CLINICAL STUDY PROTOCOL

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy, Safety, and Pharmacokinetics of KBP-5074 in Patients with Moderate-to-Severe Chronic Kidney Disease and Uncontrolled Hypertension – (BLOCK/CKD)

Investigational Product: KBP-5074
Protocol Number: KBP5074-2-001
EudraCT Number: 2019-001579-35

Sponsor:
KBP BioSciences Co., Ltd.
116 Village Blvd, Suite 210
Princeton, NJ 08540
United States
Telephone: 609-531-0889
Fax: 609-531-0892

Original Protocol: 14 February 2018
Amendment 1: 02 May 2018
Amendment 2: 05 April 2019

SIGNATURE PAGE

STUDY TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy, Safety, and Pharmacokinetics of KBP-5074 in Patients with Moderate-to-Severe Chronic Kidney Disease and Uncontrolled Hypertension – (BLOCK/CKD)

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature | Date

April 16, 2019

Daniel J. Wilson, MD, FACP, FCCP
Senior Vice-President, Clinical Development
KBP BioSciences Co., Ltd.

April 16, 2019

Vincent J. Benn, PhD, MBA
Vice President, Regulatory and Medical Affairs
KBP BioSciences Co., Ltd.

INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by KBP BioSciences Co., Ltd. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to KBP BioSciences Co., Ltd. and that it may not be further disclosed to third parties. I understand that the study may be terminated, or enrollment suspended at any time by KBP BioSciences Co., Ltd., with or without cause, or by me if it becomes necessary to protect the best interests of the study patients at my site.

I agree to conduct this study in full accordance with Food and Drug Administration Regulations, Institutional Review Board/Independent Ethics Committee Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

Summary of Changes – Amendment 2

The protocol was amended due to change in contract research organization and feedback from Investigators to ensure continued recruitment of subjects.

Specific changes include (**bolded** text reflects new wording; ~~strikethrough~~ text indicates deleted wording):

1. Sponsor signatory changed to reflect changes in personnel.

2. Medpace Reference Laboratory and Medpace changed to 'central laboratory' and Worldwide Clinical Trials, as appropriate, throughout the protocol to reflect a change in Contract Research Organization involved with the study.

3. Indication, Objectives, and Study Population in the Synopsis clarified to meet the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines for Grade 1 or 2 systolic hypertension.

4. Study design in the Synopsis and Section 3 updated to reflect current protocol.

   Original Wording:

   Added new paragraph and updated as noted below.

   Amended Wording:

   Serum potassium levels, serum creatinine, and blood pressure will be monitored throughout the study and clinically significant changes will be reported as adverse events of special interest.

   At Screening **and the end of the placebo run-in period (Visit 3)**, patients must have uncontrolled hypertension (Grade 1 to 2 systolic hypertension – ESC/ESH), defined as resting trough-cuff seated SBP ≥ 140 **and ≤ 179** mmHg, based on the mean of at least 2 current consecutive blood pressure readings **in the clinic, a serum potassium ≤ 4.8 mmol/L** at Screening and the end of the placebo run-in period (Visit 3), **and a mean (Visit 1 and Visit 3) eGFR ≥ 15 and ≤ 44 mL/min/1.73 m^2.**

5. Sites changed to reflect identification of actual study sites:

   Original Wording:

   Approximately 60 sites in the United States, Mexico, Israel, Australia, Chile, and Argentina.

   Amended Wording:

   Approximately ~~60~~ **90** sites in the ~~United States, Mexico,~~ North America, South America, Israel, ~~Australia, Chile, and Argentina~~ and Europe.

6. Inclusion and exclusion criteria updated in Sections 4.1 and 4.2 to reflection current practices and uncontrolled hypertension definition of ESC/ESH.

Original Wording:

Updated Inclusion #1 and 4. Added exclusion #2 and 23 (other criteria renumbered accordingly); updated exclusion #1, 4, 5, 8, 10, 12, 13, 14, 15, and 25.

Amended Wording:

Inclusion #1: Male or female, between 18 and **85** ~~79~~ years of age, inclusive. The lower age limit may be higher if it is legally required in the participating country

Inclusion #4: Uncontrolled hypertension **(Grade 1 to 2 systolic hypertension – ESC/ESH)**, defined as:

- ~~Trough~~ **Resting trough-cuff** seated SBP ≥ 140 and ≤ 179 mmHg based on **the** mean of at least 2 current consecutive clinic blood pressure readings at Screening **and at the end of the placebo run-in period (Visit 3)**; AND
- Currently on ~~the maximally~~ **2 or more antihypertensive medications, which have been titrated upward as** tolerated ~~dose of 2 or more~~ **to recommended** hypertension ~~medications with complementary mechanisms~~ target doses (such as diuretics [except for potassium-sparing diuretics], renin-angiotensin system blockers, and/or calcium channel blockers, **One of the antihypertensive medications must be high ceiling diuretic (loop or thiazide-like), unless there is a documented intolerance or contraindication to diuretic therapy.** ~~one of which the antihypertensive medications must be a diuretic at an appropriate dose of high ceiling [eg, loop or thiazide-like] unless not tolerated as the baseline medication), with no).~~ **The doses of the antihypertensive medications should be stable without any** dose adjustment during the 30 days prior to randomization; OR
- ~~History of~~ **Patients with uncontrolled hypertension and moderate-to-severe CKD with** documented **history of** intolerance ~~or lack of efficacy while on~~ **to** multiple ~~hypertension~~ **antihypertensive medications on fewer than 2 antihypertensive** medications;

Exclusion #1: **Resting trough** ~~Trough cuff~~ seated SBP ~~>~~**≥** 180 **or < 140** mmHg, based on **the** mean of at least 2 current consecutive clinic blood pressure readings at Screening **and the end of the placebo run-in period (Visit 3)**;

Exclusion #2: **Serum potassium > 4.8 mmol/L**;

Exclusion #4: Currently on an MRA **(eg, spironolactone or eplerenone)** other than KBP-5074, or received any MRAs during the last 3 months prior to Screening, or currently on any potassium supplements;

Exclusion #5: ~~Currently on~~ **Chronic or intermittent use of** a potassium ~~lowering agent, including insulin plus glucose infusion or have routinely or chronically used potassium-binding resins~~ **binder** for the treatment of hyperkalemia ~~within~~ **from** 3 months prior to Screening until the end of study assessments, including but not limited to calcium polystyrene sulfonates (eg, sorbisterit, calcium resonium), sodium polystyrene sulfonates

(eg, kayexalate, anti-kalium sodium), and patiromer (eg, ~~veltassa) (unless clinically indicated on an emergent basis to treat hyperkalemia until serum potassium values are within the normal range [see Section 8.12]);~~**Veltassa™) and sodium zirconium cyclosilicate (eg, Lokelma™)**;

Exclusion #8: **Clinically** ~~History of clinically~~ significant hyperkalemia while on an angiotensin converting enzyme inhibitor, angiotensin receptor blocker, direct renin inhibitor, and/or MRA, **requiring down-titration or discontinuation of above medication, or** hospitalization for hyperkalemia **within** ~~during the last~~ 3 months prior to Screening, or hyperkalemia > 5.6 mmol/L during the 2 weeks prior to Screening;

Exclusion #10: Currently receiving ~~hemodialysis/peritoneal dialysis or plan to start hemodialysis~~HD, or peritoneal dialysis within 3 months prior to Screening, ~~or history~~ **and those patients with an episode** of acute kidney injury ~~that require dialysis~~ within 3 months of Screening;

Exclusion #11: History of a ~~kidney~~ **renal** transplant, or ~~on a list for a kidney~~ **impending renal** transplant;

Exclusion #12: Acute decompensated heart failure including exacerbation of chronic heart failure manifested by signs and symptoms that may require **hospitalization and/or** intravenous diuretic therapy (New York Heart Association Class III to IV) within 3 months prior to Screening, or presence of hemodynamically significant valve diseases and/or other hemodynamically significant obstructive lesions of left ventricular outflow tract;

Exclusion #13: Major cardiac, cerebral, and/or carotid artery diseases, including but not limited to acute coronary syndrome, myocardial infarction, stroke, and/or transient ischemic attack; major cardiovascular ~~surgery~~ **or percutaneous procedures including cardiac ablation,** coronary revascularization, and carotid angioplasty within 6 months prior to Screening; OR

~~Any of those~~ **Cardiovascular** conditions ~~that are~~ likely to require surgical or percutaneous intervention within ~~3~~**6** months from Screening;

Exclusion #14: History of clinically significant arrhythmia, including but not limited to any of the following:

- Symptomatic bradycardia and/or symptomatic ventricular arrhythmia within 3 months prior to Screening; ~~or~~
- Second- or third-degree heart block; **or**
- **New onset or untreated atrial fibrillation; Note: Patients with stable (6 months) asymptomatic rate controlled atrial fibrillation on appropriate therapy, which may include anticoagulation, are permitted.**

Exclusion #15: QT interval corrected using Fridericia's formula **(QTcF)** > 450 ms for males or > 470 ms for females at Screening or Day 1; **QTcF should be the average of the required triplicate set of ECGs at each timepoint;**

Exclusion #23: **History of malignancy in the past 5 years, with the exception of basal or resected cutaneous squamous cell carcinoma of the skin or carcinoma in situ, prostate cancer in situ with a normal prostate-specific antigen post treatment, cervical carcinoma in situ, gastric cancer in situ, colon cancer in situ adequately treated with no progression over the past 2 years;**

Exclusion #25: ~~Positive screen for drugs of abuse (except for patients with a~~ A positive drug screen test (excluding a positive result secondary to a prescribed medication from a physician, or tetrahydrocannabinol) at Screening or the end of the run-in period (Visit 3);

7. Section 5.1 sentence added to reflect current practice regarding diuretic therapy.

   The duration of the double-blind treatment period will be 84 days. Patients will remain on their stable antihypertensive medication (ie, no change in antihypertensive medication) throughout the entire study (including both the run-in and treatment periods). **The dose of diuretic may be adjusted based on developing or resolved edema, weight gain or loss, or pulmonary congestion.**

8. Section 5.6 updated to reflect current practice regarding diuretic therapy.

   Section 5.6.1 Excluded Medications and/or Procedures

   Use of the following medications is not permitted during the study:

   - MRAs other than KBP-5074;
   - Potassium ~~lowering agents, including insulin plus glucose infusion or routinely or chronically~~ **binders** used for treatment of hyperkalemia ~~within~~ **from** 3 months prior to Screening until the end of study assessments, including but not limited to calcium polystyrene ~~sulfonates~~ (eg, sorbisterit, calcium resonium), sodium polystyrene (eg, kayexalate, anti-kalium sodium), patiromer (eg, ~~veltassa) (unless clinically indicated on an emergent basis to treat hyperkalemia until serum potassium values are within the normal range [see Section 8.12]);~~**Veltassa™) and sodium zirconium cyclosilicate (eg, Lokelma™);**
   - Potassium-sparing diuretics (eg, amiloride, triamterene) within 3 months prior to Screening until the end of study assessments;
   - Potassium supplements (unless clinically indicated on an emergent basis to treat hypokalemia until serum potassium values are within the normal range [see Section 8.12]);
   - Hemodialysis/peritoneal dialysis;
   - Any nutrients known to modulate CYP3A activity (based on the KBP-5074 metabolic pathway) or any strong or moderate inhibitors or inducers of CYP3A4, starting from 14 days prior to the first dose of study drug at Day 1 until the end of study assessments, including, but not limited to the following: inhibitors, such as ketoconazole, miconazole, itraconazole, fluconazole, atazanavir, erythromycin, clarithromycin, ranitidine, and cimetidine, and inducers, such as rifampicin, rifabutin, **systemic** glucocorticoids **(inhaled and topical permitted)**, carbamazepine, phenytoin, phenobarbital, and St. John's wort; and

- Any other medications (prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications) that potentially increase serum potassium levels and/or cause toxicity to the kidney, including ~~but not limited to renin inhibitors~~ **chronic or daily use of nonsteroidal anti-inflammatory drugs.** These medications should be taken only if the Investigator considers these medically necessary. It is recommended that serum potassium levels and eGFR values should be closely monitored when patients take these medications.

Section 5.6.2 Restricted Medications and/or Procedures

Patients will be advised to maintain their normal diet and **avoid unhealthy levels of** ~~not take~~ alcohol use or potassium-rich foods/drinks during the study period. See Section 8.12 for more details on monitoring of potassium and management of elevated serum potassium.

Section 5.6.3 Documentation of Prior and Concomitant Medication Use

All medications in addition to the study drug (including vitamin preparations) that are taken by the patient during the study must be documented as concomitant medications and reported on the corresponding eCRF. **The use of sodium bicarbonate or dosage adjustment for treatment of acidosis in CKD is permitted.**

Patients must currently be on ~~the maximally tolerated dose of~~ 2 or more **antihypertensive medications, which have been titrated upward as tolerated to recommended hypertension target doses** ~~**hypertension medications with complementary mechanisms**~~ (such as diuretics [except for potassium sparing diuretics], renin angiotensin system blockers, and/or calcium channel blockers.~~1 of which~~ **One of the antihypertensive medications must be high ceiling diuretic (loop or thiazide-like), unless there is a documented intolerance or contraindication to diuretic therapy.** ~~One of the antihypertensive medications must be a diuretic at an appropriate dose of high ceiling (eg, loop or thiazide-like) unless not tolerated as the baseline medication) with no medications.~~ **The doses of the antihypertensive medications should be stable without** dose adjustment during the 30 days prior to randomization. The dose ~~of and/or types of the antihypertensive medications they are receiving during the screening period and throughout the duration of the study (unless they develop symptomatic hypotension)~~ **diuretic may be adjusted based on developing or resolved edema, weight gain or loss, or pulmonary congestion.**

Section 5.6.4 Management of Other Co-Morbidities

~~For p~~**Patients** who have ~~other~~ **additional** co-morbidities (eg, diabetes, hyperlipidemia, and cardiovascular **disease** ~~diseases) appropriate treatments, such as anti-hyperlipidemia~~), **should be managed and treated with glucose lowering, lipid lowering, and** anti-platelet ~~and anti-hyperglycemia~~ therapies ~~are~~ **as** recommended **by** ~~according to~~ local **clinical practice** guidelines. It is highly recommended that any medical treatments for these co-morbidities will not be changed during the study period (from Screening to the End of Study Visit [Day 112]/Early Termination Visit).

9. Section 6 Study Procedures subsections updated to reflect use of a validated, oscillometric upper arm blood pressure monitor used to obtain blood pressure measurements.

Original Wording:

- Note: Patients must have uncontrolled hypertension, defined as resting trough-cuff seated SBP ≥ 140 mmHg, based on the mean of at least 2 current consecutive blood pressure readings in the clinic;
- Note: Blood pressure measurement: Blood pressures are obtained according to the American Heart Association (AHA) recommendations[10] for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable chair with back support for at least 10 minutes before a measurement; and remain still during the measurement. The patient's limb should be supported to measure blood pressure ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the same arm throughout the study;
- Note: Triplicate blood pressure measurements should be taken approximately 2 minutes apart with the patient in the seated position and having rested for at least 10 minutes prior to assessment. Trough-cuff SBP and DBP values will be assessed based on the pre-defined blood pressure measurement guideline throughout the study;
- Note: Blood pressure and pulse rate will be measured at the same time;
- Note: Measurement will be taken with OMRON HEM-705-CP automated blood pressure machine;

Amended Wording (all subsections replaced):

- Note: Patients must have uncontrolled hypertension, defined as resting trough-cuff seated SBP ≥ 140 **and ≤ 179** mmHg, based on the mean of at least 2 current consecutive blood pressure readings in the clinic;
- Blood pressures are to be obtained according to the AHA recommendations for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable chair with back support for at least 10 minutes before measurement and remain still during the measurement. The patient's limb should be supported to measure blood pressure to ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the

same arm throughout the study. Triplicate blood pressure measurements should be taken approximately 2 minutes apart with ~~OMRON HEM-705-CP automated blood pressure machine~~ **a validated, oscillometric upper arm blood pressure monitor**. Trough cuff SBP and DBP values will be assessed based on the pre-defined blood pressure measurement guideline throughout the study. Pulse will be obtained simultaneously with blood pressure measurements.

Clarified that laboratory samples do **NOT** need to be obtained in a fasting state.

Added where appropriate: **Note: Serum potassium should be ≤ 4.8 mmol/L (local lab) to advance or continue to the placebo run-in Period.**

Section 6.4 changed from ~~Double-Blind Treatment Period~~ to **Randomization and Treatment**

Section 6.4.2: The following procedures will be performed at Visit 4:

- Assess eligibility: **Prior to randomization, all patients are to have a serum potassium ≤ 4.8 mmol/L at both Screening and the end of the placebo run-in period; and a mean (Visit 1 and Visit 3) eGFR ≥ 15 and ≤ 44 mL/min/1.73 m$^{2.}$**

10. Section 8.2 Adverse Events of Special Interest

- Hypertensive emergency ~~defined~~;
  - **Defined** as confirmed (based on the mean of at least 2 current consecutive protocol-required blood pressure readings, or otherwise obtained blood pressure readings) **with** ~~severe elevation in~~ **SBP > 180** mmHg and/or DBP >120 mmHg with **associated new or progressive target organ damage**, neurologic, and/or cardiac symptoms. **Blood pressures of > 200 mmHg** in asymptomatic patients~~, a confirmed elevation in SBP 200 mmHg, regardless of DBP. If SBP >200 mmHg or DBP >120 mmHg and the patient is symptomatic, the blood pressure measurement~~ should be ~~repeated approximately every 10 minutes over a 30 minute period with the patient resting in a quiet, comfortable environment to confirm the~~ **recorded in the eCRF, and Investigators must differentiate between hypertensive urgency (marked elevated blood pressure) and emergency**. See Section 8.14 **and Appendix C** for **definition and** management of hypertensive emergencies **and urgencies; and**
  - **Symptomatic hypotension, or if the** ~~defined as symptoms associated with an~~ **SBP < 90 mmHg after the first dose of study drug at Day 1.**

11. Contact information updated in Section 8.4 for reporting SAEs.

- Site staff will complete the paper SAE report form and e-mail it within 24 h to the following address: drugsafety@worldwide.com

- In cases where the email system is unavailable, site staff will send the SAE by fax to: +1-866-387-5539 (US) and +44 208 043 4813 (ROW).

12. Section 8.7 Clinical Laboratory Evaluations deleted need for samples to be obtained after at least a 10 hour fast.

13. Section 8.12 Safety Surveillance and Management of Serum Potassium Levels updated to reflect more stringent surveillance of potassium levels

    Serum potassium levels of study patients will be monitored systematically throughout the study. In addition to the clinical laboratory tests pre-defined in the Schedule of Procedures (Appendix A), unscheduled assessments of serum potassium levels are recommended under certain situations (eg, vomiting and/or diarrhea for ≥ 1 day) that may impact patients' serum electrolyte levels or fluid balance.

