosylated hemoglobin
HF	Heart failure
HR	Hazard ratio
HTN	Hypertension
ICF	Informed consent form
IMP	Investigational Medicinal Product
IP	Investigational product
IRT	Interactive Response Technology
ITT	Intention to treat
kg	Kilogram
KFRT	Kidney failure with replacement therapy
L	Liter
LS mean	Least squares mean
MACE	CV death, HF events, MI, stroke
mEq	Milliequivalent
MI	Myocardial infarction
mITT	Modified Intent-to-Treat
mL	Milliliter
mmHg	Millimeters of mercury
mmol	Millimole
MMRM	Mixed-model for repeated measures

Abbreviation	Definition
µg	Microgram
MRA	Mineralocorticoid receptor antagonist
NIMP	Non-investigational medicinal product
ng	Nanogram
PACD	Primary analysis censoring date
PTDV	Premature treatment discontinuation Visit
QD	Once daily
R	Randomization
Q1	First quartile
Q3	Third quartile
QD	Quaque die (one per day)
QTcF	QT interval corrected using Fridericia's formula
RAAS	Renin-angiotensin-aldosterone system
RTSM	Randomization and Trial Supply Management
rHTN	Treatment-resistant hypertension
SAE	Serious adverse events
SBP	Systolic blood pressure
SCV	Study Closure Visit
SD	Standard deviation
SE	Standard error
SGLT2	Sodium-glucose cotransporter-2
SGLT2i	Sodium-glucose cotransporter-2 inhibitor
siSBP	Sitting SBP
siDBP	Sitting DBP
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TEAE(s)	Treatment-emergent adverse event(s)
UACR	Urinary albumin to creatinine ratio
UPCR	Urinary protein to creatinine ratio
ULN	Upper limit of normal
uHTN	Uncontrolled hypertension

Abbreviation	Definition
WOCBP	Women of child bearing potential

[00150] The following Examples are provided to illustrate some concepts described within this disclosure. While the Examples are considered to provide specific individual embodiments of formulations, methods of preparation and use, the Examples should not be considered to limit the more general embodiments described herein.

Study 1: Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

[00151] The BrighTN study was a Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension and is described in Freeman et al., N Engl J Med 2023; 388:395-405 (Clinicaltrials.gov ID: NCT04519658).

[00152] As shown in Figure 1, treatment with 2 mg/day baxdrostat showed a placebo-corrected reduction in UACR of >30% at the end of the study. Estimates based on geometric mean ratios (GMR) from ANCOVA based on log change adjusting for baseline (95% CI). Placebo: -2.8 (-20.5, 18.7); Baxdrostat 0.5 mg/day: -21.6 (-37.1, -2.3); Baxdrostat 1 mg/day: -19.9 (-35.2, -1.0); Baxdrostat 2 mg/day: -33.7 (-46.5, -17.9).

[00153] Overall 275 participants were randomized. Some participants had eGFR and UACR outside the normal range (see Levey AS, et al. Kidney Int 2005;67:2089–100) at baseline. Baseline eGFR and UACR (in the intention to treat population) are shown in the table below:

Baseline characteristic	Placebo (N=69)	Baxdrostat 0.5 mg/day (N=69)	Baxdrostat 1 mg/day (N=70)	Baxdrostat 2 mg/day (N=67)
Mean (SD) eGFR mL/min/1.73m²	85.5 (17.5)	81.0 (20.4)	83.2 (20.6)	85.2 (19.4)
eGFR <60 mL/min/1.73m ² n (%)	6 (8.7)	14 (20.3)	11 (15.7)	8 (11.9)
24-hour UACR, n	54	53	57	57
Geometric mean (logSD)	19.4 (1.5)	19.5 (1.6)	13.4 (1.2)	19.0 (1.5)
Median (25th/75th percentile), mg/g	14.5 (6.0, 43.0)	13.0 (7.0, 36.0)	9.0 (6.0, 26.0)	12.0 (7.0, 37.0)
≥30 mg/g, n (%)	18 (33.3)	14 (26.4)	12 (21.1)	16 (28.1)

[00154] All baxdrostat groups showed placebo-adjusted reductions in UACR from Day 0 to Day 85 (95% CI): Baxdrostat 0.5 mg/day: -19.3% (-40.1, 8.9); Baxdrostat 1 mg/day: -17.6% (-38.6, 1.1); Baxdrostat 2 mg/day: -31.8 (-49.2, -8.4).

[00155] Baxdrostat was well tolerated at all doses. Overall, there were six cases of hyperkalemia in the baxdrostat groups (0.5 mg/day, one; 1 mg/day, four; 2 mg/day, one), and none in the placebo group. One case of hyperkalemia in the baxdrostat 2 mg/day group was classified as serious (deemed by the investigator to be unrelated to baxdrostat).

Study 2: Study in Patients with Uncontrolled Hypertension and Chronic Kidney Disease

[00156] This study is a randomized, double-blind, placebo-controlled, multicenter, parallel group, dose-ranging study to evaluate baxdrostat for the treatment of patients with uHTN and CKD (Clinicaltrials.gov ID: NCT05432167). The primary objective of the study is to evaluate the treatment effect of baxdrostat on SBP compared to placebo at week 26. The secondary objectives are to evaluate the baxdrostat effect on SBP compared to placebo by high or low dosing strategy, to determine the percentage of patients achieving SBP <130 mmHg, to evaluate the change from baseline in urinary albumin-to-creatinine ratio (UACR), to evaluate the change from baseline in DBP with each dosing strategy and to evaluate the change from baseline in eGFR after 26 weeks of treatment. The safety objectives are to evaluate the vital signs, standing BP and heart rate, physical examinations, electrocardiography, weight measurement, and clinical laboratory evaluations, including standard safety chemistry panel, hematology, coagulation, and urinalysis. Approximately 300 patients are planned to be enrolled in 70 clinical sites in the U.S.

[00157] Male and female adult patients with uHTN and mild to severe CKD are to be recruited in the study. Patients with uHTN are defined as patients taking a stable dose of antihypertensive medication ACEI/ARB and have seated office SBP of ≥ 140 mmHg or ≥ 130 mmHg if diabetic. Patients with a mild-to-severe CKD are defined as having an eGFR (based on the CKD-EPI equation) of 25 to 75 mL/min/1.73 m². Patients taking an MRA must agree to cease dosing of the MRA to be eligible to start a 2-week run-in period in which patients will take once daily single-blind placebo tablets while continue the background antihypertensive medication. Patients who remain eligible are to be randomized to one of three treatment arms of placebo, low dose strategy and high dose strategy and start a 26-week treatment period.

[00158] Patients assigned to the low dose strategy arm are provided with baxdrostat 0.5 mg for once daily dosing. The dose level may be up-titrated to 1 mg at week 3 if a patient does not experience hyperkalemia, hyponatremia, or a significant decline in renal function based on laboratory testing of samples drawn at week 1 and if the average seated SBP is ≥ 130 mmHg at week 3. The dose may be down-titrated at 6 weeks after randomization if a patient experience hyperkalemia, hyponatremia, or declining renal function based on laboratory testing of sample drawn at week 5. No further dose titration is permitted after 6 weeks. The study design is illustrated in Figure 2.

[00159] Inclusion Criteria

Patients who meet all of the following criteria will be eligible to participate in the study:

- 1 Is an adult male or female patient ≥ 18 years of age.
- 2 Has a mean seated SBP ≥ 140 mmHg at Screening (Visit 1), Visit 2, and Visit 3.
Note: Patients with mean seated SBP ≥ 130 mmHg may be eligible if diabetic.
Note: Mean seated SBP is defined as the average of 3 seated SBP measurements at any single clinical site visit.
- 3 Has a prior diagnosis of mild-to-severe CKD, defined as eGFR (based on the CKD-EPI equation) of 25 to 75 mL/min/1.73 m², inclusive, at Visit 1.
Note: To ensure patients with moderate and severe renal impairment will be represented, the number of patients with an eGFR ≥ 60 and < 75 mL/min/1.73 m² will be capped at 45.
- 4 Has a UACR ≥ 100 mg/g (≥ 11.3 mg/mmol) in at least 2 out of 3 measurements based on first urine collected in the morning on consecutive days during the screening period.
- 5 Is currently taking an ACEi or ARB at the patient's maximum tolerated daily dose, based on investigator judgment, for > 4 weeks prior to Visit 1.
- 6 If taking a SGLT2 inhibitor at screening (Visit 1), the regimen must be stable for a period of at least 8 weeks before Visit 1 and be expected to remain at a stable dose over the study period.
Note: It is expected that patients not currently taking an SGLT2 inhibitor at screening (Visit 1) will not initiate this class of medication during the entire study period.
- 7 Is willing to be compliant with the contraception and reproductive restrictions of the study as follows:
 - Female patients of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) must have a documented negative pregnancy test at Visit 1 and the randomization visit (Visit 3); and must use a highly effective method of contraception (ie, $< 1\%$ failure rate) from Day 1 through 30 days after the last administration of study drug.
Note: Acceptable methods of contraception for female patients of childbearing potential enrolled in the study include the following:

- Surgical sterilization (tubal ligation)
 - Intrauterine device for at least 12 weeks before Visit 1
 - Hormonal contraception (oral, implant, injection, ring, or patch) for at least 12 weeks before Visit 1
 - Diaphragm used in combination with spermicide
 - Postmenopausal women must have not had menstrual bleeding for at least 1 year before initial dosing and either be > 60 years or have an elevated follicle-stimulating hormone (FSH) level > 40 mIU/mL at Visit 1.
- 8 Is able and willing to give informed consent for participation in the study.
 - 9 After the mandatory run-in period of 2 weeks, investigators must confirm the patient's BP and UACR measurements still meet the eligibility criteria.

[00160] Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

- 1 Have a documented diagnosis of type 1 diabetes.
- 2 Are not willing or not able to discontinue a mineralocorticoid receptor agonist (MRA) or a potassium-sparing diuretic as part of an existing antihypertensive regimen.
 Note: Patients taking an MRA or a potassium-sparing diuretic (eg, triamterene, amiloride, etc) as an antihypertensive agent must be willing to discontinue this agent for study eligibility. The potassium-sparing diuretic may be discontinued and replaced with a non-potassium-sparing diuretic. All patients who remain on a stable regimen of antihypertensive agents, including a non-potassium-sparing diuretic, for at least 6 weeks, will be eligible to enter the single-blind run-in. If the patient discontinues their prior MRA or potassium-sparing diuretic and/or initiates a new antihypertensive for study eligibility or has their antihypertensive dose adjusted after Visit 1, they should remain on a stable regimen of antihypertensive agents for at least 4 weeks and will have an extended screening period of up to 9 weeks from signing of informed consent to randomization (Visit 3).
- 3 Have a single occurrence of mean seated SBP > 180 mmHg or diastolic blood pressure (DBP) > 110 mmHg during the screening period (if such a BP is recorded during the screening period, the patient may attend an interim visit for an additional BP measurement and reassessment of inclusion/exclusion criteria).
 Note: Mean seated BP is defined as the average of 3 measurements obtained at any one clinical site visit. If the patient missed the regularly scheduled antihypertensive medication(s) prior to the visit (Visits 1 or 2), one BP retest is allowed ≥ 2 hours after taking the medication(s), on the following day, or later after reestablishing the regularly scheduled antihypertensive regimen.
- 4 Has a body mass index (BMI) > 50 kg/m² at Visit 1.
- 5 Has documented bilateral clinically relevant renal artery stenosis of $\geq 70\%$; if the imaging evidence is met, the patient should be excluded, since hypertension itself could

be considered 'clinically relevant'. Suspected or nondocumented renal artery stenosis is not excluded.

- 6 Has had dialysis for acute kidney injury/acute renal failure within 12 weeks prior to the screening period or has a planned dialysis or kidney transplantation during the course of the study.
- 7 Has known documented chronic heart failure New York Heart Association Class III or Class IV and/or hospitalization for heart failure within 6 months of Visit 1.
- 8 Has had a stroke, transient ischemic attack, hypertensive encephalopathy, acute coronary syndrome, or hospitalization for heart failure within 6 months of Visit 1.
- 9 Has known current severe left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy and/or severe aortic valvular disease diagnosed from a prior echocardiogram or another imaging study.
- 10 Has a planned coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) or any major surgical procedure during the study.
- 11 Has had PCI, CABG, other major cardiac surgery (eg, valve replacement), or peripheral arterial bypass surgery within 6 months of Visit 1.
- 12 Has had a prior solid organ transplant or cell transplant.
- 13 Is expected to receive or is receiving any of the exclusionary drugs such as strong inducers of cytochrome P450 (CYP)3A, chronic (medication is taken more than 3 times a week for more than 3 months) use of non-steroidal anti-inflammatory drugs, spironolactone/eplerenone, and/or chronic use of systemic steroids.
- 14 Has a known hypersensitivity to any of the following:
 - CIN-107 or drugs of the same class
 - Excipients in CIN-107 or drugs of the same classes
- 15 Has received immunotherapy for treatment of CKD within 6 months of Visit 1 or expects to receive immunotherapy for treatment of CKD during participation in the study.
- 16 Has any clinically relevant medical or surgical conditions including unstable conditions and/or conditions requiring regular transfusion or treatment with systemic immunosuppressants, including corticosteroids that, in the opinion of the investigator, would put the patient at risk by participating in the study.
- 17 Has evidence of any of the following at Visit 1 (1 retest is allowed):
 - White blood cell count $> 15 \times 10^9/L$ or absolute neutrophil count $< 1 \times 10^9/L$
 - Serum potassium < 3.5 mEq/L

Note: Patients with a serum potassium level below normal range may continue in the study without retest if the investigator elects to correct the serum potassium level with supplementation and offers to manage the condition.

 - Serum potassium > 5.0 mEq/L
 - Serum sodium < 135 mEq/L

- Serum aspartate aminotransferase or alanine aminotransferase $>3 \times$ upper limit of normal (ULN) or
 - Total bilirubin $> 2 \times$ ULN, unless due to Gilbert's syndrome
 - eGFR is < 25 or > 75 mL/min/1.73 m²
- 18 Has uncontrolled diabetes with glycosylated hemoglobin $> 10.5\%$ at Visit 1.
- 19 Is positive for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen, or hepatitis C virus (HCV) ribonucleic acid (RNA).
- 20 Has typical consumption of > 14 alcoholic drinks weekly.
Note: One drink of alcohol is equivalent to $\frac{1}{2}$ pint of beer (285 mL), one glass of spirits (25 mL), or one glass of wine (125 mL).
- 21 Has participated in another clinical study involving any investigational drug within 30 days prior to Visit 1, or plans to participate in another clinical study within 30 days of discontinuation of study drug.
- 22 Has received experimental therapy for disease intervention with a small molecule within 30 days of Visit 1 or 5 half-lives, whichever is longer, or received experimental therapy with a large molecule within 90 days of the Visit 1 or 5 half-lives, whichever is longer.
Note: Vaccinations, including those for coronavirus disease 2019 (COVID-19), will not be exclusionary.
- 23 Is pregnant, breastfeeding, or planning to become pregnant during the study.
- 24 Is considered by the investigator, after reviewing medical and psychiatric history, physical examination, and laboratory evaluations, to be unsuitable for any other reason that may either place the patient at increased risk during participation or interfere with the interpretation of the study outcomes. History of COVID-19 infection, in of itself, is not an exclusionary criterion unless the patient is subsequently considered unsuitable for the study based on criteria above.

Results

[00161] Baxdrostat low dosing strategy represents 0.5 mg/day or 1 mg/day (if tolerated). Baxdrostat high dosing strategy represents 2 mg/day or 4 mg/day (if tolerated).

[00162] Demographics and Baseline Characteristics (ITT Population):

Variable	Statistic	Low-dosing strategy group N = 65	High-dosing strategy group N = 64	Pooled treatment groups N = 129	Placebo N = 66	Total N = 195
Age (years)	n	65	64	129	66	195
	Mean	67.2	66.5	66.8	65.6	66.4
	SD	12.63	11.02	11.81	10.79	11.46
	Median	70.0	69.0	70.0	68.0	69.0
	Q1, Q3	59.0, 77.0	57.5, 75.0	58.0, 76.0	58.0, 74.0	58.0, 75.0

Variable	Statistic	Low-dosing strategy group N = 65	High-dosing strategy group N = 64	Pooled treatment groups N = 129	Placebo N = 66	Total N = 195
	Min, Max	29, 86	33, 84	29, 86	41, 91	29, 91
Sex						
Male	n (%)	42 (64.6)	43 (67.2)	85 (65.9)	47 (71.2)	132 (67.7)
Female	n (%)	23 (35.4)	21 (32.8)	44 (34.1)	19 (28.8)	63 (32.3)
BMI (kg/m ²)	n	65	64	129	66	195
	Mean	31.06	31.00	31.03	31.68	31.25
	SD	6.302	6.300	6.276	6.357	6.295
	Median	29.50	30.80	30.10	31.70	30.30
	Q1, Q3	26.90, 34.40	25.85, 35.05	26.60, 34.70	26.90, 36.80	26.60, 35.60
	Min, Max	19.4, 50.3	16.4, 44.8	16.4, 50.3	18.7, 44.9	16.4, 50.3
BMI (kg/m ²)						
< 30 kg/m ²	n (%)	34 (52.3)	29 (45.3)	63 (48.8)	29 (43.9)	92 (47.2)
≥ 30 kg/m ²	n (%)	31 (47.7)	35 (54.7)	66 (51.2)	37 (56.1)	103 (52.8)
Baseline SBP (mmHg)	n	65	64	129	66	195
	Mean	150.70	151.01	150.85	151.92	151.21
	SD	13.320	13.048	13.135	13.099	13.099
	Median	148.70	146.50	147.00	147.65	147.00
	Q1, Q3	141.30, 158.30	141.65, 162.20	141.30, 160.70	141.70, 162.70	141.30, 160.70
	Min, Max	127.7, 183.3	130.0, 178.7	127.7, 183.3	130.7, 183.3	127.7, 183.3
Baseline SBP category						
≤ 155 mmHg	n (%)	44 (67.7)	42 (65.6)	86 (66.7)	44 (66.7)	130 (66.7)
> 155 mmHg	n (%)	21 (32.3)	22 (34.4)	43 (33.3)	22 (33.3)	65 (33.3)
Baseline DBP (mmHg)	n	65	64	129	66	195
	Mean	80.77	80.78	80.78	81.65	81.07
	SD	9.507	9.930	9.681	11.095	10.161
	Median	82.00	81.35	81.70	81.85	81.70
	Q1, Q3	74.30, 85.00	74.85, 87.65	74.70, 86.70	73.00, 89.00	73.30, 87.30
	Min, Max	59.7, 105.7	53.0, 107.0	53.0, 107.0	62.7, 114.7	53.0, 114.7
Baseline eGFR (mL/min/1.73 m ²)	n	65	64	129	66	195
	Mean	45.5	43.9	44.7	43.7	44.4
	SD	14.48	13.71	14.07	14.92	14.33