    In patients with serum potassium above the normal laboratory reference range (serum potassium levels ≥ 5.0 **mmol/L**), it is advised that the Investigator should **reinforce** ~~enforce~~ dietary restriction for management of elevated potassium and consider local guideline recommendations. ~~For diabetes patients, in addition to dietary restrictions and clinical management of hyperkalemia, the investigator should also enforce adequate glycemic control.~~ Table 1 below summarizes the laboratory testing for assessment of serum potassium levels ≥ 5.0 mmol/L and guidelines for management of study drug, which includes continuation thereof, holding of study drug, and/or discontinuation of study drug. If serum potassium levels are < 5.0 mmol/L, no action is indicated. A serum potassium level of ≥ 5.6 mmol/L requires a hold of study drug and appropriate retesting and intervention as described in Table 1. A potassium level of ≥ 6.0 mmol/L necessitates immediate and permanent discontinuation of study drug.

    Because of potential issues anticipated from routine sample handling and extended transportation time to the central laboratory, ~~falsely elevated serum potassium values~~ **pseudohyperkalemia secondary to hemolysis may occur** in ~~central~~**centrally analyzed** laboratory ~~analyzed~~ samples ~~may be expected~~. For this reason, during treatment with study drug, all serum potassium assessments, including retests, will be performed at both local and central laboratories.

    In general, if the initial local and/or central laboratory test shows that a patient's serum potassium level is ≥ 5.3 mmol/L, a repeat local test is required to confirm elevation of serum potassium levels and dictate actions to be taken as outlined in Table 1. ~~In the absence of hemolysis, the more conservative value from the central or local laboratories should be used. Results from the local laboratory will usually be used for the immediate decision process and for safety purposes.~~ **All samples should be screened for hemolysis to eliminate the possibility of pseudohyperkalemia. Results from the central laboratory will be used for data analysis. If a major discrepancy exists between the local and central laboratory values, defined as a ± 0.3 mmol/L difference between values or if hemolysis is noted in the specimens, repeat blood samples should be obtained to confirm eligibility or continuation in the study. Again, decisions to enroll or randomize a patient should generally be based on the local serum potassium. However, if the central laboratory serum potassium is ≤ 4.8 mmol/L and the local potassium test is > 4.8 mmol/L, the more conservative value may be used if the difference between the 2 samples is ≤ 0.3 mmol/L.[11]**

    ~~Recheck of serum potassium values must be done as quickly as possible and at the latest~~ **Serum potassium recheck is recommended** within 24, **48, or 72** hours, ~~of the~~ **depending on the**

level of hyperkalemia, following Investigator ~~being aware of results that need retest/confirmation as outline in~~ **notification of a serum potassium ≥ 5.3 mmol/L (see Table 1).** The Investigator can perform ~~a retest at any time if it is considered necessary~~ **additional serum potassium retests when clinically** indicated for ~~routine~~ medical ~~issues~~ **conditions or procedures** that ~~might arise~~ **occur** during the study ~~to confirm the potassium concentration of either the local or central laboratory sample. The repeated test must be conducted using~~. **Blood samples should be obtained atraumatically, without fist clenching or prolonged use of a ~~non~~ tourniquet**. Non-hemolyzed~~sample~~ and **blood samples sent for rechecks or retests** will be analyzed in both local and central laboratories. In some circumstances, as outlined below in Table 1, a second retest may be indicated and should be performed within 1 week to allow the patient to adjust to the withdrawal of study drug (if indicated) and application of standard of care. **All episodes of hyperkalemia, serum potassium of > 5.0 mmol/L should be reported as an adverse event of special interest.**

The monitoring of serum potassium and the decision on whether or not to discontinue study drug, as well as other interventions, are outlined in Table 1.

Original Table 1

	Value of the First Serum Potassium Assessment			
	≥5.0 to 5.2 mmol/L	**≥5.3 to 5.5 mmol/L**	**≥5.6 to 5.9 mmol/L**	**≥6.0 mmol/L**
Laboratory test at both local and central laboratories [1]		**Repeat serum potassium test within 24 hours.**	**Repeat serum potassium test within 24 hours.**	**Repeat serum potassium test within 24 hours.**
Intervention	**Enforce dietary restriction for management of elevated potassium. For diabetic patients, also enforce adequate glycemic control.**	**Continue study drug pending retest results.**	**Withhold study drug pending retest results.**	**Permanently discontinue study drug <u>immediately</u>.**
		Manage hyperkalemia per standard of care (but no potassium-binders).	**Manage hyperkalemia per standard of care (but no potassium-binders).**	**Manage hyperkalemia per standard of care.**
		If serum potassium <5.3 mmol/L on retest, no changes are indicated.	**If serum potassium <5.3 mmol/L on retest, resume study drug.**	**Enforce dietary restriction for management of elevated potassium. For diabetes patients, also enforce adequate glycemic control.**
		1. **If serum potassium on retest is 5.3 mmol/L to 5.5 mmol/L**, temporarily discontinue study drug, consider use of loop diuretics and do second retest within 1 week.	**If serum potassium level on retest is >5.3 mmol/L, consider use of loop diuretics and do second retest within 1 week.**	

		If serum potassium on second retest is >5.3 mmol/L, permanently discontinue study drug.	**If serum potassium on second retest is >5.5 mmol/L, permanently discontinue study drug.**	
		Enforce dietary restriction for management of elevated potassium. For diabetic patients, also enforce adequate glycemic control.	**Enforce dietary restriction for management of elevated potassium. For diabetes patients, also enforce adequate glycemic control.**	

2. In the absence of hemolysis, the more conservative value from the central or local laboratories should be used.

In general, if serum potassium levels are ≥5.3 mmol/L, repeat testing is necessary and the procedures summarized above should be followed.

The Investigator should consider local guideline recommendations for management of serum potassium levels above the normal laboratory reference range. In all instances, dietary restriction for management of elevated potassium should be enforced. In addition, in diabetic patients, adequate glycemic control should be enforced. Consider use of loop diuretics as appropriate to manage hyperkalemia. If treatment with potassium-binding resins is required, the patient should be permanently discontinued from study drug.

Elevated serum potassium levels should be analyzed locally and centrally to rule out hemolysis. If the locally analyzed blood sample is missing, or the result is inconclusive, another blood sample should be taken as soon as possible but no later than 24 hours to confirm the value.

The study Sponsor or delegate will be notified by site personnel within 24 hours of the site being aware of results for any local laboratory potassium value (≥5.3 mmol/L). Retest/confirmatory testing results will be forwarded to the Sponsor or delegate within 24 hours of the site being aware of results.

Replacement Table 1 to be presented in landscape format in the protocol text.

	Alert Local and Central Laboratory Serum Potassium (K^+) Values			
	> 5.0 to 5.2 mmol/L	5.3 to 5.5 mmol/L	5.6 to 5.9 mmol/L	≥ 6.0 mmol/L
Following notification of a serum K^+ alert value[1]		Contact patient and schedule repeat serum K^+ within 24-72 hours after laboratory notification.	Contact patient and schedule repeat serum K^+ within 24-48 hours after laboratory notification.	Contact patient and schedule repeat serum K^+ within 24 hours after laboratory notification.
Management	Continue study drug.	Continue study drug pending retest results.	Hold study drug pending retest results.	**Permanently discontinue study drug.**
Treatment	Reinforce low K^+ diet.	Reinforce low- K^+ diet; manage HK per local SOC (no K^+ binders).	Reinforce low- K^+ diet; manage HK per local SOC (no K^+ binders).	Reinforce low- K^+ diet; manage HK per local SOC (may use K^+ binders)..
If first serum K^+ retest is < 5.3 mmol/L		Continue study drug.	Resume study drug.	
Management following first serum K^+ retest		If retest serum K^+ is ≥ 5.3 to 5.5 mmol/L: 1. Hold study drug, 2. Consider higher dose of diuretic, 3. Schedule second serum K^+ retest within 1 week. **If retest serum K^+ > 5.5 mmol/L,**	If retest serum K^+ is ≥ 5.3 to 5.5 mmol/L: 1. Continue to hold study drug, 2. Consider higher dose of diuretic, 3. Schedule second serum K^+ retest within 1 week. **If retest serum K^+ > 5.5 mmol/L,**	Note: Following discontinuance of study drug continue study visits and safety monitoring.

	Alert Local and Central Laboratory Serum Potassium (K^+) Values			
	> 5.0 to 5.2 mmol/L	5.3 to 5.5 mmol/L	5.6 to 5.9 mmol/L	≥ 6.0 mmol/L
		permanently discontinue study drug.	**permanently discontinue study drug.**	
Management following second serum K^+ retest		If serum K^+ on retest is < 5.3 mmol/L, continue study drug. **If serum K^+ on retest is ≥ 5.3 mmol/L, permanently discontinue study drug.**	If serum K^+ is < 5.3 mmol/L, resume study drug. **If serum K^+ on retest is ≥ 5.3 mmol/L, permanently discontinue study drug.**	Report as AE as Special Interest
Adverse Event Reporting		Report as AE of Special Interest	Report as AE of Special Interest	

1 In the absence of hemolysis, the more conservative value from the central or local laboratories should be used to guide management and treatment
Study sites should make repeated attempts to contact patients with high K^+ or HK to ensure compliance with K^+ safety monitoring and required retests.
If the serum K^+ levels are ≥ 5.3 mmol/L, repeat local and central serum K^+ testing is required in compliance with the above management strategies and procedures
The Investigator should consider local guideline and SOC for management of serum potassium levels above the normal laboratory reference range. In all instances, dietary restriction for management of elevated potassium should be reinforced**. Consider use of higher dose of loop or thiazide-like diuretics to manage HK.** If chronic or intermittent treatment with potassium-binders is required, the patient should be permanently discontinued from study drug.
If the locally analyzed blood sample is missing, or the result is inconclusive, another blood sample should be taken as soon as possible but no later than 24 to up to 72 hours to confirm the value.
The Sponsor or delegate will be notified by site personnel within 24 hours of the site being aware of results for any local laboratory potassium value (≥ 5.3 mmol/L). Retest/confirmatory testing results will be forwarded to the Sponsor or delegate within 24 hours of the site being aware of results.

Abbreviations: K^+: potassium, HK: hyperkalemia, SOC: Standard of care.

Regardless of whether a patient will discontinue study drug due to elevated serum potassium levels, he/she should be closely monitored and treated, as appropriate, per the Investigator's assessment.

14. Section 8.14 Monitoring and Management of Blood Pressure updated to reflect current practices.

    Blood pressure will be closely monitored throughout this study. At Screening, patients must have uncontrolled hypertension, defined as resting trough-cuff seated SBP ≥ 140 **and ≤ 179** mmHg based on the mean of at least 2 current consecutive blood pressure readings at Screening and the end of the run-in period in the clinic**. Blood pressures are obtained according to the AHA recommendations for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable chair with back support for at least 10 minutes before a measurement; and remain still during the measurement. The patient's limb should be supported to measure blood pressure and ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the same arm throughout the study. Measurement will be taken with a validated, oscillometric upper arm blood pressure monitor.**

    In all cases, dose and frequency of concurrent antihypertensive medications are expected to be maintained without change for 30 days prior to randomization. In general, patients should not

add or adjust dose and/or types of the antihypertensive medications they are receiving during the screening period and throughout the duration of the study (unless they develop symptomatic hypotension). **The dose of diuretic may be adjusted based on developing or resolved edema, weight gain or loss, or pulmonary congestion. Antihypertensive therapy may be modified if necessary during the safety assessment, following withdrawal of the study drug to maintain blood pressure control.**

~~The following guidelines are based on the 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults.[1] A hypertensive emergency is defined as a confirmed (based on the mean of at least 2 current consecutive protocol-required blood pressure readings, or otherwise obtained blood pressure reading) severe elevation in SBP >180 mmHg and/or DBP >120 mmHg with neurologic and/or cardiac symptoms, or, in asymptomatic patients, a confirmed elevation in SBP >200 mmHg, regardless of DBP. A confirmed (based on the mean of at least 2 current consecutive protocol-required blood pressure readings, or otherwise obtained blood pressure reading) asymptomatic DBP of >120 mmHg should also be managed as a hypertensive emergency, regardless of the SBP. If SBP >200 mmHg or DBP >120 mmHg and the patient is asymptomatic, the blood pressure measurement should be repeated approximately every 10 minutes over a 30-minute period, with the patient resting in a quiet, comfortable environment to confirm the elevated blood pressure.~~

~~Hypertensive emergencies demand immediate medical intervention to reduce blood pressure per local practice guidelines and the medical judgment of the Investigator. Reduction of blood pressure (not necessarily to normal ranges) are required to prevent or limit further target organ damage, which can include hypertensive encephalopathy, intracranial hemorrhage, acute ischemic stroke, acute myocardial infarction, acute left ventricular failure with pulmonary edema, unstable angina pectoris, dissecting aortic aneurysm, acute renal failure, and eclampsia. Employment of pharmacological classes that are available for the treatment of hypertensive emergencies should be used per local guidelines. In general, autoregulation of tissue perfusion is disturbed in hypertensive emergencies; thus, continuous infusion of short-acting titratable antihypertensive agents is often preferred; use of oral therapy is discouraged for hypertensive emergencies.~~

Diagnoses of hypertensive emergency require discontinuance of the study drug, and immediate treatment per local treatment guidelines. The occurrence of hypertensive urgency or a transient severe elevation in blood pressure may or may not require removal of a patient from the study drug but should be recorded as an adverse event and reviewed with the study Medical Monitor. AHA/American College of Cardiology definitions, clinical definitions, and treatment algorithms for hypertensive emergency, hypertensive urgency, or marked elevations in blood pressure appear in Appendix C.

~~It should be noted that hypertensive emergencies in patients presenting with acute intracranial hemorrhage and acute ischemic stroke require particularly close management; local guidelines for such patients should be followed.~~

~~If a patient develops~~**Symptomatic hypotension or** ~~(defined as~~ **a confirmed trough-seated SBP < 90 mmHg** based on the mean of at least 2 current consecutive protocol-required blood pressure readings, or otherwise obtained blood pressure reading after the first dose of study drug at Day 1, **should be reported as an adverse event of special interest**. Investigators

should evaluate and correct any potential reasons that may contribute to hypotension, such as dehydration, decreased blood volume, potential overdose of antihypertensive medication (including study drugs), etc. **If symptomatic hypotension or a confirmed trough-seated SBP < 90 mmHg occurs, Investigators** ~~the patient's hypertension still has hypotension, Investigators~~ may consider down-titration of antihypertensive medications (other than study drug) first. If symptomatic hypotension or a confirmed trough-seated SBP < 90 mmHg persists following down-titration, ~~patient's hypotension remains~~ study drug should be permanently discontinued.

15. Section 9.2.6 Independent Data Monitoring Committee updated to provide meeting schedule:

    Meeting Schedule

    After the organizational meeting, the IDMC will meet at least 4 times during the conduct of the study at the following treatment milestones:

    - Approximately 10% of patients completed are randomized in the study,
    - Approximately 25% of patients completed the 12-week treatment period,
    - Approximately 50% of patients completed the 12-week treatment period, and
    - Approximately 75% of patients completed the 12-week treatment period.

16. Section 12 Study Administrative Information updated to reflect the changes in organizations involved in the conduct of the study.

17. Section 13 References updated to add references 9, 10, and 12.

18. Appendix A updated to delete Contact IRT at Day 7; to add footnote #16 (subsequent footnote numbers updated) 'All patients must have a serum potassium ≤ 4.8 mmol/L at both Screening and the end of the placebo run-in period (Visit 3)'; updated wording of footnote #10 'At Screening **and the end of the placebo run-in period (Visit 3)**, patients must have uncontrolled hypertension, defined as resting trough-cuff seated SBP ≥ 140 mmHg **and ≤ 179 mmHg** based on the mean of at least 2 current consecutive blood pressure readings in the clinic.'; deleted need for obtaining blood samples in fasting state in footnote #14; added Assessment for Randomization; abbreviations for DBP and SBP added.

19. Appendix C added.

20. Minor typographical errors and wording preferences updated throughout the protocol.

SYNOPSIS

TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy, Safety, and Pharmacokinetics of KBP-5074 in Patients with Moderate-to-Severe Chronic Kidney Disease and Uncontrolled Hypertension – (BLOCK/CKD)

PROTOCOL NUMBER: KBP5074-2-001

INVESTIGATIONAL PRODUCT: KBP-5074

PHASE: 2

INDICATION: Uncontrolled hypertension (Grade 1 to 2 systolic hypertension – European Society of Cardiology [ESC]/European Society of Hypertension [ESH]) in patients with moderate-to-severe chronic kidney disease (CKD)

OBJECTIVES:

The primary objective of this study is to evaluate the efficacy of KBP-5074 in patients with moderate-to-severe CKD on uncontrolled hypertension (eg, Grade 1 to 2 systolic hypertension – ESC/ESH) as determined by change in trough-cuff seated systolic blood pressure (SBP) from baseline to Day 84.

The secondary objectives of this study are the following:

- To evaluate the change in trough-cuff seated diastolic blood pressure (DBP) from baseline to Day 84;
- To evaluate the change in 24-hour mean, daytime mean, nighttime mean, morning mean, last 6 hours of the dosing interval mean, SBP, DBP, mean arterial pressure (MAP), and heart rate (HR) from baseline to Day 84 in a subset of up to 40 patients per treatment group as measured by 24-hour ambulatory blood pressure monitoring (ABPM);
- To evaluate the change and percent change in urine albumin-to-creatinine ratio (UACR) from baseline to Day 84 (for patients with albuminuria [defined as UACR > 300 mg/g] or microalbuminuria [defined as UACR in the range of 30 mg/g to 300 mg/g]);
- To evaluate the change in serum aldosterone and plasma renin levels from baseline to Day 84;
- To evaluate the incidence of hyperkalemia (defined as serum potassium ≥ 5.6 mmol/L), incidence of severe hyperkalemia (defined as serum potassium ≥ 6.0 mmol/L), and incidence of patients with serum potassium > 5.0 mmol/L;
- To evaluate the change in serum potassium levels from baseline to Day 84;
- To evaluate the changes in estimated glomerular filtration rate (eGFR) and creatinine levels > 30% throughout the study period; and
- To evaluate population pharmacokinetics (PPK) of KBP-5074.

POPULATION:

The population for this study will be male and female patients 18 to 85 years of age, inclusive, with Stage 3B/4 CKD (defined as eGFR ≥ 15 and ≤ 44 mL/min/1.73 m^2, based on the isotope dilution mass spectrometry traceable Modification of Diet in Renal Disease equation version 4, according to central laboratory results at Screening). Patients are to have uncontrolled hypertension (Grade 1 to 2 systolic hypertension – ESC/ESH) defined as:

- Resting trough-cuff seated SBP ≥ 140 and ≤ 179 mmHg based on the mean of at least 2 current consecutive clinic blood pressure readings at Screening and at the end of the placebo run-in period (Visit 3) and at randomization (Visit 4), AND
- Currently on 2 or more antihypertensive medications, which have been titrated upward as tolerated to recommended hypertension target doses (such as diuretics [except for potassium-sparing diuretics], renin-angiotensin system blockers, and/or calcium channel blockers. One of the antihypertensive medications must be high ceiling diuretic (loop or thiazide-like), unless there is a documented intolerance or contraindication to diuretic therapy. The doses of the antihypertensive medications should be stable without any dose adjustment during the 30 days prior to randomization; OR
- Patients with uncontrolled hypertension and moderate-to-severe CKD with documented history of intolerance to multiple antihypertensive medications on fewer than 2 antihypertensive medications.

All patients are to have a serum potassium ≤ 4.8 mmol/L at both Screening and the end of the placebo run-in period; and a mean (Visit 1 and Visit 3) eGFR ≥ 15 and ≤ 44 mL/min/1.73 m^2.