Variable	Statistic	Low-dosing strategy group N = 65	High-dosing strategy group N = 64	Pooled treatment groups N = 129	Placebo N = 66	Total N = 195
	Median	43.0	43.0	43.0	42.0	43.0
	Q1, Q3	33.0, 56.0	33.0, 52.0	33.0, 54.0	29.0, 57.0	32.0, 54.0
	Min, Max	23, 80	20, 81	20, 81	17, 74	17, 81
Baseline eGFR category						
< 30 mL/min/1.73 m ²	n (%)	8 (12.3)	9 (14.1)	17 (13.2)	17 (25.8)	34 (17.4)
30 - < 45 mL/min/1.73 m ²	n (%)	28 (43.1)	24 (37.5)	52 (40.3)	18 (27.3)	70 (35.9)
45 - < 60 mL/min/1.73 m ²	n (%)	15 (23.1)	23 (35.9)	38 (29.5)	18 (27.3)	56 (28.7)
≥ 60 mL/min/1.73 m ²	n (%)	14 (21.5)	8 (12.5)	22 (17.1)	13 (19.7)	35 (17.9)
Baseline Potassium (mmol/L)	n	65	64	129	66	195
	Mean	4.37	4.39	4.38	4.30	4.35
	SD	0.439	0.476	0.456	0.427	0.447
	Median	4.40	4.40	4.40	4.30	4.40
	Q1, Q3	4.10, 4.70	4.10, 4.80	4.10, 4.70	3.90, 4.70	4.00, 4.70
	Min, Max	3.1, 5.3	3.3, 5.5	3.1, 5.5	3.4, 5.1	3.1, 5.5
Baseline Potassium category						
≤ 4.0 mmol/L	n (%)	11 (16.9)	9 (14.1)	20 (15.5)	17 (25.8)	37 (19.0)
> 4.0 - 4.5 mmol/L	n (%)	30 (46.2)	32 (50.0)	62 (48.1)	29 (43.9)	91 (46.7)
> 4.5 - 4.8 mmol/L	n (%)	15 (23.1)	14 (21.9)	29 (22.5)	12 (18.2)	41 (21.0)
> 4.8 mmol/L	n (%)	9 (13.8)	9 (14.1)	18 (14.0)	8 (12.1)	26 (13.3)
Serum aldosterone (ng/dL) ^a	n	63	63	126	63	189
	Mean	5.971	6.820	6.396	6.687	6.493
	SD	5.1524	5.8771	5.5210	6.2546	5.7608
	Median	4.690	5.370	4.985	4.900	4.900
	Q1, Q3	2.530, 7.570	2.490, 8.510	2.530, 8.000	2.980, 8.540	2.740, 8.120
	Min, Max	0.99, 23.60	0.99, 32.20	0.99, 32.20	0.99, 32.90	0.99, 32.90
Serum aldosterone category ^a						
< 6 ng/dL	n (%)	40 (61.5)	34 (53.1)	74 (57.4)	41 (62.1)	115 (59.0)
≥ 6 ng/dL	n (%)	23 (35.4)	29 (45.3)	52 (40.3)	22 (33.3)	74 (37.9)
UACR (mg/g)	n	65	64	129	66	195
	Mean	1291.446	1034.787	1164.111	1187.596	1172.060

Variable	Statistic	Low-dosing strategy group N = 65	High-dosing strategy group N = 64	Pooled treatment groups N = 129	Placebo N = 66	Total N = 195
	SD	1623.8153	1157.1676	1412.1053	1092.568 7	1309.8601
	Median	536.230	637.690	617.270	893.765	713.780
	Q1, Q3	283.030, 1593.490	293.160, 1174.655	283.030, 1397.830	340.600, 1428.910	306.840, 1428.910
	Min, Max	120.50, 7383.41	99.19, 5498.73	99.19, 7383.41	102.65, 5071.55	99.19, 7383.41
UACR category						
Normal	n (%)	0	0	0	0	0
Microalbuminuria	n (%)	18 (27.7)	16 (25.0)	34 (26.4)	12 (18.2)	46 (23.6)
Macroalbuminuria	n (%)	47 (72.3)	48 (75.0)	95 (73.6)	54 (81.8)	149 (76.4)
Type 2 diabetes						
Yes	n (%)	52 (80.0)	45 (70.3)	97 (75.2)	59 (89.4)	156 (80.0)
No	n (%)	13 (20.0)	19 (29.7)	32 (24.8)	7 (10.6)	39 (20.0)
Heart failure						
Yes	n (%)	1 (1.5)	2 (3.1)	3 (2.3)	3 (4.5)	6 (3.1)
No	n (%)	64 (98.5)	62 (96.9)	126 (97.7)	63 (95.5)	189 (96.9)
Use of ACEi/ARB						
ACEi only	n (%)	23 (35.4)	25 (39.1)	48 (37.2)	21 (31.8)	69 (35.4)
ARB only	n (%)	40 (61.5)	38 (59.4)	78 (60.5)	40 (60.6)	118 (60.5)
Both	n (%)	0	0	0	1 (1.5)	1 (0.5)
SGLT2 inhibitor use						
Yes	n (%)	21 (32.3)	21 (32.8)	42 (32.6)	22 (33.3)	64 (32.8)
No	n (%)	44 (67.7)	43 (67.2)	87 (67.4)	44 (66.7)	131 (67.2)
Baseline diuretics use						
Yes	n (%)	30 (46.2)	24 (37.5)	54 (41.9)	31 (47.0)	85 (43.6)
No	n (%)	35 (53.8)	40 (62.5)	75 (58.1)	35 (53.0)	110 (56.4)

^a Assume all sample collections in sitting position and reference ranges are Adult Reference Ranges: Upright 8:00-10:00 AM: ≤ 28 ng/dL, upright 4:00-6:00 PM: ≤ 21 ng/dL.

[00163] The median compliance was high for all study intervention groups (baxdrostat low-dosing strategy group: 87.1%; baxdrostat high-dosing strategy group: 87.8%, and placebo: 87.2%) with overall intake of $> 110\%$ for 11 participants, 80% to 100% for 95 participants, and $< 80\%$ for 61 participants.

Safety

[00164] Baxdrostat at low-dosing or high-dosing strategies in participants with uHTN and CKD was well tolerated and there were no new safety findings. The most commonly reported TEAE was hyperkalaemia, with a higher rate in baxdrostat low-dosing and high-dosing groups than in placebo group (30.8%, 46.0%, and 4.7%, respectively).

Efficacy

[00165] Baxdrostat was effective in lowering SBP in participants with uHTN and CKD. Treatment with baxdrostat (pooled treatment group) resulted in a reduction in mean seated SBP from baseline to Week 26 compared to placebo in the mITT population (-8.08 [95% CI: -13.36, -2.79] mmHg, $p = 0.003$).

[00166] The primary objective of the study to demonstrate that baxdrostat (pooled treatment group) is superior to placebo in mean change from baseline in seated SBP after 26 weeks of treatment in participants with uHTN and CKD was met.

[00167] Treatment with baxdrostat at low-dosing or high-dosing strategies resulted in a reduction in mean seated SBP from baseline to Week 26 compared to placebo in the mITT population (-8.99 [95% CI: -15.10, -2.87] mmHg, $p = 0.004$ and -7.22 [95% CI: -13.24, -1.19] mmHg, $p = 0.019$, respectively).

[00168] The secondary objective of the study to demonstrate that baxdrostat at high-dosing and low-dosing strategies is superior to placebo in mean change from baseline in seated SBP after 26 weeks of treatment was met.

[00169] These results were consistent across subgroups for SBP.

[00170] Thirty-eight (36.2%) participants in the baxdrostat pooled group (95% CI: 1.23, 7.23) achieved SBP < 130 mmHg by Week 26, with an odds ratio of 2.99 and p-value of 0.015 compared to 8 (16.7%) participants in placebo. For the baxdrostat low-dosing strategy group 21 (42.0%) participants (95% CI: 1.44, 10.15) achieved SBP < 130 mmHg by Week 26, with an odds ratio of 3.82 and p-value of 0.007. For the baxdrostat high-dosing strategy group 17 (30.9%) participants (95% CI: 0.88, 6.27) achieved SBP < 130 mmHg by Week 26, with an odds ratio of 2.35 and p-value of 0.088.

[00171] For participants in the baxdrostat pooled group the Week 26 mean (SD) DBP change from baseline was -5.64 (10.174) mmHg and mean (SD) DBP percentage change from baseline was -6.53 (12.533)%.

[00172] For participants in the baxdrostat low-dosing strategy group the Week 26 mean (SD) DBP change from baseline was -6.46 (11.412) mmHg and mean (SD) DBP percentage change from baseline was -7.59 (14.488)%. Participants in the baxdrostat high-dosing strategy group had a Week 26 mean (SD) DBP change from baseline of -4.89 (8.945) mmHg and mean (SD) DBP percentage change from baseline of -5.57 (10.492)%. The Week 26 mean (SD) DBP change from baseline for the placebo group was -0.99 (8.445) mmHg and mean (SD) DBP percentage change from baseline was -0.77 (10.417)%.

[00173] Treatment with baxdrostat resulted in a reduction in mean seated DBP from baseline to Week 26 compared to placebo in the mITT population. At Week 26, the MMRM adjusted LS mean difference (95% CI) between the baxdrostat pooled group and placebo was -4.84 (-7.92, -1.77) mmHg with a p-value of 0.002, for participants in the baxdrostat low-dosing strategy treatment group it was -5.04 (-8.60, -1.48) mmHg with a p-value of 0.006, and for participants in the baxdrostat high-dosing strategy treatment group it was -4.65 (-8.16, -1.14) mmHg with a p-value of 0.010.

[00174] The percentage change (95% CI) from baseline in UACR compared to placebo for participants in the baxdrostat pooled group at Week 26, was -55.17 (-67.41, -38.34)% with a p-value of < 0.001, for participants in the baxdrostat low-dosing strategy treatment group compared to placebo it was -52.02 (-66.84, -30.56)% with a p-value of 0.001, and for participants in the baxdrostat high-dosing strategy treatment group compared to placebo it was -57.97 (-70.83, -39.43)% with a p-value of < 0.001.

[00175] A 50% reduction in UACR from baseline to 6 months predicts a 48% relative risk reduction in clinical kidney endpoints (Heerspink et al., The Lancet Diabetes & Endocrinology, 2019, 7(2), 128-139).

[00176] The change (95% CI) from baseline in eGFR compared to placebo for participants in the baxdrostat pooled group at Week 26 (LS mean difference), was -2.3 (-5.06, 0.49) mL/min/1.73 m² with a p-value of 0.105, for participants in the baxdrostat low-dosing strategy treatment group it was -1.8 (-4.99, 1.43) mL/min/1.73 m² with a p-value of 0.275, and for participants in the baxdrostat high-dosing strategy treatment group it was -2.8 (-6.00, 0.35) mL/min/1.73 m² with a p-value of 0.080.

[00177] There was an indication of a larger effect on UACR in participants with higher plasma renin activity at baseline (-22.10 [95% CI: -54.00, 31.95]% for plasma renin activity < 1 ng/mL/hr, and -68.05 [95% CI: -78.30, -52.96]% for plasma renin activity ≥ 1 ng/mL/hr; interaction p-value = 0.008).

[00178] By baseline SGLT2i use, the percentage change (95% CI) from baseline in UACR compared to placebo for participants in the pooled baxdrostat group at Week 26, was -59.88 (-76.56, -31.33)% for participants with baseline SGLT2i use, and -52.32 (-67.97, -29.01)% for participants without baseline SGLT2i use (interaction p-value = 0.611).

Study 3: A Phase III, Randomised, Double Blind, Active-controlled Study to Assess the Efficacy, Safety and Tolerability of Baxdrostat in Combination with Dapagliflozin Compared with Dapagliflozin Alone on Chronic Kidney Disease (CKD) Progression in Participants with CKD and High Blood Pressure

[00179] A. Study Design

[00180] This is a Phase III, multicentre, randomised, double-blind, active-controlled, parallel group study (see Figure 3) to evaluate the effect of baxdrostat in combination with dapagliflozin versus dapagliflozin alone on eGFR change over time in participants with CKD and HTN.

[00181] Approximately 2500 participants will be randomised to study intervention. Participants ≥ 18 years of age with $\text{eGFR} \geq 30$ and $< 90 \text{ mL/min/1.73 m}^2$ with $\text{UACR} > 200$ and $< 5000 \text{ mg/g}$, $\text{SBP} \geq 130 \text{ mmHg}$, on stable and maximum tolerated daily dose of ACE inhibitor or ARB for at least 4 weeks prior to the Screening Visit, and serum potassium ≥ 3.5 and $\leq 4.8 \text{ mmol/L}$ ($\leq 4.5 \text{ mmol/L}$ for participants with $\text{eGFR} < 45 \text{ mL/min/1.73 m}^2$) at screening are eligible for participation.

[00182] Run-in period: After screening, participants treated with SGLT2i for at least 4 weeks may proceed to the randomisation visit. Participants who are not on SGLT2i at Visit 1 (ie, SGLT2i naïve participants) will receive a run-in intervention with dapagliflozin 10 mg QD (provided by the Sponsor) for at least 4-weeks prior to randomisation (see Figure 3). These participants will have a central laboratory creatinine assessment (at Visit 1.2) for eGFR calculation after 4-weeks dapagliflozin run-in and at least 72 h before Randomisation Visit (Visit 2).

[00183] Double blinded period: Participants with $\text{SBP} \geq 120 \text{ mmHg}$ at Visit 2 (randomisation) will be randomised in a 1:1 ratio to one of the 2 treatment arms:

- Baxdrostat/dapagliflozin (n = approx. 1250)
- Dapagliflozin (n = approx. 1250)

[00184] Participants on a stable dose of SGLT2i at Screening Visit 1, will take their last dose of the prescribed SGLT2i one day prior to randomisation (Day -1) and will switch to the study intervention according to their randomised assignment at Visit 2 (Day 1).

[00185] Site visits (for safety assessments, including blood pressure and potassium) will take place at 2, 4, 8, and 16 weeks following randomisation. Participants will then come to study site for visits every 4 months up to Visit 12 (EoT, at 731 ± 7 days (24 months) post-randomisation).

[00186] Participants randomised to the baxdrostat/dapagliflozin arm will initially receive a dose of baxdrostat 1 mg and dapagliflozin 10 mg. Participants randomised to the dapagliflozin arm will receive placebo matching baxdrostat 1 mg and dapagliflozin 10 mg. On Visit 3, 4 and 5, for participants that meet the up-titration criteria based on potassium, baxdrostat or matching placebo dose may be up-titrated to 2 mg (thus the participants may receive baxdrostat 2 mg/dapagliflozin 10 mg or 2 mg matching placebo/dapagliflozin 10 mg).

[00187] Open label period: After 24 months of double-blind treatment (EoT visit), participants will proceed to an open label treatment with 10 mg dapagliflozin (ie, participants who have been randomised to the baxdrostat/dapagliflozin arm will stop taking baxdrostat and participants randomised to dapagliflozin will stop taking placebo) until EoS visit (Day 787 ± 7), approximately 6 weeks later. The EoS visit consists of two separate visits, where the eGFR will be measured at 2 time points, at least 72 h apart. The purpose of this period is to collect eGFR data after baxdrostat has been discontinued to assess for irreversible disease progression independent of the anticipated haemodynamically mediated acute reduction in eGFR with treatment initiation.

[00188] In case of premature discontinuation of blinded study intervention, participants will continue in the study and receive open label dapagliflozin 10 mg monotherapy, unless the participant meets dapagliflozin specific discontinuation criteria, in which case all IMP will be discontinued and the participant will proceed to PTDV.

[00189] End-of-study Definition: For the purpose of Clinical Trial Transparency, the definition of the end of the study differs under FDA and EU regulatory requirements:

- The European Union requirements define study completion as the last visit of the last subject for any protocol related activity.
- The Food and Drug Administration requirements defines two completion dates:
 - Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome

measure, whether the clinical study concluded according to the prespecified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

- Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the prespecified protocol or is terminated.

[00190] A participant is considered to have completed the study if they have completed all phases of the study including the last scheduled procedure.

[00191] The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure for the last participant in the study globally, whichever occurs last.

[00192] B. Study Population

[00193] (i) Inclusion Criteria

[00194] Participants are eligible to be included in the study only if all the following criteria apply:

- 1 Participants of any sex and gender must be ≥ 18 years old at the time of signing the informed consent.
- 2 $\text{eGFR} \geq 30$ and $< 90 \text{ mL/min/1.73 m}^2$ at screening
- 3 Urine albumin creatinine ratio $> 200 \text{ mg/g}$ (22.6 mg/mmol) and $< 5000 \text{ mg/g}$ (565 mg/mmol) at screening
- 4 Participants with history of HTN and a SBP $\geq 130 \text{ mmHg}$ at screening and $\geq 120 \text{ mmHg}$ at the randomisation visit
- 5 Stable and maximum daily tolerated dose of an ACE inhibitor or an ARB (not both) for at least 4 weeks prior to Screening Visit
- 6 Central laboratory serum potassium must meet the following criteria at the Screening Visit, based on screening eGFR:
 - for participants with screening $\text{eGFR} \geq 45 \text{ mL/min/1.73 m}^2$, potassium must be ≥ 3.5 and $\leq 4.8 \text{ mmol/L}$ at the Screening Visit
 - for participants with screening $\text{eGFR} < 45 \text{ mL/min/1.73 m}^2$, potassium must be ≥ 3.5 and $\leq 4.5 \text{ mmol/L}$ at the Screening Visit

[00195] (ii) Exclusion Criteria

[00196] Participants are excluded from the study if any of the following criteria apply:

- 1 Systolic blood pressure > 180 mmHg, or diastolic BP > 110 mmHg at screening.
- 2 Known hyperkalaemia, defined as potassium of ≥ 5.5 mmol/L within 3 months at screening.
- 3 Serum sodium < 135 mmol/L at the Screening Visit, determined as per central laboratory.
- 4 Type 1 diabetes mellitus or uncontrolled Type 2 diabetes mellitus with HbA1c > 10.5% (> 91 mmol/mol) at Screening.
- 5 New York Heart Association functional HF class IV at screening.
- 6 Stroke, transient ischaemic cerebral attack, valve implantation or valve replacement, carotid surgery, or carotid angioplasty, acute coronary syndrome, or hospitalisation for worsening heart failure within previous 3 months prior to randomisation.
- 7 Optionally, baseline QTcF > 470 msec.
- 8 Optionally, family history of Long QT syndrome.
- 9 Known severe hepatic impairment, defined as Child-Pugh Class C, based on records that confirm documented medical history.
- 10 Documented history of adrenal insufficiency.
- 11 Any dialysis (including for acute kidney injury) within 3 months prior to Screening Visit.
- 12 Any acute kidney injury within 3 months prior to the Screening Visit.
- 13 Known hypersensitivity to the study treatment (active substance or excipients).
- 14 History of organ transplant or bone marrow transplant, or planned organ transplant within 6 months following randomisation (including kidney transplant).
- 15 History or ongoing allergy/hypersensitivity, as judged by the Investigator, to SGLT2 inhibitor (eg, empagliflozin) or ASI.
- 16 Any clinical condition requiring systemic immunosuppression therapy other than maintenance therapy (stable for at least 3 months prior to Visit 1).
- 17 Drug or alcohol abuse that in the Investigator's judgement makes the participant a poor candidate for the study.

18 Any use of mineralocorticoid receptor antagonists (such as spironolactone, eplerenone, or finerenone), potassium-sparing diuretics (such as triamterene or amiloride), or potassium binders (such as sodium zirconium cyclosilicate, patiromer, or sodium polystyrene sulfonate) within 4 weeks prior to screening.

19 Concomitant therapy with strong inducers of cytochrome P450 (CYP) 3 A (eg, apalutamide, avasimibe, carbamazepine, enzalutamide, lumacaftor, mitotane, phenytoin, rifampin, rifapentine, St. John's wort).

20 Optionally, drugs that prolong QT should be avoided, if possible, and if there are other alternatives which are next expected to prolong QT, these should be preferred. If such QT prolonging drugs are still needed, the Investigator must ensure appropriate monitoring of ECGs and electrolytes are performed, as per clinical judgement.

21 Any other condition or therapy, in the judgement of the Investigator or the Sponsor, which would make the participant unsuitable for this study, including a condition or therapy which the Investigator anticipates will not allow participation for the full planned study period (eg, active malignancy or other condition limiting life expectancy to less than 12 months).

22 Participation in another clinical study with an investigational product administered in the last 3 months prior to randomisation.

23 For WOCBP, positive pregnancy test at screening.

[00197] C. Study Intervention and Concomitant Therapy

[00198] (i) Study Intervention Administered

[00199] All the participants will receive baxdrostat and dapagliflozin, or placebo and dapagliflozin. To ensure blinding to treatment, the baxdrostat 1 mg, baxdrostat 2 mg and placebo to match baxdrostat tablets are identical in appearance (matching and indistinguishable). Study treatments to be administered and investigated in this study are described in the Table below:

Arm name	Baxdrostat/dapagliflozin		Dapagliflozin
Intervention name	Baxdrostat and dapagliflozin		Placebo and dapagliflozin.
Type	Drug		Placebo/Drug
Dose formulation	Baxdrostat tablet and dapagliflozin tablet		Placebo tablet (matching baxdrostat tablet) and dapagliflozin tablet
Unit dose strength(s)	Baxdrostat 1 mg and	Baxdrostat 2 mg and dapagliflozin 10 mg	Dapagliflozin 10 mg.