STUDY DESIGN AND DURATION:

This is a Phase 2, randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy, safety, and pharmacokinetics (PK) of KBP-5074 in patients with moderate-to-severe CKD and uncontrolled hypertension (Grade 1 to 2 systolic hypertension – ESC/ESH).

The study will enroll approximately 240 patients, randomized in a 1:1:1 ratio to 1 of 3 treatment groups (80 patients in each group): KBP-5074 0.25 mg once daily (QD), KBP-5074 0.5 mg QD, or placebo QD. Randomization will be stratified to balance enrollment for key variables that may influence safety and/or efficacy evaluations, including eGFR (≥ 30 versus < 30 mL/min/1.73 m^2) and SBP (≥ 160 versus < 160 mmHg). Approximately 30% of patients enrolled in the study should have eGFR in the range of 15 to 29 mL/min/1.73 m^2. The study will be approximately 5 months in duration with 84 days of double-blind treatment.

The study will consist of up to a 4-week screening period, 2-week open-label (placebo) run-in period, 84-day double-blind treatment period, and a 4-week post-treatment safety follow-up period.

Plasma samples for PK analysis will be collected from all patients. A total of 4 PK samples will be collected from each patient, including at Day 1 (prior to discharge), Day 14 pre-dose, Day 28 pre-dose, and the End of Study Visit (Day 112)/Early Termination Visit. The pre-dose samples assume that patients will be dosed in the unit on the days above. If patients are not dosed in the

unit on those days, a PK sample will be collected during each of these visits and the date and time of the last dose will be recorded.

Safety will be assessed systematically, and an independent data monitoring committee will perform cumulative reviews of safety data at regular intervals during the study.

Serum potassium levels, serum creatinine, and blood pressure will be monitored throughout the study and clinically significant changes will be reported as adverse events of special interest.

At Screening and the end of the placebo run-in period (Visit 3), patients must have uncontrolled hypertension (Grade 1 to 2 systolic hypertension – ESC/ESH), defined as resting trough-cuff seated SBP ≥ 140 and ≤ 179 mmHg, based on the mean of at least 2 current consecutive blood pressure readings in the clinic, a serum potassium ≤ 4.8 mmol/L at Screening and the end of the placebo run-in period (Visit 3), and a mean (Visit 1 and Visit 3) eGFR ≥ 15 and ≤ 44 mL/min/1.73 m^2.

In all cases, dose and frequency of concurrent antihypertensive medications are expected to be maintained without dose adjustment for 30 days prior to randomization in order to ensure that blood pressure is stable. In general, patients should not add or adjust dose and/or types of the antihypertensive medications they are receiving during the screening period and throughout the duration of the study (unless they develop symptomatic hypotension). The dose of diuretic may be adjusted based on developing or resolved edema, weight gain or loss, or pulmonary congestion.

Patients will be advised to maintain their normal diet and avoid unhealthy levels of alcohol use or potassium-rich foods/drinks during the study period. No potassium supplements are permitted, unless clinically indicated to treat hypokalemia on an emergent basis until serum potassium values are within the normal range. The use of potassium-sparing diuretics is not permitted within 3 months prior to Screening until the end of study assessments. Intermitted or chronic use of potassium-binding drugs is not permitted for 3 months prior to Screening until the end of study assessments.

After completion of the screening period and the qualifying Screening Visit, patients who meet all eligibility criteria (except those criteria scheduled to be assessed after the Screening Visit), will enter the 2-week, open-label (placebo) run-in period. At the end of the run-in period (Visit 3), patients will be reassessed for eligibility, including persistence of uncontrolled hypertension and compliance with open-label placebo received during the run-in period and current antihypertensive medication. If a patient's compliance is < 80% or > 120%, the patient will not be eligible for the study, and no further visits will be performed.

If a patient is found to be ineligible during Screening, a single rescreening is allowed if the Investigator believes that the patient's medical condition has changed, and the patient may be eligible before the rescreening tests. Please note that a new patient number should be assigned to any rescreened patient, and all of the procedures defined in the protocol for the Screening Visit and during the run-in period must be repeated.

Patients who meet all eligibility criteria at Visit 4/Day 1 will be randomized (stratified based on eGFR ≥ 30 versus < 30 mL/min/1.73 m^2 and SBP ≥ 160 versus < 160 mmHg) into the study on Day 1. All randomized patients will receive double-blind treatment for 84 days. Patients will be followed for 4 weeks for safety assessments after the last dose of study drug. Antihypertensive

therapy may be modified if necessary during the safety assessment, following withdrawal of the study drug, to maintain blood pressure control.

A subset of up to 40 patients per treatment group who agree to participate in 24-hour ABPM and still meet eligibility criteria at the end of the run-in period (Visit 3) will undergo 24-hour ABPM on Day -1, Day 40, and Day 82.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

At the Day 1 Visit, eligible patients will be randomized in a 1:1:1 ratio to the following treatment groups:

- KBP-5074 0.25 mg QD orally,
- KBP-5074 0.5 mg QD orally, or
- Placebo QD orally.

EFFICACY VARIABLES:

The primary efficacy variable is the change in trough-cuff resting seated SBP from baseline to Day 84.

The key secondary efficacy variables include the following:

- Change in trough-cuff seated DBP from baseline to Day 84;
- Change in 24-hour mean, daytime mean, nighttime mean, morning mean, last 6 hours of the dosing interval mean, SBP, DBP, MAP, and HR from baseline to Day 84 as measured by 24-hour ABPM in a subset of up to 40 patients per treatment group; and
- Change and percent change in UACR from baseline to Day 84 (for patients with albuminuria [defined as UACR > 300 mg/g] or microalbuminuria [defined as UACR in the range of 30 mg/g to 300 mg/g]).

PHARMACOKINETIC VARIABLES:

Plasma samples for PK analyses will be collected from all patients at the visits indicated on the Schedule of Procedures (Appendix A).

PHARMACODYNAMIC VARIABLES:

The pharmacodynamic (PD) variable of this study is change in serum aldosterone and plasma renin levels from baseline to Day 84.

Serum/plasma samples will be stored at central laboratory for determination of various additional biomarkers, including but not limited to galectin-3, N-terminal of the prohormone brain natriuretic peptide, interleukin-6, collagen biomarkers, and C-reactive protein. The panel of biomarkers and time points for analysis will be determined prior to the database lock.

SAFETY VARIABLES:

Safety variables will include adverse events, vital signs (pulse rate, respiratory rate, and oral temperature), clinical laboratory findings, 12-lead electrocardiograms (ECGs), and physical examination findings.

The following serum potassium/hyperkalemia-related parameters and renal function-related parameters will be collected and evaluated:

- Incidence of hyperkalemia (defined as serum potassium ≥ 5.6 mmol/L), incidence of severe hyperkalemia (defined as serum potassium ≥ 6.0 mmol/L), and incidence of patients with serum potassium > 5.0 mmol/L;
- Change in serum potassium levels from baseline to Day 84; and
- Change in eGFR and creatinine levels > 30% throughout the study period.

STATISTICAL ANALYSES:

The Intent-to-Treat (ITT) Population will consist of all randomized patients who take at least 1 dose of randomized study drug, have a baseline SBP measurement, and have at least 1 post-randomization SBP measurement. The ITT Population is the primary analysis population. All efficacy analyses will be performed for the ITT Population.

The Per-Protocol Population will include all ITT patients who have completed the 84-day double-blind treatment period without any major protocol deviations or violations. The Per-Protocol Population will be used to assess robustness of the primary analysis results. The major protocol deviations will be pre-specified prior to unblinding treatment codes for analyses.

The Safety Population will include all randomized patients who receive at least 1 dose of randomized study drug.

The population-pharmacokinetic (PPK) Population will include all randomized patients who receive at least 1 dose of randomized study drug and have at least 1 measurable concentration of total KBP-5074.

The primary efficacy analysis is to evaluate the change in trough-cuff seated SBP from baseline to Day 84 for the KBP-5074 doses compared to placebo. The endpoint for each patient is defined as the Day 84 cuff seated SBP measurement. If the measurement at this visit is missing or the patient discontinues early, the last post-baseline measurement during the double-blind period will be used.

The primary efficacy analysis will be carried out using a 2-way analysis of covariance (ANCOVA) model with treatment, baseline eGFR level (≥ 30 versus < 30 mL/min/1.73 m^2), and background antihypertensive medication (2 or more) as factors, and the baseline SBP value as a covariate. The least-squares means, standard errors, and the 2-tailed 95% confidence intervals (CIs) for each treatment group and for the comparison will be estimated. The treatment difference between KBP-5074 doses and placebo will be estimated from the ANCOVA model. No multiple comparison adjustment will be used for this Phase 2 study.

The primary efficacy analysis will be based on the ITT Population. Other imputation methods for the primary efficacy endpoint will be explored. The supportive analysis will be carried out for the

primary efficacy variable based on the Per-Protocol Population to examine the impact due to premature dropouts and/or major protocol deviations or violations.

For continuous secondary efficacy variables, the same ANCOVA model will be used as the primary efficacy analysis. For categorical data, logistic regression or chi-square test will be used. Treatment effects will be evaluated between KBP-5074 doses and placebo.

Safety assessments will include monitoring of adverse events, vital signs (pulse rate, respiratory rate, and oral temperature), clinical laboratory findings, 12-lead ECGs, and physical examination findings. All safety analyses will be conducted on the total patient cohort based on the Safety Population.

The assessment of safety will be based primarily on the frequency of patients with adverse events and clinical laboratory abnormalities. Other safety data will be summarized as appropriate.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. Reports will be provided to the Medical Monitor for approval of the coded terms after the database is clean, prior to unblinding. The number and frequency of patients with treatment-emergent adverse events (TEAEs) (ie, those adverse events that newly occur or worsen in severity during the study) will be summarized by system organ class and preferred term. Serious adverse events (SAEs) and TEAEs related to study drug will be summarized in the same manner. A list of patients with SAEs and those who discontinue from the study due to an adverse event will be provided.

Summary statistics by treatment group at baseline, at all post-randomization visits, and changes from baseline to the post-randomization visits for laboratory values will be provided. Occurrence of significant abnormalities in laboratory values from baseline will be summarized by treatment group. Vital signs, body weight, and physical examination findings will be summarized.

The analysis of the PK/PD relationship will be explored. Population PK models will be built using a nonlinear mixed effects modeling technique with NONMEM software based on the PPK Population. Different PK models will be attempted to fit the PK concentration-time data. After the PPK modeling, a population PD approach will be used to explore the concentration-effect relationships. Different PD models will be attempted to fit the concentration-effect data. All PD exploration will be based on the ITT Population.

SAMPLE SIZE DETERMINATION:

For this Phase 2 study, the primary efficacy endpoint is the change in trough-cuff resting seated SBP from baseline to Day 84. Assuming an observed treatment difference of SBP changes between the KBP-5074 group and the placebo group is 5 mmHg, and a standard deviation of change from baseline of 15 mmHg, with 80 patients/group, the CI of the observed difference would not include 0. Assuming 10% to 15% dropout post randomization, 80 patients/group or a total of 240 patients would be needed for this Phase 2 study. Additional sample size estimates based on sample size needed per group to ensure that the observed 95% CI does not include 0 are shown below. No multiple comparison adjustment will be applied.

Sample Size Estimates

Standard Deviation	Observed Treatment Effect		
	4 mmHg	5 mmHg	6 mmHg
14 mmHg	**109**	**70**	**48**
15 mmHg	**125**	**81**	**56**
16 mmHg	**141**	**91**	**63**

Including approximately 10% to 15% dropout.
Abbreviations: mmHg = millimeters of mercury

SITES:

Approximately 90 sites in North America, South America, Israel, and Europe

SPONSOR:

KBP BioSciences Co., Ltd.
116 Village Blvd, Suite 210
Princeton, NJ 08540
United States
Telephone: 609-531-0889
Fax: 609-531-0892

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABPM	Ambulatory blood pressure monitoring
AHA	American Heart Association
ANCOVA	Analysis of covariance
AUC	Area under the plasma concentration versus time curve
CFR	Code of Federal Regulations
CI	Confidence interval
CKD	Chronic kidney disease
C_{max}	Maximum observed plasma concentration
CRA	Clinical Research Associate
CRP	C-reactive protein
CYP	Cytochrome P450
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
ESH	European Society of Hypertension
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HD	Hemodialysis
HIV	Human immunodeficiency virus
HR	Heart rate
HRT	Hormone replacement therapy
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IL-6	Interleukin-6
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
MAP	Mean arterial pressure
MDRD	Modification of Diet in Renal Disease

Abbreviation	Definition
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonist
NF	National Formulary
NT-proBNP	N-terminal of the prohormone brain natriuretic peptide
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PPK	Population pharmacokinetic(s)
QD	Once daily
QTcF	QT interval corrected using Fridericia's formula
SAE	Serious adverse event
SBP	Systolic blood pressure
TEAE	Treatment-emergent adverse event
UACR	Urine albumin-to-creatinine ratio
ULN	Upper limit of normal
USP	United States Pharmacopeia
WOCBP	Women of childbearing potential

1 INTRODUCTION AND BACKGROUND INFORMATION

High blood pressure and hypertensive kidney damage are the leading cause of morbidity and mortality in the United States.[1] Although considerable progress has been made in the treatment of hypertension and prevention of progression of renal insufficiency, the development of new therapy remains critical. Mineralocorticoid receptor (MR), a member of the steroid receptor family, has been shown to have a major pathophysiological role in the progression of kidney diseases, and the inhibition of MR signaling considerably reduces proteinuria in patients with chronic kidney disease (CKD).[1,2,3]

Eplerenone is a highly selective aldosterone blocker developed for the treatment of hypertension and heart failure. However, MR antagonism with eplerenone causes a dose-dependent increase in serum potassium concentrations and is contraindicated in hypertensive patients with a creatinine clearance of <50 mL/min. Eplerenone should also be avoided in patients receiving potassium supplements or other potassium-sparing diuretics, such as amiloride and triamterene, particularly in patients with renal insufficiency, diabetes, and microalbuminuria.[5] In addition, eplerenone causes mild dose-dependent increases in cholesterol, triglycerides, and serum creatinine, and a decrease in serum sodium.[6] For this reason, a new MR antagonist with an improved efficacy and a low potential for adverse effects in patients with hypertension and moderate-to-severe CKD could potentially address this public health issue and an unmet medical need.

KBP BioSciences Co., Ltd. (hereafter KBP BioSciences) is developing KBP-5074, a new investigational non-steroidal MR antagonist (MRA), for the treatment of hypertension and nephropathy, including diabetic and hypertensive nephropathy. It binds to the MR and blocks the binding of aldosterone, a component of the renin-angiotensin-aldosterone system. Aldosterone binds to MR in both epithelial (eg, kidney) and non-epithelial (eg, heart, blood vessels, and brain) tissues, and increases blood pressure through induction of sodium reabsorption and possibly other mechanisms. Thus, MRAs have the potential to block the deleterious effects of aldosterone on the cardiovascular system.

As a non-steroidal MRA, KBP-5074 has the following potential advantages:

- KBP-5074 selectively binds to recombinant human MRs relative to its binding to recombinant human glucocorticoid receptor, progesterone receptor, and androgen receptor. KBP-5074 has been demonstrated to have better efficacy in lowering blood pressure and renal protection in preclinical disease models than the benchmark compound eplerenone; and
- KBP-5074 demonstrated a favorable safety profile compared to that of eplerenone; with no abnormal levels of potassium, cholesterol, triglycerides, or serum creatinine during the long-term toxicology studies. This suggests that KBP-5074 is potentially a safer and more efficacious MRA.

KBP-5074 is an investigational agent, and limited data regarding its clinical safety profile are available at this time. Because KBP-5074 has the same mechanism of action as eplerenone, common adverse events associated with eplerenone may be relevant: dizziness, diarrhea, coughing, fatigue, and flu-like symptoms.

A battery of pharmacology and toxicology studies including rat and dog acute toxicity studies, rat and dog 4-week and 13-week repeated dose toxicity studies, genotoxicity studies, and safety pharmacology studies were conducted to support the Investigational New Drug application for conducting clinical trials.

Further details regarding the preclinical safety studies of KBP-5074 and clinical development program can be found in the Investigator's Brochure.[7]

An open-label, parallel-group, single ascending dose study in healthy subjects to evaluate the safety, tolerability, and pharmacokinetics (PK) of KBP-5074 following oral administration and with a food-effect panel (Protocol KBP5074-1-001, NCT02228733) has been completed. Single oral doses of KBP-5074 at 0.5, 1.0, 5, 10, and 30 mg in the fasted state and 10 mg in the fed state were safe and well tolerated in healthy male and female subjects (a total of 46 subjects received KBP-5074). There were no drug-related adverse events reported during the study. There were no clinically meaningful trends noted based on safety laboratory assessments, including complete blood count and potassium levels, physical examinations, vital sign measurements, and electrocardiograms (ECGs) during the study. No evidence of bone marrow suppression was observed with increasing drug exposure. Specifically, no clinically meaningful trends of change in the complete blood counts (white blood cell, neutrophils, red blood cell, or platelets) with increasing drug exposure were observed. No gender difference in drug exposure was observed. The time to maximum observed concentration under fasted conditions varied from 4 hours to 7 hours, suggesting relatively fast absorption of KBP-5074 following oral administration under fasted conditions.

An open-label, multiple ascending dose study to evaluate the safety, tolerability, and PK of KBP-5074 in healthy subjects with a separate panel in patients with mild-to-moderate renal impairment (Protocol KBP5074-1-002, NCT02653014) has been completed. Administration of doses of 2.5 mg and 5 mg KBP-5074 once daily (QD) for 14 days in healthy subjects (n = 12), and 0.5 mg and 2.5 mg QD for 56 days in mild-to-moderate CKD patients (n = 14) with proteinuria was safe and well tolerated overall. There was no apparent relationship between doses and the incidence or intensity of treatment-emergent adverse events (TEAEs). Hyperkalemia was observed in the high dose group for both healthy volunteers and mild-to-moderate CKD patients with proteinuria (high risk of hyperkalemia). No hyperkalemia was observed in the 0.5 mg dose group, other than 1 patient with a protocol inclusion violation of excessive serum potassium at baseline (5.1 mmol/L) and a history of acute kidney failure who had a hyperkalemia event (defined as a single observation of potassium > 5.6 mmol/L). All hyperkalemia events (other than in the patient with the protocol violation) were resolved without treatment. A clinically meaningful reduction of urine albumin-to-creatinine ratio (UACR) was observed in both treatment groups in Part 2 of the study. An apparent trend for clinically meaningful reduction of blood pressure was also observed, especially for patients with elevated blood pressure and renal impairment in Part 2 of the study.

A Phase 1, open-label study in hemodialysis (HD) and non-HD patients with severe CKD to evaluate safety, tolerability, and PK of KBP-5074 following oral administration (Protocol KBP5074-1-003, NCT02837237) has been completed. Administration of a single dose of 0.5 mg KBP-5074 in HD patients (n = 6) and non-HD patients (n = 5) was safe and well tolerated overall. No severe TEAEs, serious adverse events (SAEs), deaths, or study discontinuations due to TEAEs occurred during the study.

A Phase 1, open-label, partial crossover, single-dose study to evaluate the PK, dose proportionality, and safety/tolerability of tablet versus capsule formulations of KBP-5074 in healthy subjects (Protocol KBP5074-1-004, NCT03340753) has been completed. The study was designed to evaluate the PK of a new tablet formulation versus that of the current capsule formulation and help determine dose selection in future studies. Twenty healthy subjects were allocated 4:1 to either the crossover study groups (Cohort 1, 16 subjects) or to the 0.25-mg tablet

single-dose treatment group (Cohort 2, 4 subjects). Subjects allocated to Cohort 1 were randomized 1:1 to 0.5 mg tablet/capsule (8 subjects) or 1.0 mg tablet/capsule (8 subjects). Within Cohort 1, subjects were further randomized to receive a single dose of KBP-5074 (0.5 mg or 1.0 mg) in either capsule or tablet formulation in a 2-period crossover design that was separated by a 2-week washout period and concluded with a 2-week follow-up period. Subjects allocated to Cohort 2 received a single dose of 0.25 mg in tablet formulation only. Cohort 2 provided additional data for the evaluation of dose exposure for the tablet formulation. The bioavailability of KBP-5074 tablet relative to KBP-5074 capsule was slightly higher: approximately 5% to 10% higher in area under the plasma concentration versus time curves (AUCs) and 15% to 20% higher in the maximum observed plasma concentration (C_{max}). Dose proportionality of KBP-5074 tablet in the range of 0.25 mg to 1.0 mg was demonstrated based on Hummel Criteria; dose proportionality of KBP-5074 tablet in the range of 0.25 mg to 1.0 mg was not demonstrated but was close to dose proportionality according to Smith Criteria. Administration of KBP-5074 0.25 mg, 0.5 mg, and 1.0 mg tablet formulations, and 0.5 mg and 1.0 mg capsule formulations was generally safe and well tolerated, and the incidence of TEAEs was similar among treatments.

The current study (Protocol KBP5074-2-001) is a randomized, double-blind, placebo-controlled, multi-center, Phase 2 study to assess the efficacy, safety, and PK of KBP-5074 0.25 mg QD and KBP-5074 0.5 mg QD versus placebo in patients with moderate-to-severe CKD (as defined by estimated glomerular filtration rate [eGFR] ≥ 15 and ≤ 44 mL/min/1.73 m^2, based on the isotope dilution mass spectrometry traceable Modification of Diet in Renal Disease [MDRD] equation version 4[8]) and uncontrolled hypertension (Grade 1 to 2 systolic hypertension – European Society of Cardiology [ESC]/European Society of Hypertension [ESH]).[9]

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of KBP-5074 in patients with moderate-to-severe CKD on uncontrolled hypertension (eg, Grade 1 to 2 systolic hypertension – ESC/ESH) as determined by change in trough-cuff seated systolic blood pressure (SBP) from baseline to Day 84.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To evaluate the change in trough-cuff seated diastolic blood pressure (DBP) from baseline to Day 84;
- To evaluate the change in 24-hour mean, daytime mean, nighttime mean, morning mean, last 6 hours of the dosing interval mean, SBP, DBP, mean arterial pressure (MAP), and heart rate (HR) from baseline to Day 84 in a subset of up to 40 patients per treatment group as measured by 24-hour ambulatory blood pressure monitoring (ABPM);
- To evaluate the change and percent change in UACR from baseline to Day 84 (for patients with albuminuria [defined as UACR > 300 mg/g] or microalbuminuria [defined as UACR in the range of 30 mg/g to 300 mg/g]);
- To evaluate the change in serum aldosterone and plasma renin levels from baseline to Day 84;
- To evaluate the incidence of hyperkalemia (defined as serum potassium ≥ 5.6 mmol/L), incidence of severe hyperkalemia (defined as serum potassium ≥ 6.0 mmol/L), and incidence of patients with serum potassium > 5.0 mmol/L;
- To evaluate the change in serum potassium levels from baseline to Day 84;
- To evaluate the changes in eGFR and creatinine levels > 30% throughout the study period; and
- To evaluate population PK (PPK) of KBP-5074.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy, safety, and PK of KBP-5074 in patients with moderate-to-severe CKD and uncontrolled hypertension (Grade 1 to 2 systolic hypertension – ESC/ESH).

The study will enroll approximately 240 patients, randomized in a 1:1:1 ratio to 1 of 3 treatment groups (80 patients in each group): KBP-5074 0.25 mg QD, KBP-5074 0.5 mg QD, or placebo QD. Randomization will be stratified to balance enrollment for key variables that may influence safety and/or efficacy evaluations, including eGFR (≥ 30 versus < 30 mL/min/1.73 m^2) and SBP (≥ 160 versus < 160 mmHg). Approximately 30% of patients enrolled in the study should have eGFR in the range of 15 to 29 mL/min/1.73 m^2. The study will be approximately 5 months in duration with 84 days of double-blind treatment.

The study will consist of up to a 4-week screening period, 2-week open-label (placebo) run-in period, 84-day double-blind treatment period, and a 4-week post-treatment safety follow-up period.

Plasma samples for PK analysis will be collected from all patients. A total of 4 PK samples will be collected from each patient, including at Day 1 (prior to discharge), Day 14 pre-dose, Day 28 pre-dose, and the End of Study Visit (Day 112)/Early Termination Visit. The pre-dose samples assume that patients will be dosed in the unit on the days above. If patients are not dosed in the unit on those days, a PK sample will be collected during each of these visits and the date and time of the last dose will be recorded.

Safety will be assessed systematically, and an independent data monitoring committee (IDMC) will perform cumulative reviews of safety data at regular intervals during the study.

Serum potassium levels, serum creatinine, and blood pressure will be closely monitored throughout the study and clinically significant changes will be reported as adverse events of special interest.

At Screening and the end of the placebo run-in period (Visit 3), patients must have uncontrolled hypertension (Grade 1 to 2 systolic hypertension – ESC/ESH), defined as resting trough-cuff seated SBP ≥ 140 and ≤ 179 mmHg, based on the mean of at least 2 current consecutive blood pressure readings in the clinic and a serum potassium ≤ 4.8 mmol/L at Screening and the end of the placebo run-in period (Visit 3), and a mean (Visit 1 and Visit 3) eGFR ≥ 15 and ≤ 44 mL/min/1.73 m^2.

In all cases, dose and frequency of concurrent antihypertensive medications are expected to be maintained without dose adjustment for 30 days prior to randomization in order to ensure that blood pressure is stable. In general, patients should not add or adjust dose and/or types of the antihypertensive medications they are receiving during the screening period and throughout the duration of the study (unless they develop symptomatic hypotension). The dose of diuretic may be adjusted based on developing or resolved edema, weight gain or loss, or pulmonary congestion.

Patients will be advised to maintain their normal diet and avoid unhealthy levels of alcohol use or potassium-rich foods/drinks during the study period. No potassium supplements are permitted, unless clinically indicated to treat hypokalemia on an emergent basis until serum potassium values

are within the normal range. The use of potassium-sparing diuretics is not permitted within 3 months prior to Screening until the end of study assessments. Intermitted or chronic use of potassium-binding drugs is not permitted for 3 months prior to Screening until the end of study assessments.

After completion of the screening period and the qualifying Screening Visit, patients who meet all eligibility criteria (except those criteria scheduled to be assessed after the Screening Visit), will enter the 2-week, open-label (placebo) run-in period. At the end of the run-in period (Visit 3), patients will be reassessed for eligibility, including persistence of uncontrolled hypertension and compliance with open-label placebo received during the run-in period and current antihypertensive medication. If a patient's compliance is < 80% or > 120%, the patient will not be eligible for the study, and no further visits will be performed.

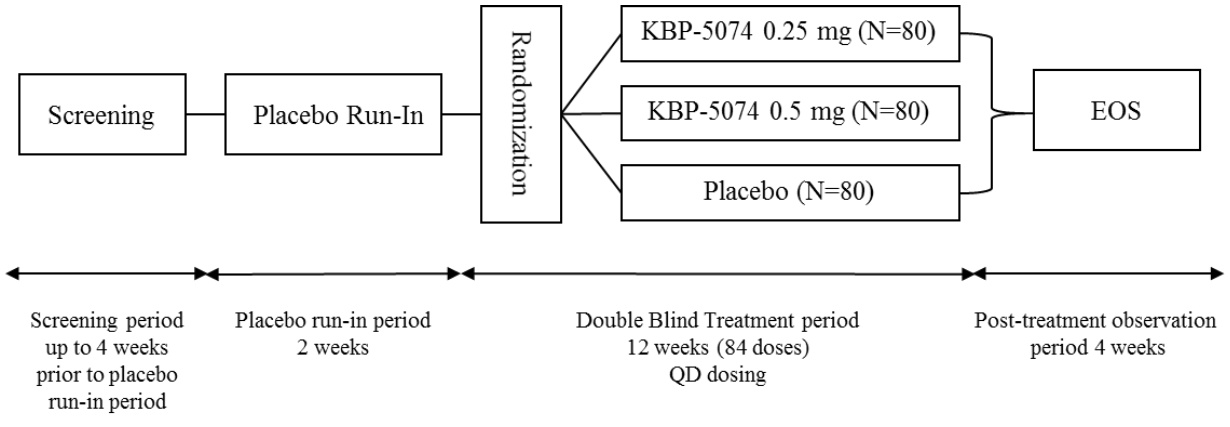
If a patient is found to be ineligible during Screening, a single rescreening is allowed if the Investigator believes that the patient's condition has changed, and the patient may be eligible before the rescreening tests. Please note that a new patient number should be assigned to any rescreened patient, and all of the procedures defined in the protocol for the Screening Visit and during the run-in period must be repeated.

Patients who meet all eligibility criteria at Visit 4/Day 1 will be randomized (stratified based on eGFR ≥ 30 versus < 30 mL/min/1.73 m^2 and SBP ≥ 160 versus < 160 mmHg) into the study on Day 1. All randomized patients will receive double-blind treatment for 84 days. Patients will be followed for 4 weeks for safety assessments after the last dose of study drug. Antihypertensive therapy may be modified if necessary during the safety assessment, following withdrawal of the study drug to maintain blood pressure control.

A subset of up to 40 patients per treatment group who agree to participate in 24-hour ABPM and still meet eligibility criteria at the end of the run-in period (Visit 3) will undergo 24-hour ABPM on Day -1, Day 40, and Day 82.

A study schematic is presented in Figure 1.

Figure 1. Study Schematic



EOS = end of study; QD = Once daily.

3.2 Risk Management

3.2.1 Independent Data Monitoring Committee

An IDMC will be established to monitor this study. The IDMC will independently review the safety data and determine if it is safe to continue the study according to the protocol. An IDMC charter will be developed accordingly.

The following will be closely monitored throughout the study:

- Serum potassium levels (see Section 8.12 for details),
- Serum creatinine (see Section 8.13 for details), and
- Blood pressure (see Section 8.14 for details).

3.3 Study Indication

Uncontrolled hypertension in patients with moderate-to-severe CKD.

4 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

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

1. Male or female, between 18 and 85 years of age, inclusive. The lower age limit may be higher if it is legally required in the participating country;
2. Body mass index between 19 and 45 kg/m^2, inclusive;
3. Stage 3B/4 CKD (defined as eGFR ≥ 15 and ≤ 44 mL/min/1.73 m^2, based on the isotope dilution mass spectrometry traceable MDRD equation version 4, according to central laboratory results at Screening [single retest is allowed]);
4. Uncontrolled hypertension (Grade 1 to 2 systolic hypertension – ESC/ESH), defined as:
    - Resting trough-cuff seated SBP ≥ 140 and ≤ 179 mmHg based on the mean of at least 2 current consecutive clinic blood pressure readings at Screening and at the end of the placebo run-in period (Visit 3); AND
    - Currently on 2 or more antihypertensive medications, which have been titrated upward as tolerated to recommended hypertension target doses (such as diuretics [except for potassium-sparing diuretics], renin-angiotensin system blockers, and/or calcium channel blockers. One of the antihypertensive medications must be high ceiling diuretic (loop or thiazide-like), unless there is a documented intolerance or contraindication to diuretic therapy. The doses of the antihypertensive medications should be stable without any dose adjustment during the 30 days prior to randomization; OR
    - Patients with uncontrolled hypertension and moderate-to-severe CKD with documented history of intolerance to multiple antihypertensive medications on fewer than 2 antihypertensive medications;
5. Serum potassium ≤ 4.8 mmol/L at both Screening and the end of the placebo run-in period. A single retest is allowed to exclude laboratory error or hemolyzed samples;
6. Women of childbearing potential (WOCBP) must agree to use 2 medically accepted, effective methods of birth control during the study and for 90 days after the end of the study. Adequate methods of contraception are defined as those that result in a low failure rate (< 1% per year) when used consistently and correctly. Such methods include the use of oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products (such as an intrauterine diaphragm, condoms, or spermicides);
    - WOCBP are defined as women who are not surgically or chemically sterilized, including hysterectomy or bilateral oophorectomy (tubal ligation is not acceptable), and who are between menarche and 1-year post-menopause; and
    - Post-menopausal is defined as amenorrheic for at least 1 year, AND if aged under 60 years, have a serum follicle-stimulating hormone (FSH) level > 20 mIU/L. Women who are taking hormone replacement therapy (HRT) do not have to have FSH assessments, but the amenorrhea (before starting HRT) must have been naturally (spontaneously) occurring and

have been accompanied by an appropriate clinical profile (eg, age appropriate and history of vasomotor symptoms);

7. Males with partners who are WOCBP must agree to use condoms plus spermicide and their female partner must also be using contraception (eg, hormonal or intra-uterine device). This double contraception must be used from the first dose of study drug until at least 90 days after the last dose of study drug;
8. Males must also refrain from donating sperm during the study and for 90 days after the last dose; and
9. Capable of understanding the written informed consent, provide signed and witnessed written informed consent before any study-specific procedure, and agree to comply with protocol requirements.

4.2 Exclusion Criteria

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

1. Resting trough-cuff seated SBP ≥ 180 or < 140 mmHg, based on the mean of at least 2 current consecutive clinic blood pressure readings at Screening and the end of the placebo run-in period (Visit 3);
2. Serum potassium > 4.8 mmol/L;
3. Compliance with medications (including both open-label placebo and current antihypertensive medications) < 80% or > 120% during the run-in period (assessed at Visit 3);
4. Currently on an MRA (eg, spironolactone or eplerenone) other than KBP-5074, or received any MRAs during the last 3 months prior to Screening, or currently on any potassium supplements;
5. Chronic or intermittent use of a potassium binder for the treatment of hyperkalemia from 3 months prior to Screening until the end of study assessments, including but not limited to calcium polystyrene sulfonates (eg, sorbisterit, calcium resonium), sodium polystyrene sulfonates (eg, kayexalate, anti-kalium sodium), and patiromer (eg, Veltassa™) and sodium zirconium cyclosilicate (eg, Lokelma™);
6. Have routinely or chronically used or required potassium-sparing diuretics (eg, amiloride, triamterene) within 3 months prior to Screening until the end of study assessments;
7. History of known/suspected contraindications, allergy, or intolerance to MRAs (eg, spironolactone, eplerenone) or has a known hypersensitivity to KBP-5074, other MRAs, or related compounds;
8. Clinically significant hyperkalemia while on an angiotensin converting enzyme inhibitor, angiotensin receptor blocker, direct renin inhibitor, and/or MRA, requiring down-titration or discontinuation of above medication, or hospitalization for hyperkalemia within 3 months prior to Screening, or hyperkalemia > 5.6 mmol/L during the 2 weeks prior to Screening;
9. History/diagnosis of renal artery stenosis or history/diagnosis of renovascular hypertension;
10. Currently receiving HD, or peritoneal dialysis within 3 months prior to Screening, and those patients with an episode of acute kidney injury within 3 months of Screening;

11. History of a renal transplant, or impending renal transplant;
12. Acute decompensated heart failure including exacerbation of chronic heart failure manifested by signs and symptoms that may require hospitalization and/or intravenous diuretic therapy (New York Heart Association Class III to IV) within 3 months prior to Screening, or presence of hemodynamically significant valve diseases and/or other hemodynamically significant obstructive lesions of left ventricular outflow tract;
13. Major cardiac, cerebral, and/or carotid artery diseases, including but not limited to acute coronary syndrome, myocardial infarction, stroke, and/or transient ischemic attack; major cardiovascular or percutaneous procedures including cardiac ablation, coronary revascularization, and carotid angioplasty within 6 months prior to Screening; OR
    - Cardiovascular conditions likely to require surgical or percutaneous intervention within 6 months from Screening;
14. History of clinically significant arrhythmia, including but not limited to any of the following:
    - Symptomatic bradycardia and/or symptomatic ventricular arrhythmia within 3 months prior to Screening;
    - Second- or third-degree heart block; or
    - New onset or untreated atrial fibrillation; Note: Patients with stable (6 months) asymptomatic rate controlled atrial fibrillation on appropriate therapy, which may include anticoagulation, are permitted.
15. QT interval corrected using Fridericia's formula (QTcF) > 450 ms for males or > 470 ms for females at Screening or Day 1; QTcF should be the average of the required triplicate set of ECGs at each timepoint;
16. History of prolonged QT interval;
17. History or family history of sudden cardiac death or long QT syndrome;
18. History of cardiac transplant, on a heart transplant list, or has a left ventricular assistance device;
19. History of clinically significant acute or chronic hepatitis (including infectious, metabolic, autoimmune, genetic, ischemic, or other forms), hepatocirrhosis, or hepatic tumors;
20. History of gastrointestinal surgery that might affect absorption/oral bioavailability of oral antihypertensive therapies including KBP-5074;
21. Clinically significant abnormal liver function test at Screening or the end of the run-in period (Visit 3), defined as aspartate aminotransferase or alanine aminotransferase > 3 × the upper limit of normal (ULN) or total bilirubin > 2 × ULN;
    - Note: Patients with total bilirubin > 2 × ULN and history of Gilbert's syndrome may be included.
22. Positive blood screen for human immunodeficiency virus (HIV), hepatitis B surface antigen (HbsAg), or hepatitis C virus (HCV) antibody;
23. History of malignancy in the past 5 years, with the exception of basal or resected cutaneous squamous cell carcinoma of the skin or carcinoma in situ, prostate cancer in situ with a normal

prostate-specific antigen post treatment, cervical carcinoma in situ, gastric cancer in situ, colon cancer in situ adequately treated with no progression over the past 2 years;

24. History of prescription drug abuse, illicit drug use, or alcohol abuse according to medical history within 6 months prior to Screening;
25. A positive drug screen test (excluding a positive result secondary to a prescribed medication from a physician, or tetrahydrocannabinol) at Screening or the end of the run-in period (Visit 3);
26. Female patients who are known to be pregnant or breastfeeding;
27. Previously enrolled in any KBP-5074 study;
28. Receipt of any other investigational product within 30 days or 5 half-lives (whichever is longer) prior to Screening;
29. Use of any nutrients known to modulate cytochrome P450 (CYP)3A activity (based on the KBP-5074 metabolic pathway) or any strong or moderate inhibitors or inducers of CYP3A4, starting from 14 days prior to the first dose of study drug at Day 1 until the end of study assessments, including but not limited to the following: inhibitors, such as ketoconazole, miconazole, itraconazole, fluconazole, atazanavir, erythromycin, clarithromycin, ranitidine, and cimetidine, and inducers, such as rifampicin, rifabutin, glucocorticoids, carbamazepine, phenytoin, phenobarbital, and St. John's wort;
30. Has donated or lost a significant volume (> 500 mL) of blood or plasma within 30 days prior to Screening;
31. An employee or family member of the Investigator or study site personnel;
32. Unlikely to comply with the protocol requirements, instructions, and/or study-related restrictions (eg, uncooperative attitude, unavailable for follow up call, and/or improbability of completing the clinical study); and
33. History of any other prior or concomitant clinical condition or acute and/or unstable systemic disease not listed above that, in the opinion of the Investigator, compromises patient inclusion, such as a history or presence of clinically decompensated or unstable cardiovascular, pulmonary, hepatic, gallbladder or biliary tract, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or psychiatric disease, or concomitant morbidity of such severity that the patient is likely to die within 1 year from Screening.