Arm name	Baxdrostat/dapagliflozin	Dapagliflozin
	dapagliflozin 10 mg	
Dosage level(s)	One tablet of baxdrostat and one tablet of dapagliflozin once daily	One placebo tablet matching baxdrostat and one tablet of dapagliflozin once daily
Route of administration	Oral	Oral
Regimen	One per day, preferably in the morning	One per day, preferably in the morning
Use	Experimental	Experimental
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by AstraZeneca	
Packaging and labelling	Baxdrostat/matching placebo will be provided in blister packs containing IMP tablets. Each blister pack will be labelled as required per country requirements. Dapagliflozin 10 mg tablets will be provided in bottles.	

[00200] All participants who meet all the eligibility criteria will be centrally assigned to randomised, blinded study intervention using an automated IRT/RTSM that will allocate participants 1:1 into one of the 2 different treatment arms (ie, either baxdrostat/dapagliflozin or dapagliflozin arm).

[00201] The number of randomised participants with UACR > 200 to < 500 mg/g and the number of participants with eGFR ≥ 30 to < 45 mL/min/1.73 m², shown with laboratory tests at enrolment (Visit 1), will be monitored and randomisation in IxRS will be capped to ensure that the number of participants in each subpopulation does not exceed approximately 20%.

[00202] (ii) Dose Modification

[00203] If at any timepoint during study treatment, blood potassium is elevated to > 5.5 mmol/L, baxdrostat/matching placebo should be temporary discontinued, see details below. All participants will start with the lower dose (1 mg) of baxdrostat, or matching placebo, and the Investigator may up-titrate to the targeted dose (2 mg).

[00204] Up-titration: Up-titration to 2 mg should be performed at Visit 3, 4, or 5 provided that the potassium concentration (local laboratory value) is ≤ 4.8 mmol/L. Once the above local laboratory parameters are confirmed, up-titration will happen within 7 days and preferably as soon as possible. Note: participants who experience potassium > 5.5 mmol/L or sodium < 130 mmol/L at any point during the study, should not be up-titrated and should remain on the 1 mg dose.

[00205] Down-titration: For participants previously up-titrated, down-titration can be considered at any point throughout the trial, for example based on potassium, systolic

blood pressure, or sodium or for other safety or tolerability concerns. These decisions should be reviewed with the medical monitor when possible. Following down-titration, an unscheduled safety visit may be performed within 2 weeks, at the Investigator's discretion. Participants who are down-titrated from 2 mg to 1 mg during the trial, should remain on 1 mg for the rest of the study.

[00206] (iii) Potassium Monitoring Measurements

[00207] Hyperkalaemia is a frequent event in subjects with CKD and one of the main risks identified from previous studies with baxdrostat. Therefore, serum potassium levels will be monitored systemically throughout the study. Instructions for management of serum potassium measurements are described below:

[00208] Serum potassium ≤ 4.8 mmol/L:

[00209] If participant is on 1 mg baxdrostat, up-titrate to 2 mg.

[00210] If participant is on 2 mg baxdrostat, continue at the same dose.

[00211] Serum potassium 4.9 to 5.5 mmol/L: continue on the same dose.

[00212] Serum potassium > 5.5 mmol/L: withhold baxdrostat and re-check potassium within 72 hours. If subsequent sample is ≤ 5.0 mmol/L, optionally ≤ 4.8 mmol/L, re-start baxdrostat at 1 mg. Serum potassium should be re-checked within 2 weeks (+/- 7 days) in an unscheduled visit. NOTE: participants who experienced serum potassium > 5.5 mmol/L should not be up-titrated during the course of the study.

[00213] If subsequent sample is > 5.0 mmol/L, optionally > 4.8 mmol/L: continue to withhold baxdrostat; continue to monitor serum potassium and restart baxdrostat at 1 mg when potassium is ≤ 5.0 mmol/L, optionally ≤ 4.8 mmol/L. Serum potassium should be re-checked within 2 weeks (+/- 7 days) in an unscheduled visit. NOTE: participants who experienced serum potassium > 5.5 mmol/L should not be up-titrated during the course of the study.

[00214] (iv) Prohibited Concomitant Medications

[00215] The medications and supplements listed below are prohibited during this study.

- Potassium-sparing diuretics (eg, amiloride, triamterene) and direct renin inhibitor (eg, Aliskiren).
- Mineralocorticoid receptor antagonists or aldosterone antagonists (eg, eplerenone, finerenone, spironolactone) or aldosterone synthetase inhibitors.

- Strong CYP3A4 inducers (eg, apalutamide, avasimibe, carbamazepine, enzalutamide, lumacaftor, mitotane, phenytoin, rifampin, rifapentine, St. John's wort).
- Concomitant treatment with open label SGLT2 inhibitors.
- Treatment with potassium supplements are not prohibited but should only be prescribed to individuals for whom the Investigator considers these agents to be required to avoid hypokalaemia.

[00216] C. Objectives/Endpoints

Objectives	Endpoints
Primary	
To determine whether baxdrostat/dapagliflozin is superior to dapagliflozin alone to slow CKD progression, assessed as the effect on change in eGFR	Change from baseline in eGFR to post treatment at 2 years.
Secondary	
To determine whether baxdrostat/dapagliflozin is superior to dapagliflozin alone at reducing UACR.	Change from baseline in UACR at 16 weeks.
To determine whether baxdrostat/dapagliflozin is superior to dapagliflozin alone at reducing SBP.	Change from baseline in mean SBP at 16 weeks.
To determine whether baxdrostat/dapagliflozin compared with dapagliflozin alone slows CKD progression and reduces the risk of ESKD.	Kidney hierarchical composite endpoint ^a
To determine whether baxdrostat/dapagliflozin compared with dapagliflozin alone slows the rate of kidney function decline after the haemodynamically-mediated acute effect on eGFR.	Change in eGFR from 8 weeks following randomisation to end of treatment
To determine whether baxdrostat/dapagliflozin is superior to dapagliflozin alone in reducing the risk of MACE	Time to the first occurrence of any of the components of the composite of: 1 CV death 2 HF with and without hospitalisation 3 MI 4 Stroke
Safety	
To assess the safety and tolerability of baxdrostat/dapagliflozin compared with dapagliflozin alone	Safety and tolerability will be evaluated in terms of the following endpoints: • Occurrence and time to first occurrence of AEs, SAEs, SAEs with outcome death, DAEs, possibly related AE as assessed by Investigator. • Observed values, change from baseline and time to first treatment emergent abnormality in laboratory parameters. • Observed values, change from baseline and time to first treatment emergent abnormality in vital signs, ECG.

Objectives	Endpoints
	Occurrence and time to first occurrence of AESIs: hyperkalaemia, hyponatraemia, and hypotension events that require medical intervention.
Exploratory	
To characterise the plasma exposure of baxdrostat and dapagliflozin.	Plasma concentrations of baxdrostat and dapagliflozin.

^a The hierarchical composite endpoint is defined as the most severe outcome of a participant according to the following severity of outcomes - death, KFRT (chronic dialysis or kidney transplant as defined in the Clinical Event Adjudication charter), sustained GFR < 15 mL/min/1.73 m²; sustained GFR decline from baseline of ≥ 57%; ≥ 50%; or individual change from baseline to post-treatment eGFR at 24 months if none of the outcomes occurred.

[00217] Participant eGFR for the determination of eligibility, assessment for titration eligibility and assessment of the primary and applicable key secondary endpoints will be calculated according to the CKD-EPI 2021 equation, based on serum creatinine concentration alone (Inker et al. N Engl J Med. 2021;385(19):1737-49)

[00218] The UACR is calculated as follows:

UACR(mg/g = urine albumin [mg/dL]/urine creatinine [g/dL])

[00219] The potential HF events (with and without hospitalisation) are defined as either HF event with and without hospitalisation in accordance with the HF Academic Research Consortium (Abraham et al., Eur J Heart Fail., 2020;22(12):2175-86).

[00220] Primary estimand definition

[00221] The estimand is described by the following attributes:

[00222] Population: Participants with CKD and HTN as defined by the inclusion and exclusion criteria.

[00223] Endpoint: Change from baseline in eGFR.

[00224] Treatment condition: The investigational interventions (randomisation to baxdrostat/dapagliflozin or dapagliflozin) regardless of discontinuation for any reason, with or without change in background medication (treatment policy strategy).

[00225] Remaining intercurrent events:

[00226] • KFRT or renal death: Composite strategy, implemented by analysing eGFR as a value 0-10 mL/min/1.73 m² after the event has occurred

[00227] • Non renal death: Hypothetical strategy, implemented by handling eGFR after the event in the framework for missing data.

[00228] **Population level summary measure:** Difference between treatment groups in mean change from baseline to post-treatment at 2 years (approximately 6 weeks post-EoT), expressed as the average change per year.

Study 4: A Phase III, Randomised, Double-blind, Placebo-controlled, Event-driven Study to Assess the Efficacy, Safety and Tolerability of Baxdrostat in Combination with Dapagliflozin Compared with Dapagliflozin Alone on Renal Outcomes and Cardiovascular Mortality in Participants with Chronic Kidney Disease and High Blood Pressure

[00229] A. Study Design

[00230] This is a Phase III, multicentre, randomised, double-blind, placebo-controlled, event-driven study to evaluate whether baxdrostat/dapagliflozin is superior to placebo/dapagliflozin, when added to standard of care, in reducing the risk of renal composite events (50% sustained decline in eGFR, kidney failure, or CV death) in participants with CKD and HTN. Approximately 5000 participants will be randomised to study intervention in this study. The study design is illustrated in Figure 4.

[00231] The purpose of this study is to investigate the efficacy, safety, and tolerability of baxdrostat in combination with dapagliflozin, compared with placebo and dapagliflozin, in reducing the (risk of) the composite of > 50% decline in eGFR, kidney failure, or CV death, in individuals with CKD and HTN.

[00232] This study consists of a 4-week dapagliflozin Run-in Period for participants untreated with SGLT2i at screening, and a double-blinded period where participants will receive either baxdrostat/dapagliflozin or placebo/dapagliflozin.

[00233] Site visits will take place at 2-, 4-, 8-, 16-, 34, and 52-weeks following randomisation. Thereafter visits will occur approximately every 4 months.

[00234] The study closure procedures will be initiated when the predetermined number of primary endpoint events is predicted to have occurred (N = 845) ie, the PACD. All randomised participants including any participants who have prematurely discontinued study intervention will be scheduled for a SCV within 6 weeks of the PACD.