4.3 Withdrawal Criteria

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- The patient withdraws consent or requests discontinuation from the study for any reason;
- Significant protocol violation, including major protocol violations, such as taking prohibited medication or inability to comply with protocol procedure;

- Any clinically significant adverse event, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient, including:
  - Hypertensive Emergency;
  - Hyperkalemia defined in Table 1; or
  - Sustained increase in serum creatinine defined as an increase > 50% in serum creatinine from baseline and confirmed by a repeated test (see Section 8.13);
- Pregnancy;
- Termination of the study by the Sponsor or regulatory authority; or
- Lost to follow-up.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the Early Termination Visit (see Section 6.6). The reason for patient withdrawal must be documented in the electronic Case Report Form (eCRF).

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records.

Withdrawn patients will not be replaced.

5 STUDY TREATMENTS

5.1 Treatment Groups

After completion of the screening period and qualifying Screening Visit, patients who meet all eligibility criteria (except those criteria scheduled to be assessed after the Screening Visit) will enter a 2-week run-in period. During this time, all patients will be given open-label placebo.

At the Day 1 Visit (scheduled within 4 ±2 days after the end of the run-in period [Visit 3]), eligible patients will be randomized by Interactive Response Technology (IRT) in a 1:1:1 ratio to the following treatment groups:

- KBP-5074 0.25 mg QD orally,
- KBP-5074 0.5 mg QD orally, or
- Placebo QD orally

The duration of the double-blind treatment period will be 84 days. Patients will remain on their stable antihypertensive medication (ie, no change in antihypertensive medication) throughout the entire study (including both the run-in and treatment periods). The dose of diuretic may be adjusted based on developing or resolved edema, weight gain or loss, or pulmonary congestion.

5.2 Rationale for Dosing

As outlined in Section 1, based on data from preclinical and clinical efficacy, safety, PK, and relative bioavailability studies, KBP BioSciences has determined that 0.25 mg and 0.5 mg QD are the appropriate dosage for a planned Phase 2b study using the KBP-5074 tablet formulation. Clinical data were derived from 102 study subjects who participated in 4 Phase 1 studies, which included healthy normal subjects and patients with mild, moderate, and severe CKD, including patients receiving HD. Data show that study drug exposure, as expressed by several PK measures (AUC, C_{max}), is similar for healthy subjects and patients with mild-to-moderate CKD. Exposure is increased, however, in patients with severe CKD (up to around 60% higher AUC and C_{max}). Analysis of safety data from the Phase 1 studies suggests a possible correlation between increased exposure (AUC > 3000 ng*h/ml) and risk of hyperkalemia. The fragility of patients with severe CKD implies that sensitivity to drug and/or increases in free drug levels could substantially potentiate wanted and unwanted pharmaceutical effects in this population. These effects may be amplified with the use of the tablet formulation of KBP-5074, which has an approximately 18% higher C_{max} than the capsule formulation.

5.3 Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Patients will be randomized to one of the 3 treatment groups listed in Section 5.1. Randomization will be stratified based on the following values at baseline:

- eGFR: ≥ 30 versus < 30 mL/min/1.73 m^2, and
- SBP: ≥ 160 versus < 160 mmHg.

Individual treatment assignments will be blinded to the Sponsor, Investigator, study personnel, and patients throughout the course of the study. All individuals directly involved in the conduct of the study, including data management personnel, will remain blinded to treatment assignments.

5.4 Breaking the Blind

At all times, study personnel will attempt to safeguard the integrity of the blinding in order to minimize bias in the conduct of the study. Breaking of the blind should not occur except in the case of a medical emergency and should occur after discussion with the Medical Monitor. In such a case, the Investigator may access this information by contacting the Sponsor or its designee. If the blind is broken for an individual patient, the blinding should be preserved for the remainder of the patients throughout the duration of the study. In such a case, study personnel may be notified of that individual patient's treatment assignment without jeopardizing study blinding for the overall study.

If the blind is broken for a patient, the patient may or may not be asked to withdraw from the study. This decision will be based on Investigator consultation with the Medical Monitor. All patients will be asked to continue study visits to the end of the study whether or not they remain on study drug. If a patient must temporarily discontinue study drug, they may or may not be able to restart study drug. This decision will be based on Investigator consultation with the Medical Monitor.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

KBP-5074 tablets are supplied as 0.25 mg and 0.5 mg strengths for this study. The weight of the 0.25 mg and 0.5 mg tablets are 109.5 mg and 111.0 mg, respectively.

For the 0.25 mg strength, each unit of KBP-5074 drug product contains 0.23% KBP-5074 drug substance, 36.53% of microcrystalline cellulose PH101 (FMC, United States Pharmacopeia [USP]/National Formulary [NF]) as filler, 54.79% of lactose monohydrate (MEGGLE, USP/NF) as filler, 3.2% of croscarmellose sodium (FMC, USP/NF) as disintegrant agent, 2.28% of hydroxypropyl methyl cellulose E50 (DOW, USP/NF) as binder, 1.14% of sodium lauryl sulfate (BASF, USP/NF) as solubilizer, 0.91% magnesium stearate (GREVEN, USP/NF) as lubricant, and 0.91% silicon dioxide (GRACE, USP/NF) as flow agent.

For the 0.5 mg strength, each unit of KBP-5074 drug product contains 0.45% KBP-5074 drug substance, 36.04 % of microcrystalline cellulose PH101 (FMC, USP/NF) as filler, 54.05% of lactose monohydrate (MEGGLE, USP/NF) as filler, 3.15% of croscarmellose sodium (FMC, USP/NF) as disintegrant agent, 2.25% of hydroxypropyl methyl cellulose E50 (DOW, USP/NF) as binder, 2.25% of sodium lauryl sulfate (BASF, USP/NF) as solubilizer, 0.90% magnesium stearate (GREVEN, USP/NF) as lubricant, and 0.90% silicon dioxide (GRACE, USP/NF) as flow agent.

For the placebo, each unit of placebo contains 36.20% of microcrystalline cellulose PH101 (FMC, USP/NF) as filler, 54.30% of lactose monohydrate (MEGGLE, USP/NF) as filler, 3.17% of croscarmellose sodium (FMC, USP/NF) as disintegrant agent, 2.26% of hydroxypropyl methyl cellulose E50 (DOW, USP/NF) as binder, 2.26% of sodium lauryl sulfate (BASF, USP/NF) as solubilizer, 0.90% magnesium stearate (GREVEN, USP/NF) as lubricant, and 0.90% silicon dioxide (GRACE, USP/NF) as flow agent.

KBP-5074 tablets will be packaged in polypropylene bottles and closed by low-density polyethylene bottle caps with drying agent. Each polypropylene bottle will contain 35 tablets of drug product.

Each bottle will be labeled in English, the language appropriate to the investigational site participating in the study, and according to country-specific requirements. Label text will be approved according to the Sponsor's agreed procedures.

For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice will be used, ensuring that each dose of study drug can be traced back to the respective bulk ware of the ingredients. A complete record of batch numbers and expiry dates of all study drug, as well as the labels, will be maintained in the Sponsor's study file.

5.5.2 Study Drug Preparation and Dispensing

Study drug will be dispensed as indicated on the Schedule of Procedures (Appendix A). At each visit where study drug is dispensed, the Investigator or designee will provide patients with sufficient study drug until the next scheduled dispensing visit.

5.5.3 Study Drug Administration

Patients will take 1 tablet of either KBP-5074 0.25 mg, KBP-5074 0.5 mg, or placebo orally QD.

5.5.4 Treatment Compliance

If a patient's compliance with open-label placebo and/or current antihypertensive medications is < 80% or > 120% during the run-in period, the patient will not be eligible for the study, and no further visits will be performed.

Patient compliance with study drug will be assessed by clinical site personnel via tablet counts of returned study drug and by questioning the patient, if necessary, at every post-randomization visit. A patient who is not compliant (has taken < 80% or > 120% of study drug) will be counseled at each visit on the importance of taking study drug as instructed.

5.5.5 Storage and Accountability

Study drug must be stored in a secure area according to local regulations so that only the Investigator and other designated personnel have access to the study drug. The study drug should be stored at 15ºC to 25ºC and protected from light and moisture.

The study drugs will be shipped to the investigational site.

All unused and/or partially used study drug, except retention samples, must be returned to Worldwide Clinical Trials (Worldwide), if not authorized by the Sponsor to be destroyed at the site, prior to or upon completion or termination of the study.

All study drugs returned to Worldwide must be accompanied by the appropriate documentation and be clearly identified. Returned supplies should be in their original containers. Empty bottles may be returned to Worldwide; however, it is the Investigator's responsibility to arrange disposal of all empty containers. The return of unused study drug should be arranged by the assigned site monitor.

5.6 Prior and/or Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Use of the following medications is not permitted during the study:

- MRAs other than KBP-5074;
- Potassium binders used for treatment of hyperkalemia from 3 months prior to Screening until the end of study assessments, including but not limited to calcium polystyrene (eg, sorbisterit, calcium resonium), sodium polystyrene (eg, kayexalate, anti-kalium sodium), patiromer (eg, Veltassa), and sodium zirconium cyclosilicate (eg, Lokelma);
- Potassium-sparing diuretics (eg, amiloride, triamterene) within 3 months prior to Screening until the end of study assessments;
- Potassium supplements (unless clinically indicated on an emergent basis to treat hypokalemia until serum potassium values are within the normal range [see Section 8.12]);
- Hemodialysis/peritoneal dialysis;
- Any nutrients known to modulate CYP3A activity (based on the KBP-5074 metabolic pathway) or any strong or moderate inhibitors or inducers of CYP3A4, starting from 14 days prior to the first dose of study drug at Day 1 until the end of study assessments, including, but not limited to the following: inhibitors, such as ketoconazole, miconazole, itraconazole, fluconazole, atazanavir, erythromycin, clarithromycin, ranitidine, and cimetidine, and inducers, such as rifampicin, rifabutin, systemic glucocorticoids (inhaled and topical permitted), carbamazepine, phenytoin, phenobarbital, and St. John's wort; and
- Any other medications (prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications) that potentially increase serum potassium levels and/or cause toxicity to the kidney, including chronic or daily use of nonsteroidal anti-inflammatory drugs. These medications should be taken only if the Investigator considers these medically necessary. It is recommended that serum potassium levels and eGFR values should be closely monitored when patients take these medications.

5.6.2 Restricted Medications and/or Procedures

Patients will be advised to maintain their normal diet and avoid unhealthy levels of alcohol use or potassium-rich foods/drinks during the study period. See Section 8.12 for more details on monitoring of potassium and management of elevated serum potassium.

5.6.3 Documentation of Prior and Concomitant Medication Use

All medications in addition to the study drug (including vitamin preparations) that are taken by the patient during the study must be documented as concomitant medications and reported on the corresponding eCRF. The use of sodium bicarbonate or dosage adjustment for treatment of acidosis in CKD is permitted

Patients must currently be on 2 or more antihypertensive medications, which have been titrated upward as tolerated to recommended hypertension target doses (such as diuretics [except for potassium sparing diuretics], renin angiotensin system blockers, and/or calcium channel blockers. One of the antihypertensive medications must be high ceiling diuretic (loop or thiazide-like),

unless there is a documented intolerance or contraindication to diuretic therapy. The doses of the antihypertensive medications should be stable without dose adjustment during the 30 days prior to randomization. The dose of diuretic may be adjusted based on developing or resolved edema, weight gain or loss, or pulmonary congestion.

5.6.4 Management of Other Co-Morbidities

Patients who have additional co-morbidities (eg, diabetes, hyperlipidemia, and cardiovascular disease), should be managed and treated with glucose lowering, lipid lowering, and anti-platelet therapies as recommended by local clinical practice guidelines. It is highly recommended that any medical treatments for these co-morbidities will not be changed during the study period (from Screening to the End of Study Visit [Day 112]/Early Termination Visit).

6 STUDY PROCEDURES

6.1 Informed Consent

Written informed consent for the study will be obtained from all patients before any protocol-specific procedures are carried out.

6.2 Screening Visit (Visit 1)

The following procedures will be performed at Visit 1:

- Obtain informed consent;
- Assess eligibility criteria;
- Record demographics and medical history;
- Perform physical examination;
- Record height and weight;
- Calculate body mass index;
- Contact IRT;
- Perform 12-lead ECG in triplicate (patients should be resting in a supine position for at least 10 minutes prior to assessment);
- Obtain vital signs, including pulse rate, respiratory rate, and oral temperature;
- Obtain blood pressure;
    - Note: Patients must have uncontrolled hypertension, defined as resting trough-cuff seated SBP ≥ 140 and ≤ 179 mmHg, based on the mean of at least 2 current consecutive blood pressure readings in the clinic;
    - Blood pressures are to be obtained according to the AHA recommendations for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable chair with back support for at least 10 minutes before measurement and remain still during the measurement. The patient's limb should be supported to measure blood pressure to ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the same arm throughout the study. Triplicate blood pressure measurements should be taken approximately 2 minutes apart with a validated, oscillometric upper arm blood pressure monitor. Trough cuff SBP and DBP values will be assessed based on the pre-defined blood pressure measurement guideline throughout the study. Pulse will be obtained simultaneously with blood pressure measurements;
- Obtain blood samples for:
    - HIV, HbsAg, and HCV tests;
    - Clinical laboratory tests (central laboratory; see Appendix B); and
    - FSH (post-menopausal women only);

- Obtain urine sample for:
  - Drug screen;
  - Urinalysis (central laboratory; see Appendix B); and
  - UACR;
- Obtain serum sample for potassium (local and central laboratories);
  - Note: Serum potassium should be ≤ 4.8 mmol/L (local lab) to advance or continue to the placebo run-in Period;
- Obtain serum sample for creatinine (central laboratory);
- Obtain serum sample for pregnancy test (WOCBP only); and
- Record adverse events and concomitant medications.

If a patient is found to be not eligible during Screening, a single rescreening is allowed if the Investigator believes that the patient's condition has changed, and the patient may be eligible before the rescreening tests. Please note that a new patient number should be assigned to any rescreened patients, and all of the procedures defined in the protocol for the Screening Visit must be repeated.

6.3 Open-Label Placebo Run-In Period

6.3.1 Start of Open-Label Placebo Run-In Period (Visit 2)

The following procedures will be performed at Visit 2:

- Record weight;
- Contact IRT;
- Obtain vital signs, including pulse rate, respiratory rate, and oral temperature;
- Obtain blood pressure;
  - Note: Patients must have uncontrolled hypertension, defined as resting trough-cuff seated SBP ≥ 140 and ≤ 179 mmHg, based on the mean of at least 2 current consecutive blood pressure readings in the clinic;
  - Blood pressures are to be obtained according to the AHA recommendations for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable chair with back support for at least 10 minutes before measurement and remain still during the measurement. The patient's limb should be supported to measure blood pressure to ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the same arm throughout the study. Triplicate blood pressure measurements should be taken approximately 2 minutes apart with a validated, oscillometric upper arm blood pressure monitor. Trough cuff SBP and DBP values will be assessed based on the pre-defined blood pressure measurement guideline throughout the study. Pulse will be obtained simultaneously with blood pressure measurements;

- Record adverse events and concomitant medications; and
- Instruct patient on study drug and dispense study drug.
    - Note: Open-label placebo will be dispensed.

6.3.2 End of Open-Label Placebo Run-In Period (Visit 3)

The following procedures will be performed at Visit 3:

- Assess eligibility criteria;
- Check study drug accountability and collect unused study drug;
    - Note: If a patient's compliance to medications (including both open-label placebo and current antihypertensive medications) is < 80% or > 120%, he/she will not be eligible for the study and no further visits will be required;
- Record weight;
- Obtain vital signs, including pulse rate, respiratory rate, and oral temperature;
- Obtain blood pressure;
    - Note: Patients must have uncontrolled hypertension, defined as resting trough-cuff seated SBP ≥ 140 and ≤ 179 mmHg, based on the mean of at least 2 current consecutive blood pressure readings in the clinic;
    - Blood pressures are to be obtained according to the AHA recommendations for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable chair with back support for at least 10 minutes before measurement and remain still during the measurement. The patient's limb should be supported to measure blood pressure to ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the same arm throughout the study. Triplicate blood pressure measurements should be taken approximately 2 minutes apart with a validated, oscillometric upper arm blood pressure monitor. Trough cuff SBP and DBP values will be assessed based on the pre-defined blood pressure measurement guideline throughout the study. Pulse will be obtained simultaneously with blood pressure measurements;
- Obtain urine sample for drug screen;
- Obtain serum sample for potassium (local and central laboratories);
    - Note: Serum potassium should be ≤ 4.8 mmol/L (local lab) to advance to randomization;
- Obtain serum sample for creatinine (central laboratory);
- Obtain blood sample for clinical chemistry (central laboratory; see Appendix B);
- Record adverse events and concomitant medications; and

- Instruct patient on 24-hour urine collection to be provided at Visit 4 and dispense laboratory materials for collection.

6.4 Randomization and Treatment

6.4.1 Day -1 (ABPM Visit)

This visit is for patients undergoing 24-hour ABPM only (a subset of up to 40 patients per treatment group who agree to participate in 24-hour ABPM and still meet eligibility criteria at the end of the run-in period [Visit 3]) and is to be scheduled within 3 days of the end of the run-in period (Visit 3).

The following procedure will be performed at the ABPM Visit:

- 24-hour ABPM device placement and start. Blood pressure and HR measurements will be obtained every 20 minutes during the interval of 06:00:00 hours to 21:59:59 hours (to coincide with the daytime, awake period) and every 30 minutes during the interval of 22:00:00 hours to 05:59:59 hours (to coincide with the nighttime, sleeping period). During the 24-hour ABPM recording period, a diary will be provided to the patient. Instructions and training will be provided to the site staff who will in turn provide instructions to the patient.

6.4.2 Day 1 (Visit 4) ±2 Days

This visit is to be scheduled within 4 ±2 days after the end of the run-in period (Visit 3).

The following procedures will be performed at Visit 4:

- Assess eligibility: Patients must have uncontrolled hypertension, defined as resting trough-cuff seated SBP ≥ 140 and ≤ 179 mmHg, based on the mean of at least 2 current consecutive blood pressure readings in the clinic. Prior to randomization, all patients are to have a serum potassium ≤ 4.8 mmol/L at both Screening and the end of the placebo run-in period; and a mean (Visit 1 and Visit 3) eGFR ≥ 15 and ≤ 44 mL/min/1.73 $m^{2.}$
- Record weight;
- Perform physical examination (pre-dose);
- Perform 12-lead ECG in triplicate (patients should be resting in a supine position for at least 10 minutes prior to assessment);
- Obtain vital signs, including pulse rate, respiratory rate, and oral temperature;
- Obtain blood pressure prior to study drug administration;
    - Blood pressures are to be obtained according to the AHA recommendations for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable chair with back support for at least 10 minutes before measurement and remain still during the measurement. The patient's limb should be supported to measure blood pressure to ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the same arm throughout the study. Triplicate blood pressure measurements should be taken approximately 2 minutes apart with a validated, oscillometric upper arm blood pressure

monitor. Trough cuff SBP and DBP values will be assessed based on the pre-defined blood pressure measurement guideline throughout the study. Pulse will be obtained simultaneously with blood pressure measurements;

- Obtain blood sample for clinical laboratory tests (central laboratory; see Appendix B);
- Obtain urine sample for:
  - Urinalysis (central laboratory; see Appendix B);
  - Urine pregnancy test for WOCBP only (pre-dose);
  - UACR; and
  - 24-hour urine for UACR;
- Obtain serum sample for potassium (local and central laboratories);
- Obtain serum sample for creatinine (central laboratory);
- Obtain plasma sample for PK from all patients (prior to patient's release from the unit);
- Obtain serum sample for aldosterone;
- Obtain plasma sample for renin;
- Obtain serum/plasma samples that will be stored at central laboratory for determination of various additional biomarkers, including but not limited to galectin-3, N-terminal of the prohormone brain natriuretic peptide (NT-proBNP), interleukin-6 (IL-6), collagen biomarkers, and C-reactive protein (CRP). The panel of biomarkers and time points for analysis will be determined prior to the database lock;
- Record adverse events and concomitant medications;
- After above laboratory and procedures, administer first dose of study drug and record time;
- Instruct patient on study drug and dispense study drug; and
- Download 24-hour ABPM readings at site (for a subset of up to 40 patients per treatment group who agree to participate in 24-hour ABPM and still meet eligibility criteria at the end of the run-in period [Visit 3] who undergo 24-hour ABPM).

6.4.3 Day 7 (Visit 5) ±2 Days

The following procedures will be performed at Visit 5:

- Record weight;
- Perform 12-lead ECG in triplicate (patients should be resting in a supine position for at least 10 minutes prior to assessment);
- Obtain vital signs, including pulse rate, respiratory rate, and oral temperature;
- Obtain blood pressure prior to study drug administration;
  - Blood pressures are to be obtained according to the AHA recommendations for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable

chair with back support for at least 10 minutes before measurement and remain still during the measurement. The patient's limb should be supported to measure blood pressure to ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the same arm throughout the study. Triplicate blood pressure measurements should be taken approximately 2 minutes apart with a validated, oscillometric upper arm blood pressure monitor. Trough cuff SBP and DBP values will be assessed based on the pre-defined blood pressure measurement guideline throughout the study. Pulse will be obtained simultaneously with blood pressure measurements;

- Obtain blood sample for clinical laboratory tests (central laboratory; see Appendix B);
- Obtain urine sample for:
  - Urinalysis (central laboratory; see Appendix B); and
  - UACR;
- Obtain serum sample for potassium (local and central laboratories);
- Obtain serum sample for creatinine (central laboratory);
- Record adverse events and concomitant medications;
- Check study drug accountability and collect unused study drug;
- Administer daily dose of study drug and record time; and
- Instruct patient on study drug and re-dispense study drug.

6.4.4 Day 14 (Visit 6) ±2 Days

The following procedures will be performed at Visit 6:

- Record weight;
- Obtain vital signs including pulse rate, respiratory rate, and oral temperature;
- Obtain blood pressure prior to study drug administration;
  - Blood pressures are to be obtained according to the AHA recommendations for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable chair with back support for at least 10 minutes before measurement and remain still during the measurement. The patient's limb should be supported to measure blood pressure to ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the same arm throughout the study. Triplicate blood pressure measurements should be taken approximately 2 minutes apart with a validated, oscillometric upper arm blood pressure monitor. Trough cuff SBP and DBP values will be assessed based on the pre-defined blood pressure measurement guideline throughout the study. Pulse will be obtained simultaneously with blood pressure measurements;
- Obtain blood sample for clinical laboratory tests (central laboratory; see Appendix B);

- Obtain urine sample for:
  - Urinalysis (central laboratory; see Appendix B); and
  - UACR;
- Obtain serum sample for potassium (local and central laboratories);
- Obtain serum sample for creatinine (central laboratory);
- Obtain plasma sample for PK from all patients (pre-dose). If patients are not dosed in the unit on this day, a PK sample will be collected, and the date and time of the last dose will be recorded;
- Record adverse events and concomitant medications;
- Check study drug accountability and collect unused study drug;
- Administer daily dose of study drug and record time; and
- Instruct patient on study drug and re-dispense study drug.

6.4.5 Day 28 (Visit 7) ±3 Days

The following procedures will be performed at Visit 7:

- Record weight;
- Contact IRT;
- Obtain vital signs including pulse rate, respiratory rate, and oral temperature;
- Obtain blood pressure prior to study drug administration;
  - Blood pressures are to be obtained according to the AHA recommendations for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable chair with back support for at least 10 minutes before measurement and remain still during the measurement. The patient's limb should be supported to measure blood pressure to ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the same arm throughout the study. Triplicate blood pressure measurements should be taken approximately 2 minutes apart with a validated, oscillometric upper arm blood pressure monitor. Trough cuff SBP and DBP values will be assessed based on the pre-defined blood pressure measurement guideline throughout the study. Pulse will be obtained simultaneously with blood pressure measurements;
- Obtain blood sample for clinical laboratory tests (central laboratory; see Appendix B);
- Obtain urine sample for:
  - Urinalysis (central laboratory; see Appendix B); and
  - UACR;
- Obtain serum sample for potassium (local and central laboratories);

- Obtain serum sample for creatinine (central laboratory);
- Obtain plasma sample for PK from all patients (pre-dose). If patients are not dosed in the unit on this day, a PK sample will be collected, and the date and time of the last dose will be recorded;
- Record adverse events and concomitant medications;
- Check study drug accountability and collect unused study drug;
- Instruct patient on study drug and re-dispense study drug;
- Administer daily dose of study drug and record time; and
- Instruct patient on 24-hour urine collection to be provided at Visit 8 and dispense laboratory materials for collection.

6.4.6 Day 40 (ABPM Visit) ±3 Days

This visit is for 24-hour ABPM patients only (a subset of up to 40 patients per treatment group who agree to participate in 24-hour ABPM and still meet eligibility criteria at the end of the run-in period [Visit 3]).

The following procedure will be performed at the ABPM Visit:

- 24-hour ABPM device placement and start. Blood pressure and HR measurements will be obtained every 20 minutes during the interval of 06:00:00 hours to 21:59:59 hours (to coincide with the daytime, awake period) and every 30 minutes during the interval of 22:00:00 hours to 05:59:59 hours (to coincide with the nighttime, sleeping period). During the 24-hour ABPM recording period, a diary will be provided to the patient. Instructions and training will be provided to the site staff, who will in turn provide instructions to the patient.

6.4.7 Day 42 (Visit 8) ±3 Days

The following procedures will be performed at Visit 8:

- Record weight;
- Obtain vital signs including pulse rate, respiratory rate, and oral temperature;
- Obtain blood pressure prior to study drug administration;
    - Blood pressures are to be obtained according to the AHA recommendations for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable chair with back support for at least 10 minutes before measurement and remain still during the measurement. The patient's limb should be supported to measure blood pressure to ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the same arm throughout the study. Triplicate blood pressure measurements should be taken approximately 2 minutes apart with a validated, oscillometric upper arm blood pressure monitor. Trough cuff SBP and DBP values will be assessed based on the pre-defined blood pressure measurement guideline throughout the study. Pulse will be obtained simultaneously with blood pressure measurements;

- Obtain blood sample for clinical laboratory tests (central laboratory; see Appendix B);
- Obtain urine sample for:
  - Urinalysis (central laboratory; see Appendix B);
  - UACR; and
  - 24-hour urine for UACR;
- Obtain serum sample for potassium (local and central laboratories);
- Obtain serum sample for creatinine (central laboratory);
- Record adverse events and concomitant medications;
- Check study drug accountability and collect unused study drug;
- Instruct patient on study drug and re-dispense study drug;
- Administer daily dose of study drug and record time; and
- Download 24-hour ABPM readings at site (for a subset of up to 40 patients per treatment group who agree to participate in 24-hour ABPM and still meet eligibility criteria at the end of the run-in period [Visit 3] who undergo 24-hour ABPM).

6.4.8 Day 56 (Visit 9) ±3 Days

The following procedures will be performed at Visit 9:

- Record weight;
- Contact IRT;
- Obtain vital signs including pulse rate, respiratory rate, and oral temperature;
- Obtain blood pressure prior to study drug administration;
  - Blood pressures are to be obtained according to the AHA recommendations for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable chair with back support for at least 10 minutes before measurement and remain still during the measurement. The patient's limb should be supported to measure blood pressure to ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the same arm throughout the study. Triplicate blood pressure measurements should be taken approximately 2 minutes apart with a validated, oscillometric upper arm blood pressure monitor. Trough cuff SBP and DBP values will be assessed based on the pre-defined blood pressure measurement guideline throughout the study. Pulse will be obtained simultaneously with blood pressure measurements;
- Obtain blood sample for clinical laboratory tests (central laboratory; see Appendix B);

- Obtain urine sample for:
  - Urinalysis (central laboratory; see Appendix B); and
  - UACR;
- Obtain serum sample for potassium (local and central laboratories);
- Obtain serum sample for creatinine (central laboratory);
- Record adverse events and concomitant medications;
- Check study drug accountability and collect unused study drug;
- Instruct patient on study drug and re-dispense study drug;
- Administer daily dose of study drug and record time; and
- Instruct patient on 24-hour urine collection to be provided at Visit 10 and dispense laboratory materials for collection.

6.4.9 Day 82 (ABPM Visit) ±3 Days

This visit is for 24-hour ABPM patients only (a subset of up to 40 patients per treatment group who agree to participate in 24-hour ABPM and still meet eligibility criteria at the end of the run-in period [Visit 3]).

The following procedure will be performed at the ABPM Visit:

- 24-hour ABPM device placement and start. Blood pressure and HR measurements will be obtained every 20 minutes during the interval of 06:00:00 hours to 21:59:59 hours (to coincide with the daytime, awake period), and every 30 minutes during the interval of 22:00:00 hours to 05:59:59 hours (to coincide with the nighttime, sleeping period). During the 24-hour ABPM recording period, a diary will be provided to the patient. Instructions and training will be provided to the site staff, who will in turn provide instructions to the patient.

6.4.10 Day 84 (Visit 10) ±3 Days

The following procedures will be performed at Visit 10:

- Perform physical examination;
- Record weight;
- Calculate body mass index;
- Obtain vital signs including pulse rate, respiratory rate, and oral temperature;
- Obtain blood pressure;
  - Blood pressures are to be obtained according to the AHA recommendations for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable chair with back support for at least 10 minutes before measurement and remain still during the measurement. The patient's limb should be supported to measure blood pressure to ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the

same arm throughout the study. Triplicate blood pressure measurements should be taken approximately 2 minutes apart with a validated, oscillometric upper arm blood pressure monitor. Trough cuff SBP and DBP values will be assessed based on the pre-defined blood pressure measurement guideline throughout the study. Pulse will be obtained simultaneously with blood pressure measurements;

- Obtain blood sample for clinical laboratory tests (central laboratory; see Appendix B);
- Obtain urine sample for:
  - Urinalysis (central laboratory; see Appendix B);
  - UACR; and
  - 24-hour urine for UACR;
- Obtain serum sample for aldosterone;
- Obtain plasma sample for renin;
- Obtain serum sample for potassium (local and central laboratories);
- Obtain serum sample for creatinine (central laboratory);
- Obtain serum/plasma samples that will be stored at the central laboratory for determination of various additional biomarkers, including but not limited to galectin-3, NT-proBNP, IL-6, collagen biomarkers and CRP. The panel of biomarkers and time points for analysis will be determined prior to the database lock;
- Record adverse events and concomitant medications;
- Check study drug accountability and collect unused study drug; and
- Download 24-hour ABPM readings at site (for a subset of up to 40 patients per treatment group who agree to participate in 24-hour ABPM and still meet eligibility criteria at the end of the run-in period [Visit 3] who undergo 24-hour ABPM).

6.5 Day 112 (Visit 11) End of Study (Safety Follow-Up) ±5 Days

The following procedures will be performed at the End of Study (Safety Follow-Up) Visit (Visit 11):

- Record weight;
- Perform physical examination;
- Perform 12-lead ECG in triplicate (patients should be resting in a supine position for at least 10 minutes prior to assessment);
- Obtain vital signs including pulse rate, respiratory rate, and oral temperature;
- Obtain blood pressure;
  - Blood pressures are to be obtained according to the AHA recommendations for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable chair with back support for at least 10 minutes before measurement and remain still during

the measurement. The patient's limb should be supported to measure blood pressure to ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the same arm throughout the study. Triplicate blood pressure measurements should be taken approximately 2 minutes apart with a validated, oscillometric upper arm blood pressure monitor. Trough cuff SBP and DBP values will be assessed based on the pre-defined blood pressure measurement guideline throughout the study. Pulse will be obtained simultaneously with blood pressure measurements;

- Obtain blood sample for clinical laboratory tests (central laboratory; see Appendix B);
- Obtain urine sample for:
  - Urinalysis (central laboratory; see Appendix B); and
  - UACR;
- Obtain plasma sample for PK from all patients;
- Obtain serum sample for pregnancy test (WOCBP only);
- Obtain serum sample for potassium (local and central laboratories);
- Obtain serum sample for creatinine (central laboratory); and
- Record adverse events and concomitant medications.

6.6 Early Termination Visit and Withdrawal Procedures

For patients who are withdrawn from the study prior to completion, the following procedures will be performed at an Early Termination Visit (as early as feasible after discontinuation of the study drug):

- Perform physical examination;
- Record weight;
- Contact IRT;
- Perform 12-lead ECG in triplicate (patients should be resting in a supine position for at least 10 minutes prior to assessment);
- Obtain vital signs including pulse rate, respiratory rate, and oral temperature;
- Obtain blood pressure;
  - Blood pressures are to be obtained according to the AHA recommendations for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable chair with back support for at least 10 minutes before measurement and remain still during the measurement. The patient's limb should be supported to measure blood pressure to ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the same arm throughout the study. Triplicate blood pressure measurements should be taken approximately 2 minutes apart with a validated, oscillometric upper arm blood pressure

monitor. Trough cuff SBP and DBP values will be assessed based on the pre-defined blood pressure measurement guideline throughout the study. Pulse will be obtained simultaneously with blood pressure measurements;

- Obtain blood sample for clinical laboratory tests (central laboratory; see Appendix B);
- Obtain urine sample for:
  - Urinalysis (central laboratory; see Appendix B); and
  - UACR;
- Obtain plasma sample for PK from all patients;
- Obtain serum sample for aldosterone;
- Obtain plasma sample for renin;
- Obtain serum/plasma samples that will be stored at the central laboratory for determination of various additional biomarkers, including but not limited to galectin-3, NT-proBNP, IL-6, collagen biomarkers, and CRP. The panel of biomarkers and time points for analysis will be determined prior to the database lock;
- Obtain serum sample for pregnancy test (WOCBP only);
- Obtain serum sample for potassium (local and central laboratories);
- Obtain serum sample for creatinine (central laboratory);
- Record adverse events and concomitant medications;
- Check study drug accountability and collect unused study drug; and
- Download 24-hour ABPM readings at site if a patient has completed the 24-hour ABPM recording since their last visit (for a subset of up to 40 patients per treatment group who agree to participate in 24-hour ABPM and still meet eligibility criteria at the end of the run-in period [Visit 3] who undergo 24-hour ABPM).

7 EFFICACY ASSESSMENTS

7.1 Primary Efficacy Assessment

The primary efficacy variable is the change in trough-cuff resting seated SBP from baseline to Day 84.

Blood pressure must be measured in triplicate prior to study drug administration at the visits indicated on the Schedule of Procedures (Appendix A). Trough-cuff SBP values will be assessed based on the pre-defined blood pressure measure guideline throughout the study.

7.2 Secondary Efficacy Assessments

Twenty-four-hour ABPM monitoring will be assessed at the visits indicated on the Schedule of Procedures (Appendix A) in a subset of up to 40 patients per treatment group. At the end of the run-in period (Visit 3), ABPM will only be assessed for those patients who agree to participate in 24-hour ABPM and still meet all of the eligibility criteria. Blood pressure and HR measurements will be obtained every 20 minutes during the interval of 06:00:00 hours to 21:59:59 hours (to coincide with the daytime, awake period) and every 30 minutes during the interval of 22:00:00 hours to 05:59:59 hours (to coincide with the nighttime, sleeping period).

During the 24-hour ABPM recording period, a diary will be provided to the patient. Instructions and training will be provided to the site staff, who will in turn provide instructions to the patient.

The key secondary efficacy variables include the following:

- Change in trough-cuff seated DBP from baseline to Day 84;

Note: Blood pressure must be measured in triplicate prior to study drug administration at the visits indicated on the Schedule of Procedures (Appendix A). Trough-cuff DBP values will be assessed based on the pre-defined blood pressure measure guideline throughout the study.

- Change in 24-hour mean, daytime mean, nighttime mean, morning mean, last 6 hours of the dosing interval mean, SBP, DBP, MAP, and HR from baseline to Day 84 as measured by 24-hour ABPM in a subset of up to 40 patients per treatment group; and
- Change and percent change in UACR from baseline to Day 84 (for patients with albuminuria [defined as UACR >300 mg/g] or microalbuminuria [defined as UACR in the range of 30 mg/g to 300 mg/g]).

7.3 Pharmacokinetic Assessment

Plasma samples for PK analyses will be collected from all patients at the visits indicated on the Schedule of Procedures (Appendix A).

7.4 Pharmacodynamic Assessment

The pharmacodynamic (PD) variable of this study is the change in levels of serum aldosterone and plasma renin from baseline to Day 84. Serum samples for aldosterone and plasma samples for renin will be collected at the visits indicated on the Schedule of Procedures (Appendix A).

Serum/plasma samples will be stored at the central laboratory for determination of various additional biomarkers, including but not limited to galectin-3, NT-proBNP, IL-6, collagen

biomarkers, and CRP. The panel of biomarkers and time points for analysis will be determined prior to the database lock.

8 SAFETY ASSESSMENTS

Safety variables will include adverse events, vital signs (pulse rate, respiratory rate, and oral temperature), clinical laboratory findings, 12-lead ECGs, and physical examination findings.

The following serum potassium/hyperkalemia-related parameters and renal function-related parameters will be collected and evaluated:

- Incidence of hyperkalemia (defined as serum potassium ≥ 5.6 mmol/L), incidence of severe hyperkalemia (defined as serum potassium ≥ 6.0 mmol/L), and incidence of patients with serum potassium > 5.0 mmol/L;
- Change in serum potassium level from baseline to Day 84; and
- Change in eGFR and creatinine levels > 30% throughout the study period.