[00235] In case of premature discontinuation of blinded study intervention, participants will continue in the study and receive dapagliflozin 10 mg, unless the participant meets dapagliflozin specific discontinuation criteria. If study intervention is temporarily or permanently discontinued, the participant should remain in the study, and it is important that

the scheduled study visits (including the PTDV for participants with permanent discontinuation of study intervention) and data collection continue according to the study protocol until the SCV.

Eligible participants will be ≥ 18 years of age with CKD and HTN. Specific inclusion criteria include $\text{eGFR} \geq 30$ and ≤ 75 mL/min/1.73 m², $\text{UACR} \geq 30$ and ≤ 5000 mg/g, $\text{SBP} \geq 130$ mmHg (the most recent value within 4 weeks of screening or at the Screening Visit) and ≥ 120 mmHg at randomisation, on stable and maximum tolerated daily dose of ACEi or ARB for at least 4 weeks prior to the Screening Visit, and potassium ≥ 3.0 and ≤ 4.8 mmol/L (≤ 4.5 mmol/L for participants with $\text{eGFR} < 45$ mL/min/1.73 m²). Results for eGFR, potassium, and sodium used for assessing inclusion/exclusion criteria should be obtained on the same day, should be the most recent values within 4 weeks of screening or at the Screening Visit, and should be either all local or all central laboratory values.

[00236] Where allowed by local regulations, the study will include an optional Pre-screening Period, where participants will be assessed for at least one of the following parameters: eGFR, UACR, potassium, sodium, HbA1c, and BP. This is intended to facilitate sites' identification of participants who could be considered to enter the full screening assessments as described in the SoA. All participants who participate in the optional Pre-screening Period will be required to sign an additional pre-screening ICF.

[00237] All consented participants (after signature of the ICF) will be screened during an up to 2-week Screening Period. Participants who are untreated with SGLT2i (or treated for less than 4 weeks) at the time of the Screening Period will complete a Run-in Period with dapagliflozin for at least 4-weeks (and not more than 6 weeks) after the Screening Period and prior to randomisation. Participants who fulfil the screening eligibility criteria and have been on SGLT2i (regardless of SGLT2i prior dose) for at least 4 weeks before screening may proceed to the Randomisation Visit.

[00238] Eligible participants with $\text{SBP} \geq 120$ mmHg at Visit 2 (randomisation) will be randomised in a 1:1 ratio to one of the 2 intervention groups:

- Baxdrostat 1 mg and dapagliflozin 10 mg (n = approximately 2500)
- Placebo matching baxdrostat 1 mg and dapagliflozin 10 mg (n = approximately 2500)

[00239] Participants randomised to the baxdrostat/dapagliflozin arm will initially receive a dose of baxdrostat 1 mg and dapagliflozin 10 mg. Participants randomised to the placebo/dapagliflozin arm will receive placebo matching baxdrostat 1 mg and dapagliflozin

10 mg. On Visit 5, for participants that meet the up-titration criteria based on local laboratory potassium levels measured from Visits 3, 4, and 5, baxdrostat or matching placebo could be up-titrated to 2 mg (thus the participants may receive baxdrostat 2 mg/dapagliflozin 10 mg or 2 mg matching placebo/dapagliflozin 10 mg).

[00240] Study visits are scheduled as follows: Visit 1 (Screening/Enrolment); Visit 2 (Randomisation, Day 1); Visit 3 (Day 15 ± 3 days); Visit 4 (Day 29 ± 3 days); Visit 5 (Day 57 ± 3 days); Visit 6 (Day 113 ± 7 days); Visit 7 (Day 240 ± 14 days); Visits 8 onwards (Day 365 and every 4 months ± 14 days).

[00241] The anticipated total study duration is approximately 3.5 years for any study participant, with an expected maximum duration of up to 5 years for the participants who joined early, dependent on randomisation rate and event rate. The participants in the study may be in the study shorter or longer depending on when the participant enters the study. The study duration may change if the event rate or randomisation rate is different than anticipated.

Statistical methods

[00242] Primary analysis: The primary endpoint of the study is the time to first occurrence of any component of the composite endpoint of: $\geq 50\%$ sustained decline in eGFR, kidney failure, and CV death. The main estimator for the primary endpoint is a Cox proportional hazards model for time to first event with a factor for treatment group and adjusting for covariates baseline eGFR, baseline UACR, SGLT2i use at screening, and baseline T2DM status. Study dropouts and other missing data will not be imputed. The HR, 95% CI, and p-value comparing the treatment groups will be presented.

[00243] Multiple testing procedure: Formal hypothesis testing of the treatment effect of baxdrostat/dapagliflozin versus placebo/dapagliflozin will be made for the primary and secondary efficacy endpoints with an overall one-sided Type I error control of 2.5%. To preserve the family-wise error rate, a prespecified hierarchical ordering of primary and secondary endpoints will be applied for the confirmatory test procedure assessing statistical significance.

[00244] Sample size: Approximately 5000 participants will be randomised to study intervention. Assuming a true HR of 0.80 for the primary endpoint between treatment groups, 845 events in total will provide 90% power for the primary test at a one-sided $\alpha = 0.025$. The event rate is assumed to be gradually increasing as characterised with a Weibull hazard with scale parameter 0.029 and shape parameter 1.578 in the placebo/dapagliflozin treatment

group. A total sample size of 5000 participants is estimated to provide the required number of events in an average follow-up of approximately 41 months.

Objectives/Endpoints

Objectives	Endpoints
Primary	
To determine whether baxdrostat/dapagliflozin is superior to placebo/dapagliflozin in reducing the risk of the composite endpoint of $\geq 50\%$ sustained decline in eGFR, kidney failure, or CV death.	Time to the first occurrence of any of the components of the composite of: $\geq 50\%$ sustained decline in eGFR - Onset of kidney failure: - Sustained eGFR < 15 mL/min/1.73 m² or - Chronic dialysis treatment or - Receiving a kidney transplant or - Death with a renal primary cause (death due to kidney failure when dialysis is not given) - CV death
Secondary	
To determine whether baxdrostat/dapagliflozin is superior to placebo/dapagliflozin in reducing UACR.	Change from baseline in UACR at 16 weeks
To determine whether baxdrostat/dapagliflozin is superior to placebo/dapagliflozin in reducing SBP.	Change from baseline in mean SBP at 16 weeks
To determine whether baxdrostat/dapagliflozin is superior to placebo/dapagliflozin in reducing the risk of MACE (CV death, HF events, MI, stroke).	Time to the first occurrence of any of the components of the composite of: - CV death - HF with and without hospitalisation - MI - Stroke
To determine whether baxdrostat/dapagliflozin is superior to placebo/dapagliflozin in reducing the risk of CV death.	Time to CV death
To determine whether baxdrostat/dapagliflozin is superior to placebo/dapagliflozin in reducing the risk of all-cause death.	Time to death
Safety	
To assess the safety and tolerability of baxdrostat/dapagliflozin compared with placebo/dapagliflozin.	Safety and tolerability will be evaluated in terms of the following endpoints: - Occurrence and time to first occurrence of AEs, SAEs, SAEs with outcome death, DAEs, possibly related AEs as assessed by Investigator. - Observed values, change from baseline and time to first treatment-emergent abnormality in laboratory parameters. - Observed values, change from baseline and time to first treatment-emergent abnormality in

	- vital signs, ECG. - Occurrence and time to first occurrence of AESIs: hyperkalaemia, hyponatraemia, and hypotension events that require medical intervention.
Exploratory	
To determine whether baxdrostat/dapagliflozin is superior to placebo/dapagliflozin in reducing the risk of the composite endpoint of $\geq 50\%$ sustained decline in eGFR or kidney failure.	Time to the first occurrence of any of the components of the composite of: $\geq 50\%$ sustained decline in eGFR - Onset of kidney failure: - Sustained eGFR < 15 mL/min/1.73 m² or - Chronic dialysis treatment or - Receiving a kidney transplant or - Death with a renal primary cause (death due to kidney failure when dialysis is not given)
To determine whether baxdrostat/dapagliflozin is superior to placebo/dapagliflozin in reducing SBP	Change from baseline in mean SBP over time from baseline to Week 52.
To explore whether baxdrostat/dapagliflozin compared with placebo/dapagliflozin has an effect on the risk of the composite endpoint of HF events or CV death.	Time to first occurrence of any of the components of the composite of: - CV death - HF with and without hospitalisation
To explore whether baxdrostat/dapagliflozin compared with placebo/dapagliflozin has an effect on the rate of the composite endpoint of HF events or CV death.	Time to each occurrence (first and recurrent) of the components of the composite of: - CV death - HF with and without hospitalisation
To explore whether baxdrostat/dapagliflozin compared with placebo/dapagliflozin has an effect on the rate hospitalisation for HF.	Time to each occurrence (first and recurrent) of HF hospitalisation.
To determine whether baxdrostat/dapagliflozin compared with placebo/dapagliflozin slows the rate of kidney function decline after the haemodynamically-mediated acute effect on eGFR.	Change in eGFR from 8 weeks following randomisation to end of treatment.

Note: baxdrostat/dapagliflozin = baxdrostat in combination with dapagliflozin; placebo/dapagliflozin = placebo in combination with dapagliflozin.

[00245] Participant eGFR for the determination of eligibility, and assessment of the primary and applicable endpoints will be calculated according to the CKD-EPI 2021 equation, based on serum creatinine, age, and sex (Inker et al. N Engl J Med. 2021;385(19):1737-49).

[00246] The UACR is calculated as follows:

[00247] $\text{UACR}(\text{mg/g}) = \text{urine albumin} [\text{mg/dL}] / \text{urine creatinine} [\text{g/dL}]$.

[00248] The potential HF events (with and without hospitalisation) are defined as either HF event with and without hospitalisation in accordance with the HF Academic Research Consortium (Abraham et al., Eur J Heart Fail., 2020;22(12):2175-86).