8.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include clinical laboratory test variables, will be monitored and documented from the time of informed consent until study participation is complete. Patients should be instructed to report any adverse event that they experience to the Investigator. Beginning with the Screening Visit, Investigators should make an assessment for adverse events at each visit and record the event on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure.

Any medical condition already present at Screening should not be reported as an adverse event unless the medical condition or signs or symptoms present at baseline changes in severity or seriousness at any time during the study. In this case, it should be reported as an adverse event.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at Screening and significantly worsen during the study should be reported as adverse events. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

8.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, ie, the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For KBP-5074, the reference safety information is included in Section 5.1.6 of the Investigator's Brochure[7] currently in force. The reference safety information will be reviewed yearly, and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to study drug using the categories of yes or no.

Assessment of Severity:

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Causality Assessment:

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes (related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from study drug administration-
  - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases-
  - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

- Concomitant drug-
  - The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug-
  - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses-
  - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and PK of the study drug-
  - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

8.2 Adverse Events of Special Interest

The following adverse events of special interest must be reported to the Sponsor within 24 hours of the Investigator's awareness, even if not meeting the definition of an SAE:

- Hyperkalemia;
  - Mild hyperkalemia defined as serum potassium 5.0 mmol/L to 5.5 mmol/L (central or local laboratory);
  - Moderate hyperkalemia defined as serum potassium 5.6 mmol/L to 5.9 mmol/L (central or local laboratory); and
  - Severe hyperkalemia defined as serum potassium ≥ 6.0 mmol/L;
- Reduction from Day 1 eGFR levels ≥ 30% throughout the duration of the study;
- Hypertensive emergency;
  - Defined as confirmed (based on the mean of at least 2 current consecutive protocol-required blood pressure readings, or otherwise obtained blood pressure readings) with SBP > 180 mmHg and/or DBP > 120 mmHg with associated new or progressive target organ damage, neurologic, and/or cardiac symptoms. Blood pressures of > 200 mmHg in asymptomatic patients should be recorded in the eCRF, and Investigators must differentiate between hypertensive urgency (markedly elevated blood pressure) and emergency. See Section 8.14 and Appendix C for definition and management of hypertensive emergencies and urgencies; and
- Symptomatic hypotension, or if the SBP < 90 mmHg after the first dose of study drug at Day 1.

8.3 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
    - Note: An adverse event or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations,
    - Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly/birth defect, or
- An important medical event.
    - Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.4 Serious Adverse Event Reporting − Procedures for Investigators

Initial Reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study drug must be reported to Worldwide Drug Safety within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 30-day follow-up period must be reported to the Sponsor.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Worldwide Drug Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, contact Worldwide Drug Safety by email or phone, and fax

the completed paper SAE form (e-mail address and phone and fax numbers listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours.

- Safety Contact Information: Site staff will complete the paper SAE report form and e-mail it within 24 hours to the following address: drugsafety@worldwide.com.

- In cases where the email system is unavailable, site staff will send the SAE by fax to: +1-866-387-5539 (US) and +44 208 043 4813 (ROW).

Follow-Up Reports

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to Worldwide Drug Safety via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.5 Pregnancy Reporting

If the patient or partner of a patient participating in the study becomes pregnant during the study or within 90 days of discontinuing study drug, the Investigator should report the pregnancy to Worldwide Drug Safety within 24 hours of being notified. Worldwide Drug Safety will then forward the Exposure In Utero form to the Investigator for completion.

A patient becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The patient or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Worldwide Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.6 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions in accordance with International Council for Harmonisation (ICH) for Good Clinical Practices, Food and Drug Administration (FDA) guidelines, Directive 2001/20/EC of the European Parliament and the CT3 Guideline, and any other local regulations applicable in the participating countries.

The Sponsor or designee will also inform all Investigators as required. When required due to local regulations, the Investigator will provide expedited reports to the Institutional Review Board (IRB)/Independent Ethics Committees (IECs).

8.7 Clinical Laboratory Evaluations

Detailed procedures of sampling preparation, storage, and shipment will be described in a specific laboratory manual, which will be provided to all sites. The visits at which these samples will be collected are shown in the Schedule of Procedures (Appendix A) and the data captured will be forwarded to the central laboratory for evaluation, unless otherwise specified. See Appendix B for a list of clinical laboratory analytes to be measured.

The Investigator should review and evaluate out of range laboratory results. Any clinically relevant abnormal laboratory value should be immediately rechecked whenever possible, for confirmation before making any decision for the concerned patient. It should be documented as an adverse event/SAE as applicable.

8.8 Vital Signs

Vital signs include pulse rate, respiratory rate, and oral temperature. Vital signs will be assessed at the visits indicated on the Schedule of Procedures (Appendix A). Triplicate blood pressure should be taken approximately 2 minutes apart with the patient in the seated position and having rested for at least 10 minutes prior to assessment. Blood pressure and pulse rate will be measured at the same time.

8.9 Electrocardiograms

A 12-lead ECG will be performed in triplicate at the visits indicated on the Schedule of Procedures (Appendix A). Patients should be resting in the supine position for at least 10 minutes prior to the assessment. The Investigator will assess ECG data as normal, abnormal not clinically significant, or abnormal clinically significant. Any clinically significant abnormalities should be documented as an adverse event/SAE as applicable. All ECG traces will be kept as source data.

8.10 Physical Examinations

The Investigator or a licensed study team member, per local regulations, will perform physical examinations according to the Schedule of Procedures (Appendix A). Physical examinations will evaluate the following body systems/organs: general appearance; dermatological; head and eyes; ears, nose, mouth, and throat; pulmonary; cardiovascular; abdominal; genitourinary (optional); lymphatic; musculoskeletal/extremities; and neurological. If a system is not assessed, the Investigator or designee will note the reason in the source documents. If a new clinically significant abnormality or worsening from baseline is detected after randomization, then an adverse event should be reported and the patient should be considered for further clinical investigations and/or specialist consultation as per the Investigator's medical judgment.

8.11 Height, Weight, and Body Mass Index

Height will be measured at Screening only. Weight will be measured at the visits indicated in the Schedule of Procedures (Appendix A). Body mass index will be calculated and recorded at Screening and at Day 84.

8.12 Safety Surveillance and Management of Serum Potassium Levels

Serum potassium levels of study patients will be monitored systematically throughout the study. In addition to the clinical laboratory tests pre-defined in the Schedule of Procedures (Appendix A), unscheduled assessments of serum potassium levels are recommended under certain situations (eg, vomiting and/or diarrhea for ≥ 1 day) that may impact patients' serum electrolyte levels or fluid balance.

In patients with serum potassium above the normal laboratory reference range (serum potassium levels ≥ 5.0 mmol/L), it is advised that the Investigator should reinforce dietary restriction for management of elevated potassium and consider local guideline recommendations. Table 1 below summarizes the laboratory testing for assessment of serum potassium levels ≥ 5.0 mmol/L and guidelines for management of study drug, which includes continuation thereof, holding of study drug, and/or discontinuation of study drug. If serum potassium levels are < 5.0 mmol/L, no action is indicated. A serum potassium level of ≥ 5.6 mmol/L requires a hold of study drug and appropriate retesting and intervention as described in Table 1. A potassium level of ≥ 6.0 mmol/L necessitates immediate and permanent discontinuation of study drug.

Because of potential issues anticipated from routine sample handling and extended transportation time to the central laboratory, pseudohyperkalemia secondary to hemolysis may occur in centrally analyzed laboratory samples. For this reason, during treatment with study drug, all serum potassium assessments, including retests, will be performed at both local and central laboratories.

In general, if the initial local and/or central laboratory test shows that a patient's serum potassium level is ≥ 5.3 mmol/L, a repeat local test is required to confirm elevation of serum potassium levels and dictate actions to be taken as outlined in Table 1. All samples should be screened for hemolysis to eliminate the possibility of pseudohyperkalemia. Results from the central laboratory will be used for data analysis. If a major discrepancy exists between the local and central laboratory values, defined as a ±0.3 mmol/L difference between values or if hemolysis is noted in the specimens, repeat blood samples should be obtained to confirm eligibility or continuation in the study. Again, decisions to enroll or randomize a patient should generally be based on the local serum potassium. However, if the central laboratory serum potassium is ≤ 4.8 mmol/L and the local potassium test is > 4.8 mmol/L, the more conservative value may be used if the difference between the 2 samples is ≤ 0.3 mmol/L.[10]

Serum potassium recheck is recommended within 24, 48, or 72 hours, depending on the level of hyperkalemia, following Investigator notification of a serum potassium ≥ 5.3 mmol/L (see Table 1). The Investigator can perform additional serum potassium retests when clinically indicated for medical conditions or procedures that occur during the study. Blood samples should be obtained atraumatically, without fist clenching or prolonged use of a tourniquet. Non-hemolyzed blood samples sent for rechecks or retests will be analyzed in both local and central laboratories. In some circumstances, as outlined below in Table 1, a second retest may be indicated and should be performed within 1 week to allow the patient to adjust to the withdrawal of study drug (if indicated) and application of standard of care. All episodes of hyperkalemia, serum potassium of > 5.0 mmol/L should be reported as an adverse event of special interest.

The monitoring of serum potassium and the decision on whether or not to discontinue study drug, as well as other interventions, are outlined in Table 1.

Table 1. Potassium Safety Monitoring – Reporting / Management of Hyperkalemia

	Alert Local and Central Laboratory Serum Potassium (K^+) Values			
	> 5.0 to 5.2 mmol/L	**5.3 to 5.5 mmol/L**	**5.6 to 5.9 mmol/L**	**≥ 6.0 mmol/L**
Following notification of a serum K^+ alert value[1]		Contact patient and schedule repeat serum K^+ within 24-72 hours after laboratory notification.	Contact patient and schedule repeat serum K^+ within 24-48 hours after laboratory notification.	Contact patient and schedule repeat serum K^+ within 24 hours after laboratory notification.
Management	Continue study drug.	Continue study drug pending retest results.	Hold study drug pending retest results.	**Permanently discontinue study drug.**
Treatment	Reinforce low K^+ diet.	Reinforce low- K^+ diet; manage HK per local SOC (no K^+ binders).	Reinforce low- K^+ diet; manage HK per local SOC (no K^+ binders).	Reinforce low- K^+ diet; manage HK per local SOC (may use K^+ binders)..
If first serum K^+ retest is < 5.3 mmol/L		Continue study drug.	Resume study drug.	
Management following first serum K^+ retest		If retest serum K^+ is ≥ 5.3 to 5.5 mmol/L: 1. Hold study drug, 2. Consider higher dose of diuretic, 3. Schedule second serum K^+ retest within 1 week. **If retest serum K^+ > 5.5 mmol/L, permanently discontinue study drug.**	If retest serum K^+ is ≥ 5.3 to 5.5 mmol/L: 1. Continue to hold study drug, 2. Consider higher dose of diuretic, 3. Schedule second serum K^+ retest within 1 week. **If retest serum K^+ > 5.5 mmol/L, permanently discontinue study drug.**	Note: Following discontinuance of study drug continue study visits and safety monitoring.
Management following second serum K^+ retest		If serum K^+ on retest is < 5.3 mmol/L, continue study drug. **If serum K^+ on retest is ≥ 5.3 mmol/L, permanently discontinue study drug.**	If serum K^+ is < 5.3 mmol/L, resume study drug. **If serum K^+ on retest is ≥ 5.3 mmol/L, permanently discontinue study drug.**	
Adverse Event Reporting		Report as AE of Special Interest	Report as AE of Special Interest	Report as AE as Special Interest

1 In the absence of hemolysis, the more conservative value from the central or local laboratories should be used to guide management and treatment
Study sites should make repeated attempts to contact patients with high K^+ or HK to ensure compliance with K^+ safety monitoring and required retests.
If the serum K^+ levels are ≥ 5.3 mmol/L, repeat local and central serum K^+ testing is required in compliance with the above management strategies and procedures
The Investigator should consider local guideline and SOC for management of serum potassium levels above the normal laboratory reference range. In all instances, dietary restriction for management of elevated potassium should be reinforced**. Consider use of higher dose of loop or thiazide like diuretics to manage HK.** If chronic or intermittent treatment with potassium-binders is required, the patient should be permanently discontinued from study drug.
If the locally analyzed blood sample is missing, or the result is inconclusive, another blood sample should be taken as soon as possible but no later than 24 to up to 72 hours to confirm the value.
The Sponsor or delegate will be notified by site personnel within 24 hours of the site being aware of results for any local laboratory potassium value (≥ 5.3 mmol/L).
Retest/confirmatory testing results will be forwarded to the Sponsor or delegate within 24 hours of the site being aware of results.
Abbreviations: K^+: potassium, HK: hyperkalemia, SOC: Standard of care.

Regardless of whether a patient will discontinue study drug due to elevated serum potassium levels, he/she should be closely monitored and treated, as appropriate, per the Investigator's assessment.

8.13 Safety Management of Serum Creatinine

Serum creatinine may increase, at least temporarily, with the initiation of MRA treatment, especially in patients with more advanced CKD, most likely reflecting hemodynamic alterations. Therefore, serum creatinine will be measured at baseline and closely monitored systematically throughout this Phase 2 study. Study drug will be discontinued permanently if serum creatinine increases ≥ 50% from baseline during the study treatment period.

8.14 Monitoring and Management of Blood Pressure

Blood pressure will be closely monitored throughout this study. At Screening, patients must have uncontrolled hypertension, defined as resting trough-cuff seated SBP ≥ 140 and ≤ 179 mmHg based on the mean of at least 2 current consecutive blood pressure readings at Screening and the end of the run-in period in the clinic. Blood pressures are obtained according to the AHA recommendations for accurate blood pressure measurement. Patients should avoid smoking, caffeine, or exercise within 30 minutes before measurement; empty his or her bladder; then sit quietly in a comfortable chair with back support for at least 10 minutes before a measurement; and remain still during the measurement. The patient's limb should be supported to measure blood pressure and ensure that the blood pressure cuff is at heart level, using the correct cuff size. Do not take the measurement over clothes. Blood pressure measurements should be performed in the same arm throughout the study. Measurement will be taken with a validated, oscillometric upper arm blood pressure monitor.

In all cases, dose and frequency of concurrent antihypertensive medications are expected to be maintained without change for 30 days prior to randomization. In general, patients should not add or adjust dose and/or types of the antihypertensive medications they are receiving during the screening period and throughout the duration of the study (unless they develop symptomatic hypotension). The dose of diuretic may be adjusted based on developing or resolved edema, weight gain or loss, or pulmonary congestion. Antihypertensive therapy may be modified if necessary during the safety assessment, following withdrawal of the study drug to maintain blood pressure control.

Diagnoses of hypertensive emergency require discontinuance of the study drug, and immediate treatment per local treatment guidelines. The occurrence of hypertensive urgency or a transient severe elevation in blood pressure may or may not require removal of a patient from the study drug but should be recorded as an adverse event and reviewed with the study Medical Monitor. AHA/American College of Cardiology definitions, clinical definitions, and treatment algorithms for hypertensive emergency, hypertensive urgency, or marked elevations in blood pressure appear in Appendix C.

Symptomatic hypotension or a confirmed trough-seated SBP < 90 mmHg based on the mean of at least 2 current consecutive protocol-required blood pressure readings, or otherwise obtained blood pressure reading) after the first dose of study drug at Day 1, should be reported as an adverse event of special interest. Investigators should evaluate and correct any potential reasons that may contribute to hypotension, such as dehydration, decreased blood volume, potential overdose of

antihypertensive medication (including study drugs), etc. If symptomatic hypotension or a confirmed trough-seated SBP < 90 mmHg occurs, Investigators may consider down-titration of antihypertensive medications (other than study drug) first. If symptomatic hypotension or a confirmed trough-seated SBP < 90 mmHg persists following down titration study drug should be permanently discontinued.

9 STATISTICS

9.1 Analysis Populations

The Intent-to-Treat (ITT) Population will consist of all randomized patients who take at least 1 dose of randomized study drug, have a baseline SBP measurement, and have at least 1 post-randomization SBP measurement. The ITT Population is the primary analysis population. All efficacy analyses will be performed for the ITT Population.

The Per-Protocol Population will include all ITT patients who have completed the 84-day double-blind treatment period without any major protocol deviations or violations. The Per-Protocol Population will be used to assess robustness of the primary analysis results. The major protocol deviations will be pre-specified prior to unblinding treatment codes for analyses.

The Safety Population will include all randomized patients who receive at least 1 dose of randomized study drug.

The PPK Population will include all randomized patients who receive at least 1 dose of randomized study drug and have at least 1 measurable concentration of total KBP-5074.

9.2 Statistical Methods

9.2.1 Demographic and Baseline Comparability

Patient disposition and analysis population data will be tabulated by treatment group with number and percentage of patients. Summary statistics will be provided by treatment group for demographics (eg, age, sex, race, and ethnicity) and for baseline efficacy variables (such as SBP, serum potassium, eGFR, creatinine, DBP, and UACR). For efficacy variables, baseline will be defined as the Day 1 (Visit 4) measurement. If the measurement at this visit is missing, then the last measurement prior to the first dose of randomized study drug will be used.

9.2.1.1 Study drug exposure, compliance, and concomitant therapies

Overall percent compliance to study drug dosage regimen, calculated as percent of doses taken relative to doses scheduled to be taken, will be summarized by treatment group. Extent of exposure in days will be evaluated and summarized from the first dose date to the last dose date of randomized study drug.

Concomitant medication/therapy verbatim terms will be coded using the latest version of the World Health Organization Drug Dictionary. The number and percentage of patients taking new concomitant medications after first dose date will be summarized by Anatomic Therapeutic Chemical classification and preferred term for each treatment group.

9.2.2 Analysis of Efficacy

9.2.2.1 Primary efficacy analysis

The primary efficacy analysis is to evaluate the change in trough-cuff seated SBP from baseline to Day 84 for the KBP-5074 doses compared to placebo. The endpoint for each patient is defined as the Day 84 cuff seated SBP measurement. If the measurement at this visit is missing or the patient discontinues early, the last post-baseline measurement during the double-blind period will be used.

The primary efficacy analysis will be carried out using a 2-way analysis of covariance (ANCOVA) model with treatment, baseline eGFR level (≥ 30 versus < 30 mL/min/1.73 m^2), and background antihypertensive medication (2 or more) as factors, and the baseline SBP value as a covariate. The least-squares means, standard errors, and the 2-tailed 95% confidence intervals (CIs) for each treatment group and for the comparison will be estimated. The treatment difference between KBP-5074 doses and placebo will be estimated from the ANCOVA model. No multiple comparison adjustment will be used for this Phase 2 study.

The primary efficacy analysis will be based on the ITT Population. Other imputation methods for the primary efficacy endpoint will be explored. The supportive analysis will be carried out for the primary efficacy variable based on the Per-Protocol Population to examine the impact due to premature dropouts and/or major protocol deviations or violations.

9.2.2.2 Secondary efficacy analyses

For continuous secondary efficacy variables, the same ANCOVA model will be used as the primary efficacy analysis. For categorical data, logistic regression or chi-square test will be used. Treatment effects will be evaluated between KBP-5074 doses and placebo.

9.2.3 Analysis of Safety

The assessment of safety will be based primarily on the frequency of patients with adverse events and clinical laboratory abnormalities. Other safety data will be summarized as appropriate.