[00249] Primary Estimand Definition: The estimand is described by the following attributes:

- **Population:** Patients with CKD and HTN as defined by the inclusion and exclusion criteria
- **Variable:** Time to first event in the composite of $\geq 50\%$ sustained decline in eGFR, kidney failure (defined as any of: sustained eGFR < 15 mL/min/1.73 m², chronic dialysis treatment, receiving a kidney transplant, or death with a renal primary cause [death due to kidney failure when dialysis is not given]), and CV death.
- **Treatment:** Baxdrostat/dapagliflozin or placebo/dapagliflozin regardless of discontinuation of investigational intervention (treatment policy strategy), and irrespective of initiation or change in concomitant medications (treatment policy strategy).

[00250] Intercurrent Event Strategies:

- Non-CV death will be handled using a hypothetical strategy, by assuming participants cannot die from non-CV death, implemented by censoring at time of death and not imputing data after death.

[00251] Population Level Summary for the Variable:

- HR between treatment groups.

[00252] All efforts will be made so that, to the extent possible, randomised participants are followed up and data collected regardless of study intervention compliance and use of concomitant medications.

[00253] B. Study Population

[00254] (i) Inclusion Criteria

[00255] Participants are eligible to be included in the study only if all the following criteria apply:

1 Participants of any sex and gender must be ≥ 18 years old at the time of signing the informed consent.

2 Participants with

- (a) eGFR ≥ 30 and < 60 mL/min/1.73 m² (local or central laboratory values), AND UACR ≥ 30 mg/g (3.39 mg/mmol) and < 500 mg/g (56.5 mg/mmol) (central laboratory values only), or

- (b) $\text{eGFR} \geq 30$ and ≤ 75 mL/min/1.73 m² (local or central laboratory values), AND
 $\text{UACR} \geq 500$ mg/g (56.5 mg/mmol) and ≤ 5000 mg/g (565 mg/mmol) or $\text{UPCR} \geq 700$ mg/g (79 mg/mmol) and ≤ 7000 mg/g (790 mg/mmol) (local or central laboratory values).

3 Participants with history of HTN and a SBP ≥ 130 mmHg (the most recent value within 4 weeks of screening or at the Screening Visit) and ≥ 120 mmHg at the Randomisation Visit.

4 Stable and maximum tolerated dose of an ACEi or an ARB (not both) for at least 4 weeks prior to Screening Visit.

5 Participants with:

- (a) Serum or plasma potassium ≥ 3.0 and ≤ 4.8 mmol/L if $\text{eGFR} \geq 45$ mL/min/1.73 m² (local or central laboratory values), or
 (b) Serum or plasma potassium ≥ 3.0 and ≤ 4.5 mmol/L if $\text{eGFR} < 45$ mL/min/1.73 m² (local or central laboratory values).

5 Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

[00256] Results for eGFR, potassium, and sodium used for assessing inclusion/exclusion criteria should be obtained on the same day, should be the most recent values within 4 weeks of screening or at the Screening Visit, and should be either all local or all central laboratory values.

[00257] (ii) Exclusion Criteria

[00258] Participants are excluded from the study if any of the following criteria apply:

- 1 Systolic blood pressure > 180 mmHg, or diastolic BP > 110 mmHg at screening.
- 2 Known hyperkalaemia, defined as potassium of ≥ 5.5 mmol/L within 3 months prior to screening.
- 3 Serum sodium < 135 mmol/L (central or local laboratory values obtained within 4 weeks prior to screening or at the Screening Visit).
- 4 Type 1 diabetes mellitus:
 - (a) For US only: patients with T1DM treated with SGLT2i for at least 4 months, without DKA during that period, and who have experience with ketone monitoring are eligible for inclusion.

- (b) For Japan only: patients with T1DM treated with dapagliflozin 10 mg for at least 4 months, without DKA during the period of dapagliflozin treatment are eligible for inclusion.
- 5 Uncontrolled T2DM with HbA1c > 10.5% (> 91 mmol/mol) (central or local laboratory values obtained within 3 months prior to screening or at the Screening Visit).
 - 6 New York Heart Association functional HF class IV at screening.
 - 7 Stroke, transient ischaemic cerebral attack, valve implantation or valve replacement, carotid surgery, or carotid angioplasty, acute coronary syndrome, or hospitalisation for worsening heart failure within previous 3 months prior to randomisation.
 - 8 Known severe hepatic impairment, defined as Child-Pugh Class C, based on records that confirm documented medical history.
 - 9 Documented history of adrenal insufficiency.
 - 10 Any dialysis (including for acute kidney injury) within 3 months prior to Screening Visit.
 - 11 Any acute kidney injury within 3 months prior to the Screening Visit.
 - 12 Known hypersensitivity to the study treatment (active substance or excipients).
 - 13 History of organ transplant or bone marrow transplant, or planned organ transplant within 6 months following randomisation (including kidney transplant).
 - 14 History or ongoing allergy/hypersensitivity, as judged by the Investigator, to SGLT2 inhibitor (eg, empagliflozin) or ASI.
 - 15 Any clinical condition requiring systemic immunosuppression therapy other than maintenance therapy (stable for at least 3 months prior to Visit 1).
 - 16 Drug or alcohol abuse that in the Investigator's judgement makes the participant a poor candidate for the study.
 - 17 Any use of mineralocorticoid receptor antagonists (such as spironolactone, eplerenone, or finerenone), ASI, or potassium-sparing diuretics (such as triamterene or amiloride) within 4 weeks prior to screening.
 - 18 Concomitant therapy with strong inducers of cytochrome P450 (CYP) 3 A (eg, apalutamide, avasimibe, carbamazepine, enzalutamide, lumacaftor, mitotane, phenytoin, rifampin, rifapentine, St. John's wort).

19 Any use of potassium binders (such as sodium zirconium cyclosilicate, patiomer, or sodium polystyrene sulfonate) within 4 weeks prior to screening. However, their use is allowed after randomisation based on the Investigator and treating physician's judgement.

20 Any other condition or therapy, in the judgement of the Investigator or the Sponsor, which would make the participant unsuitable for this study, including a condition or therapy which the Investigator anticipates will not allow participation for the full planned study period (eg, active malignancy or other condition limiting life expectancy to less than 12 months).

21 Participation in another clinical study with a study intervention administered in the last 3 months prior to randomisation.

22 For WOCBP, positive pregnancy test and/or being breastfeeding.

[00259]

[00260] C. Study Intervention and Concomitant Therapy

[00261] (i) Study Intervention Administered

[00262] Participants will receive either baxdrostat/dapagliflozin, or placebo/dapagliflozin. To ensure blinding to treatment, the baxdrostat 1 mg, baxdrostat 2 mg and placebo to match baxdrostat tablets are identical in appearance (matching and indistinguishable). Study interventions to be administered and investigated in this study are described in the Table below

Arm name	Baxdrostat/dapagliflozin		Dapagliflozin	
Intervention name	Baxdrostat and dapagliflozin		Placebo and dapagliflozin.	
Type	Drug/Drug		Placebo/Drug	
Dose formulation	Baxdrostat tablet and dapagliflozin tablet		Placebo tablet (matching baxdrostat tablet) and dapagliflozin tablet	
Unit dose strength(s)	Baxdrostat 1 mg and dapagliflozin 10 mg	Baxdrostat 2 mg and dapagliflozin 10 mg	Placebo 1 mg and dapagliflozin 10 mg	Placebo 2 mg and dapagliflozin 10 mg
Dosage level(s)	One tablet of baxdrostat and one tablet of dapagliflozin once daily		One placebo tablet matching baxdrostat and one tablet of dapagliflozin once daily	
Route of administration	Oral		Oral	
Regimen	One per day, preferably in the morning		One per day, preferably in the morning	
Use	Experimental		Experimental	

Arm name	Baxdrostat/dapagliflozin	Dapagliflozin
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by AstraZeneca	
Packaging and labelling	Baxdrostat/matching placebo will be provided in blister packs containing IMP tablets. Each blister pack will be labelled as required per country requirements. Dapagliflozin 10 mg tablets will be provided in bottles.	

[00263] All participants who meet all the eligibility criteria will be centrally assigned to randomised, blinded study intervention using an automated IRT/RTSM that will allocate participants 1:1 into 1 of the 2 study intervention groups (ie, either baxdrostat/dapagliflozin or placebo/dapagliflozin).

[00264] The number of randomised participants with UACR and eGFR within certain ranges shown with laboratory tests at enrolment (Visit 1) will be monitored and randomisation in IRT/RTSM will be capped to ensure that the number of participants in these subpopulations does not approximately exceed a set percentage. The following population caps will be implemented for all patients:

- eGFR ≥ 60 to ≤ 75 mL/min/1.73 m²: capped at approximately 10% of the total population.

[00265] Additionally, for patients included according to inclusion criteria 2(a), the following population caps will also be implemented:

- UACR ≥ 30 to < 200 mg/g: capped at approximately 10% of the total population
- UACR ≥ 200 to < 500 mg/g: capped at approximately 10% of the total population

[00266] (ii) Dose Modification

[00267] All participants will start with the lower dose (1 mg) of baxdrostat, or matching placebo, and the Investigator may up-titrate to the targeted dose (2 mg). If at any timepoint during study treatment, local blood potassium is elevated to > 5.5 mmol/L, baxdrostat/matching placebo should be temporarily discontinued; see details below.

[00268] Up-titration: Up-titration to 2 mg should be performed at Visit 5 provided that the potassium concentration (local laboratory value) is ≤ 4.8 mmol/L at Visits 3, 4, and 5. Once the above local laboratory parameters are confirmed, up-titration will happen within 7 days and preferably as soon as possible. Potassium levels must be checked 14 (± 5) days after dose upward titration by the local and central laboratories. Note: participants who experience potassium > 5.5 mmol/L, recurrent sodium < 130 mmol/L, or symptomatic hypotension with

SBP $\leq$ 90 mmHg at any point during the study, should not be up-titrated and should remain on the 1 mg dose after restart.

[00269] Down-titration: For participants previously up-titrated, down-titration can be considered at any point throughout the study, for example based on potassium, SBP, or sodium or for other safety or tolerability concerns. Following down-titration, an unscheduled safety visit may be performed within 2 weeks, at the Investigator's discretion. Participants who are down-titrated from 2 mg to 1 mg during the study, should remain on 1 mg for the rest of the study.

[00270] (iii) Potassium Monitoring Measurements

[00271] Hyperkalaemia is a frequent event in patients with CKD and has been identified from previous studies as a risk with baxdrostat. Therefore, potassium levels will be monitored systematically throughout the study. Instructions for management of potassium measurements are described below:

[00272] Up-titration: At Visit 5, if participant is on 1 mg baxdrostat/placebo, and potassium $\leq$ 4.8 mmol/L at Visits 3, 4 and 5, then up-titrate to 2 mg.

[00273] Management of serum potassium:

[00274] Serum potassium $\leq$ 5.5 mmol/L: continue on the same dose of baxdrostat/placebo.

[00275] Serum potassium $>$ 5.5 mmol/L: withhold baxdrostat/placebo, manage hyperkalemia (e.g. potassium binders) and re-check potassium based on clinical judgment. If subsequent sample is $\leq$ 4.8 mmol/L, re-start baxdrostat/placebo at 1 mg. Serum potassium should be re-checked within 2 weeks (+/- 5 days) in an unscheduled visit. NOTE: participants who experienced serum potassium $>$ 5.5 mmol/L should not be up-titrated during the course of the study.

[00276] If subsequent sample is $>$ 4.8 mmol/L: continue to withhold baxdrostat/placebo; continue to monitor serum potassium and restart baxdrostat/placebo at 1 mg when potassium is $\leq$ 4.8 mmol/L. Serum potassium should be re-checked within 2 weeks (+/- 5 days) in an unscheduled visit. NOTE: participants who experienced serum potassium $>$ 5.5 mmol/L should not be up-titrated during the course of the study.

[00277] (iv) Prohibited Concomitant Medications

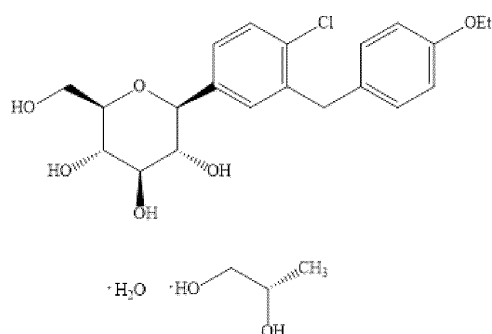
[00278] The medications and supplements listed below are prohibited during this study.

- Potassium-sparing diuretics (eg, amiloride, triamterene) and direct renin inhibitor (eg, aliskiren, zankiren).
- Mineralocorticoid receptor antagonists or aldosterone antagonists (eg, eplerenone, finerenone, spironolactone) or aldosterone synthetase inhibitors.
- Strong CYP3A4 inducers (eg, apalutamide, avasimibe, carbamazepine, enzalutamide, lumacaftor, ivacaftor, ivosidenib, mitotane, phenytoin, fosphenytoin, rifampin, and St John's wort).
- Concomitant treatment with SGLT2i other than the dapagliflozin supplied during the study, including homeopathic preparations containing phlorizin.
- Treatment with potassium supplements are not prohibited but should only be prescribed to individuals for whom the Investigator considers these agents to be required to avoid hypokalaemia.

Claims

1. A method of treating chronic kidney disease (CKD) and hypertension in a patient in need thereof, the method comprising administering to the patient a combination comprising a first amount of baxdrostat or a pharmaceutically acceptable salt thereof and a second amount of a sodium-glucose co-transporter 2 (SGLT2) inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount.
2. The method according to claim 1, wherein the baxdrostat or a pharmaceutically acceptable salt thereof is administered at a dosage of about 0.5 mg/day, about 1 mg/day or about 2 mg/day.
3. The method according to claim 1, wherein the baxdrostat or a pharmaceutically acceptable salt thereof is administered at a dosage of about 1 mg/day or about 2 mg/day.
4. The method according to any one of the preceding claims, wherein the baxdrostat or a pharmaceutically acceptable salt thereof is administered once daily.
5. The method according to any one of the preceding claims, wherein the baxdrostat or pharmaceutically acceptable salt thereof is baxdrostat.
6. The method according to any one of the preceding claims, wherein the SGLT2 inhibitor is selected from dapagliflozin, canagliflozin, empagliflozin, sotagliflozin, ipragliflozin, ertugliflozin, tofogliflozin, and luseogliflozin, or a pharmaceutically acceptable salt thereof.
7. The method according to any one of the preceding claims, wherein the SGLT2 inhibitor is dapagliflozin.
8. The method according to claim 7, wherein the dapagliflozin is administered at a dosage of about 10 mg/day.
9. The method according to claim 7 or claim 8, wherein the dapagliflozin is administered once daily.

10. The method according to any one of the preceding claims, the method comprising administering to the patient a combination comprising about 1 mg or about 2 mg, once daily, of baxdrostat and about 10 mg, once daily, of dapagliflozin.
11. The method according to any one of the preceding claims, wherein the baxdrostat or pharmaceutically acceptable salt thereof is in a form suitable for oral administration.
12. The method according to any one of claims 7 to 11, wherein the dapagliflozin is in a form suitable for oral administration.
13. The method according to claim 11 or claim 12, wherein the form suitable for oral administration is a tablet.
14. The method according to any one of claims 7 to 13, wherein the dapagliflozin is in the form of a (S)-propylene glycol ((S)-PG) solvate which has the structure



15. The method according to any one of the preceding claims, wherein the baxdrostat or pharmaceutically acceptable salt thereof is administered before, after, or concurrently with the SGLT2 inhibitor, such as dapagliflozin.
16. The method according to any one of the preceding claims, wherein the patient has a SBP ≥ 130 mmHg.
17. The method according to any one of the preceding claims, wherein the patient has a SBP ≥ 140 mmHg.
18. The method according to any one of the preceding claims, wherein the patient has an estimated glomerular filtration rate (eGFR) ≥ 30 and < 90 mL/min/1.73 m².

19. The method according to any one of the preceding claims, wherein the patient has an $\text{eGFR} \geq 30$ and $< 60 \text{ mL/min/1.73 m}^2$.
20. The method according to any one of claims 1 to 17, wherein the patient has an $\text{eGFR} \geq 25$ and $\leq 75 \text{ mL/min/1.73 m}^2$.
21. The method according to any one of the preceding claims, wherein the patient has a urine albumin creatinine ratio (UACR) $\geq 100 \text{ mg/g}$.
22. The method according to any one of the preceding claims, wherein the patient has a $\text{UACR} \geq 200 \text{ mg/g}$.
23. The method according to any one of the preceding claims, wherein the patient has serum potassium of 3.5 to 4.8 mmol/L.
24. The method according to any one of the preceding claims, wherein the patient has serum potassium of 3.5 to 4.8 mmol/L and an eGFR of $\geq 45 \text{ mL/min/1.73 m}^2$.
25. The method according to any one of claims 1 to 23, wherein the patient has serum potassium of 3.5 to 4.5 mmol/L and an eGFR of $< 45 \text{ mL/min/1.73 m}^2$.
26. The method according to any one of the preceding claims, wherein the patient is not treated with a mineralocorticoid receptor antagonist (MRA) during treatment with the combination.
27. The method according to any one of the preceding claims, wherein the method comprises administering one or more standard of care agents for CKD to the patient.
28. The method according to any one of the preceding claims, wherein the method reduces the rate of decline in kidney function of the patient.
29. The method according to any one of the preceding claims, wherein the method reduces the rate of decline in kidney function of the patient to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.
30. The method according to any one of the preceding claims, wherein the method reduces the decline in kidney function of the patient from baseline to a greater extent than

treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.

31. The method according to any one of the preceding claims, wherein the method reduces the rate of decline in eGFR of the patient.
32. The method according to any one of the preceding claims, wherein the method reduces the rate of decline in eGFR of the patient to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.
33. The method according to any one of the preceding claims, wherein the method reduces the decline in eGFR of the patient from baseline to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.
34. The method according to any one of the preceding claims, wherein the method reduces UACR of the patient from baseline.
35. The method according to any one of the preceding claims, wherein the method reduces UACR of the patient from baseline to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.
36. The method according to any one of the preceding claims, wherein the method reduces SBP of the patient from baseline.
37. The method according to any one of the preceding claims, wherein the method reduces SBP of the patient from baseline to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.
38. The method according to any one of the preceding claims, wherein the method reduces SBP of the patient to <120 mmHg.
39. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline.
40. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline to a greater extent

than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.

41. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of sustained eGFR decline of $\geq 57\%$ from baseline.
42. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of sustained eGFR decline of $\geq 57\%$ from baseline to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.
43. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of end-stage kidney disease (ESKD).
44. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of ESKD to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.
45. The method according to any one of the preceding claims, wherein the method reduces chronic eGFR slope of the patient.
46. The method according to any one of the preceding claims, wherein the method reduces chronic eGFR slope of the patient to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.
47. The method according to claim 45 or claim 46, wherein the chronic eGFR slope is the rate of decline in eGFR of the patient between about 8 weeks and about 2 years into treatment with the combination.
48. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline, reaching ESKD, or cardiovascular (CV) death.
49. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline, reaching ESKD, or CV death to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.

50. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline or ESKD.
51. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of sustained eGFR decline of $\geq 50\%$ from baseline or ESKD to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.
52. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of CV death, heart failure event, myocardial infarction or stroke.
53. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of CV death, heart failure event, myocardial infarction or stroke to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.
54. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of CV death or heart failure event.
55. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of CV death or heart failure event to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.
56. The method according to any one of claims 52 to 55, wherein the heart failure event is heart failure with or without hospitalisation.
57. The method according to any one of claims 52 to 55, wherein the heart failure event is heart failure with hospitalisation.
58. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of CV death.
59. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of CV death to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.

60. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of death.
61. The method according to any one of the preceding claims, wherein the method reduces the patient's risk of death to a greater extent than treatment wherein baxdrostat or a pharmaceutically acceptable salt thereof is replaced with placebo.
62. Baxdrostat or a pharmaceutically acceptable salt thereof for use in the method of any one of the preceding claims.
63. An SGLT2 inhibitor for use in the method of any one of claims 1 to 61.
64. Use of baxdrostat or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the method of any one of claims 1 to 61.
65. Use of an SGLT2 inhibitor in the manufacture of a medicament for use in the method of any one of claims 1 to 61.
66. A kit comprising: (a) baxdrostat or a pharmaceutically acceptable salt thereof and/or an SGLT2 inhibitor, and (b) instructions for use of the baxdrostat or a pharmaceutically acceptable salt thereof and/or an SGLT2 inhibitor in the method of any one of claims 1 to 61.