All safety analyses will be conducted on the total patient cohort based on the Safety Population.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities. Reports will be provided to the Medical Monitor for approval of the coded terms after the database is clean, prior to unblinding. The number and frequency of patients with TEAEs (ie, those adverse events that newly occur or worsen in severity during the study) will be summarized by system organ class and preferred term. Serious adverse events and TEAEs related to study drug will be summarized in the same manner. A list of patients with SAEs and those who discontinue from the study due to an adverse event will be provided.

Summary statistics by treatment group at baseline, at all post-randomization visits, and changes from baseline to the post-randomization visits for laboratory values will be provided. Occurrence of significant abnormalities in laboratory values from baseline will be summarized by treatment group. Vital signs, body weight, and physical examination findings will be summarized.

9.2.4 Analysis of Pharmacokinetics

The analysis of the PK/PD relationship will be explored. Population PK models will be built using a nonlinear mixed effects modeling technique with NONMEM software based on the PPK Population. Different PK models will be attempted to fit the PK concentration-time data. After the PPK modeling, a population PD approach will be used to explore the concentration-effect relationships. Different PD models will be attempted to fit the concentration-effect data. All PD exploration will be based on the ITT Population.

9.2.5 Interim Analysis

No interim analysis is planned.

9.2.6 Independent Data Monitoring Committee

An IDMC will be utilized in this study. The committee will consist of members external to Worldwide and KBP BioSciences. The objective of the committee is to monitor safety data on an ongoing basis. The approved IDMC charter will be on file and available for inspection as requested.

Meeting Schedule

After the organizational meeting, the IDMC will meet at least 4 times during the conduct of the study at the following treatment milestones:

- Approximately 10% of patients completed are randomized in the study,
- Approximately 25% of patients completed the 12-week treatment period,
- Approximately 50% of patients completed the 12-week treatment period, and
- Approximately 75% of patients completed the 12-week treatment period.

The analysis for the IDMC report will be conducted by an independent group not involved with the study conduct. A blinded summary of all adverse events and SAEs will be provided every 4 weeks to the IDMC and the Sponsor for ongoing safety data monitoring.

No formal inferential hypothesis testing will be conducted from the interim. The study will not stop early based on interim efficacy findings. Therefore, no further multiple testing adjustments nor any sample size adjustments will be implemented for the final analysis CIs.

9.2.7 Sample Size Determination

For this Phase 2 study, the primary efficacy endpoint is the change in trough-cuff resting seated SBP from baseline to Day 84. Assuming an observed treatment difference of SBP changes between the KBP-5074 group and the placebo group is 5 mmHg, and a standard deviation of change from baseline of 15 mmHg, with 80 patients/group, the CI of the observed difference would not include 0. Assuming 10% to 15% dropout post randomization, 80 patients/group or a total of 240 patients would be needed for this Phase 2 study. Additional sample size estimates based on sample size needed per group to ensure that the observed 95% CI does not include 0 are shown in Table 2. No multiple comparison adjustment will be applied.

Table 2. Sample Size Estimates

Standard Deviation	Observed Treatment Effect		
	4 mmHg	**5 mmHg**	**6 mmHg**
14 mmHg	109	70	48
15 mmHg	125	81	56
16 mmHg	141	91	63
Including approximately 10% to 15% dropout.			

Abbreviations: mmHg = millimeters of mercury.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following dictionaries will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and adverse events, and
- World Health Organization Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of patients, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board/Independent Ethics Committee

The IRB or IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, Informed Consent Form (ICF), advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

Federal regulations and ICH Guidelines require that approval be obtained from an IRB/IEC prior to participation of patients in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB/IEC.

No drug will be released to the site for dosing until written IRB/IEC authorization has been received by the Sponsor.

11.3 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/IEC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/IEC and/or regulatory agencies. A copy of the signed ICF will be given to the patient.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any patient in this study, the Sponsor or their designee will review with the

Investigator and site personnel the following documents: protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC as appropriate. Patients or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by Worldwide or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/IEC, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

12.2 Address List

12.2.1 Sponsor

KBP BioSciences Co., Ltd.
116 Village Blvd, Suite 210
Princeton, NJ 08540
United States
Telephone: +1-609-531-0889
Fax: +1-609-531-0892

12.2.2 Contract Research Organization

Worldwide Clinical Trials
3800 Paramount Parkway
Suite 400
Morrisville, NC 27560
United States
Telephone: +1 610-964-2000

12.2.3 Drug Safety

Worldwide Clinical Trials
3800 Paramount Parkway
Suite 400
Morrisville, NC 27560
United States

Worldwide Clinical Trials SAE reporting line:
Fax: +1-866-387-5539 (US) and +44 208 043 4813 (ROW).
e-mail: drugsafety@worldwide.com

12.2.4 Biological Specimens

Central Laboratory

Contact information provided separately to sites.

Central Laboratory (For PK Samples Only)

Contact information provided separately to sites.

13 REFERENCES

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APPENDIX A: SCHEDULE OF PROCEDURES

Study Period	Screening[1] (≤ 4 weeks)	Open-Label Placebo Run-In (2 weeks)			Double-Blind Treatment									EOS	ET[2]
Study Day	≤ -42 days	≤ -18	≤ -4	-1	1	7	14	28	40	42	56	82	84	112	
Visit	1	2	3	ABPM[3,4]	4[5]	5	6	7	ABPM[4]	8	9	ABPM[4]	10	11	
Visit Window					±2 days			±3 days						±5 days	
Assessment															
Signed informed consent	X														
Eligibility assessment	X		X		X										
Randomization					X										
Demographics	X														
Medical history	X														
Physical examination	X				X[6]								X	X	X
Height (cm)	X														
Weight (kg)	X	X	X		X	X	X	X		X	X		X	X	X
Body mass index	X												X		
Contact IRT	X	X			X			X			X				X
Triplicate standard 12-lead ECG[7]	X				X	X								X	X
Vital signs (PR, RR, OT)[8]	X	X	X		X	X	X	X		X	X		X	X	X
Blood pressure[8,9]	X[10]	X	X[10]		X[11]	X[11]	X[11]	X[11]		X[11]	X[11]		X	X	X
24-hour ABPM device placement and start[4,12]				X					X			X			
24-hour ABPM download at site[4]					X					X			X		X[13]
HIV, HbsAg, and HCV	X														
Urine drug screen	X		X												
Clinical laboratory samples (central laboratory)[14]	X		X[15]		X	X	X	X		X	X		X	X	X
Serum potassium (local and central laboratories)[16]	X		X		X	X	X	X		X	X		X	X	X
Serum creatinine (central laboratory)	X		X		X	X	X	X		X	X		X	X	X
Pregnancy test on WOCBP only[17]	X				X									X	X
FSH[18]	X														
Serum samples for aldosterone					X								X		X
Plasma samples for renin					X								X		X
Serum and plasma samples for additional biomarkers[19]					X								X		X
Plasma samples for PK					X[20]		X[21]	X[21]						X	X
Urine samples for UACR	X				X	X	X	X		X	X		X	X	X

Study Period	Screening[1] (≤ 4 weeks)	Open-label Placebo Run-In (2 weeks)			Double-Blind Treatment									EOS	ET[2]
Study Day	≤ -42 days	≤ -18	≤ -4	-1	1	7	14	28	40	42	56	82	84	112	
Visit	1	2	3	ABPM[3,4]	4[5]	5	6	7	ABPM[4]	8	9	ABPM[4]	10	11	
Visit Window					±2 days			±3 days						±5 days	
Provide 24-hour urine collection instruction and supplies			X					X			X				
24-hour urine samples for UACR					X					X			X		
Adverse event and concomitant medications	X	X	X		X	X	X	X		X	X		X	X	X
Study drug instruction and dispensing		X[22]			X	X	X	X		X	X				
Administer first/daily dose and record time					X[23]	X[24]	X[24]	X[24]		X[24]	X[24]				
Study drug accountability and collection of unused study drug			X[25]			X	X	X		X	X		X		X

1. If a patient is found to be not eligible during Screening, a single rescreening is allowed if the Investigator believes that the patient's condition has changed, and the patient may be eligible before the rescreening tests.
2. The Early Termination Visit should be scheduled only for patients who discontinue the study prematurely; assessments should be performed as early as feasible after discontinuation of study drug.
3. This visit is to be scheduled within 3 days after the end of the run-in period (Visit 3) for patients undergoing 24-hour ABPM.
4. This visit/procedure is for patients undergoing 24-hour ABPM only (a subset of up to 40 patients per treatment group who agree to participate in 24-hour ABPM and still meet eligibility criteria at the end of the run-in period [Visit 3]).
5. This visit is to be scheduled within 4 ±2 days after the end of the run-in period (Visit 3).
6. A physical examination will be performed pre-dose.
7. Patients should be resting in a supine position for at least 10 minutes prior to assessment.
8. Blood pressure and PR will be measured at the same time.
9. Triplicate blood pressure measurements should be taken approximately 2 minutes apart with a validated, oscillometric upper arm blood pressure monitor with the patient in the seated position and having rested for at least 10 minutes prior to assessment. Trough-cuff SBP and DBP values will be assessed based on the pre-defined blood pressure measurement guideline throughout the study.
10. At Screening and the end of the placebo run-in period (Visit 3), patients must have uncontrolled hypertension, defined as resting trough-cuff seated SBP ≥ 140 mmHg and ≤ 179 mmHg based on the mean of at least 2 current consecutive blood pressure readings in the clinic.
11. Blood pressure must be measured prior to study drug administration.
12. Blood pressure and heart rate measurements will be obtained every 20 minutes during the interval of 06:00:00 hours to 21:59:59 hours (to coincide with the daytime, awake period), and every 30 minutes during the interval of 22:00:00 hours to 05:59:59 hours (to coincide with the nighttime, sleeping period). During the 24-hour ABPM recording period, a diary will be provided to the patient. Instructions and training will be provided to the site staff, who will in turn provide instructions to the patient.
13. If a patient has completed the 24-hour ABPM recording since their last visit, 24-hour ABPM data will be downloaded at the site during the ET Visit.
14. Clinical laboratories include chemistry, hematology, coagulation, and urinalysis. See Appendix B for the complete list of clinical laboratory analytes assessed for this study.
15. Only clinical chemistry will be conducted at the end of run-in period (Visit 3).
16. All patients must have a serum potassium ≤ 4.8 mmol/L at both Screening and the end of the placebo run-in period (Visit 3).
17. Serum pregnancy tests will be obtained at Screening, EOS, and ET. A urine pregnancy test will be obtained at pre-dose on Day 1.

18. Post-menopausal women only.
19. Serum/plasma samples taken during the study will be stored at a central laboratory for determination of various additional biomarkers, including but not limited to galectin-3, N-terminal of the prohormone brain natriuretic peptide, interleukin-6, collagen biomarkers, and C-reactive protein. The panel of biomarkers and time points for analysis will be determined prior to the database lock.
20. Plasma samples are to be collected prior to patient's discharge from the unit.
21. Plasma samples are to be collected pre-dose. If patients are not dosed in the unit on those days, a PK sample will be collected, and the date and time of the last dose will be recorded.
22. Open-label placebo will be dispensed at Visit 2.
23. The first dose of the study drug is to be administered.
24. The daily dose of the study drug is to be administered.
25. If a patient's compliance to medications (including both open-label placebo and current antihypertensive medications) is < 80% or > 120% at Visit 3, he/she will not be eligible for the study and no further visits will be performed.

Abbreviations: ABPM = ambulatory blood pressure monitoring; DBP = diastolic blood pressure; ECG = electrocardiogram; EOS = end of study; ET = early termination; FSH = follicle-stimulating hormone; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IRT = Interactive Response Technology; OT = oral temperature; PK = pharmacokinetic; PR = pulse rate; RR = respiratory rate; SBP = systolic blood pressure; UACR = urine albumin-to-creatinine ratio; WOCBP = women of childbearing potential.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate[1]
Gamma-glutamyl transferase	Glucose
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total protein	Uric acid

[1] Calculated by the central laboratory using the Modification of Diet in Renal Disease equation version 4.

Endocrinology

Follicle-stimulating hormone (FSH) for post-menopausal women only[1]

[1] Post-menopausal is defined as amenorrheic for at least 1 year AND have a serum FSH level of > 20 mIU/mL.

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential	

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy[1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

[1] Microscopy is performed only as needed based on positive dipstick test results.

Additional Urinalysis

Urine drug screen
Percent change in urine albumin-to-creatinine ratio (UACR) for spot urine specimen
UACR for 24-hour urine specimen

Coagulation

Activated partial thromboplastin time
Prothrombin time
International normalized ratio

Serology

Hepatitis B surface antigen
Hepatitis C virus
Human immunodeficiency virus

Biomarkers

Aldosterone
Renin

Serum/plasma samples taken during the study will be stored at a central laboratory for determination of various additional biomarkers, including but not limited to galectin-3, N-terminal of the prohormone brain natriuretic peptide, interleukin-6, collagen biomarkers, and C-reactive protein. The panel of biomarkers and time points for analysis will be determined prior to the database lock.

Pregnancy Test

Serum/urine pregnancy tests will be administered to all women patients of childbearing potential.

APPENDIX C: DEFINITION AND MANAGEMENT OF HYPERTENSIVE CRISIS, EMERGENCY, AND URGENCY

Hypertensive Emergency

The protocol definition for hypertensive emergency is consistent with that proposed by the 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (see Figure 2). In this study, a hypertensive emergency is defined as a confirmed (based on the mean of 2 or more consecutive blood pressures readings) severe elevation in systolic blood pressure (SBP) > 180 mmHg and/or diastolic blood pressure (DBP) > 120 mmHg in conjunction with new or progressive target organ damage (eg, Grade III or IV, etc.), neurologic, or cardiac symptoms. Hypertensive emergencies require immediate attention and generally require hospitalization in an intensive care unit and the use of parenteral medication for control of blood pressure.

Reduction of blood pressure (not necessarily to normal ranges) is required to prevent or limit further target organ damage, which can include, hypertensive encephalopathy, intracranial hemorrhage, acute ischemic stroke, acute myocardial infarction, acute left ventricular failure with pulmonary edema, unstable angina pectoris, dissecting aortic aneurysm, acute renal failure, and eclampsia.

Selection of a specific agent for blood pressure reduction should be based on a patient's clinical presentation and national or local clinical practice guidelines. In general, autoregulation of tissue perfusion is disturbed in hypertensive emergencies; thus, continuous or intermittent infusions of short-acting titratable antihypertensive agents is often preferred; use of oral therapy is discouraged for hypertensive emergencies.

It should be noted that hypertensive emergencies in patients presenting with acute intracranial hemorrhage and acute ischemic stroke require particularly close management; local guidelines for such patients should be followed. Documented hypertensive emergency will require termination of the study drug.

Hypertensive Urgency or Markedly Elevated Blood Pressure

Confirmed blood pressures where SBP > 180 mmHg and/or DBP > 120 mmHg without neurologic, cardiac symptom, or new or progressive hypertensive target organ damage will be classified as a hypertensive urgency or markedly elevated blood pressure.

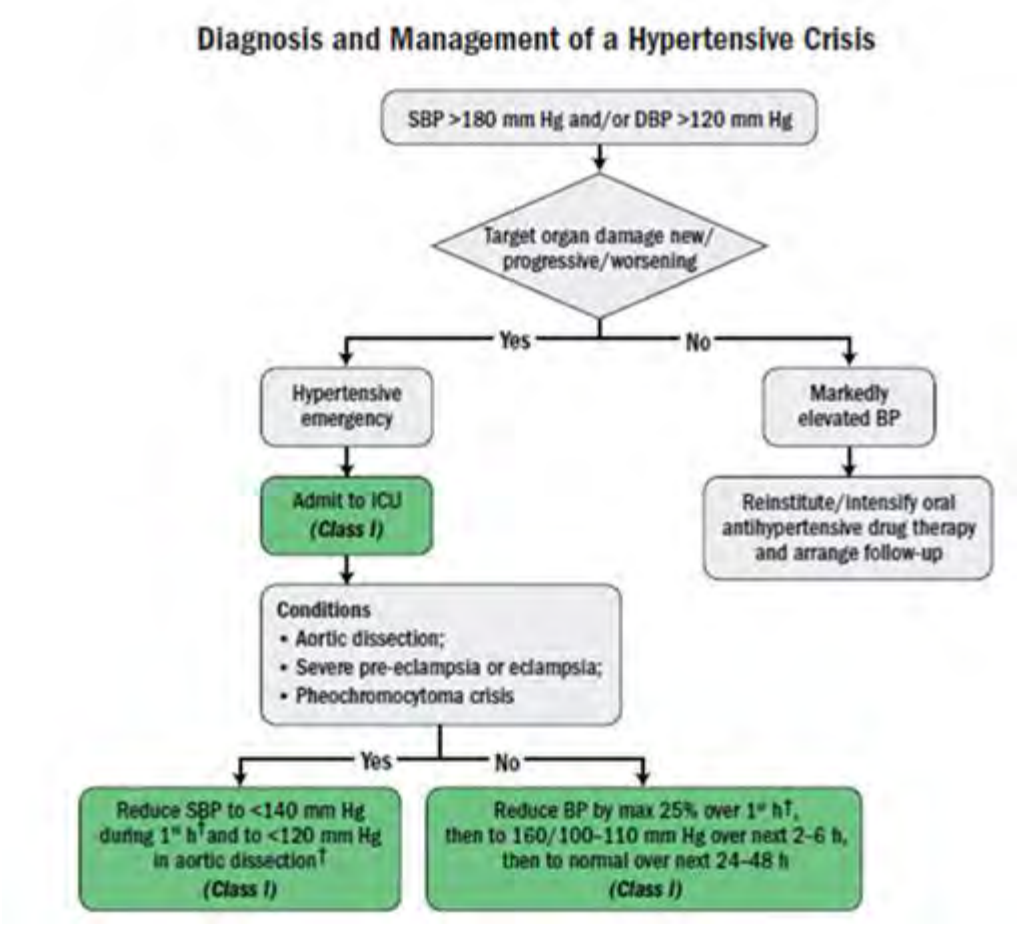
Management of a hypertensive urgency usually involves reinstitution/intensification of oral antihypertensive drug therapy and follow-up. Ideally, blood pressure measurements should be repeated approximately every 10 minutes over a 30-minute period in patients with severe uncontrolled hypertension, with the patient resting in a quiet, comfortable environment to confirm the elevated blood pressure, and to minimize white coat effect, anxiety, stress, pain, etc.

Hypertensive urgencies are situations associated with severe blood pressure elevation in otherwise stable patients without acute or impending change in target organ damage or dysfunction. Many of these patients have withdrawn from or are noncompliant with antihypertensive therapy and do not have clinical or laboratory evidence of acute target organ damage.

These patients should not be considered as having a hypertensive emergency and instead are treated by reinstitution or intensification of antihypertensive drug therapy and treatment of anxiety as applicable. There is no indication for referral to the emergency department, immediate reduction in blood pressure in the emergency department, or hospitalization for such patients.

A documented episode of hypertensive urgency or severe uncontrolled hypertension, pending response to drug therapy, may or may not require termination of the study drug.

Figure 2. Diagnosis and Management of a Hypertensive Crisis



BP = blood pressure; DBP = diastolic blood pressure; h = hour; ICU = intensive care unit; SBP = systolic blood pressure.
Source: Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/ AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 07 November 2017; Epub ahead of print.