Cover Page for Protocol

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NCT number:	NCT04968184
Sponsor trial ID:	KBP5074-3-001
Official title of the study:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of KBP-5074, a Mineralocorticoid Receptor Antagonist, in Subjects with Uncontrolled Hypertension Who Have Moderate or Severe (Stage 3b/4) Chronic Kidney Disease
Document date:	22-December-2023

Clinical Trial Protocol: KBP5074-3-001

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of KBP-5074, a Mineralocorticoid Receptor Antagonist, in Subjects with Uncontrolled Hypertension Who Have Moderate or Severe (Stage 3b/4) Chronic Kidney Disease
Study Number:	KBP5074-3-001
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IND Number:	117743
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-Sponsor:	KBP BioSciences PTE. Ltd. 10 Anson Road #17-26 International Plaza Singapore 079903
Sponsor Contact:	KBP BioSciences USA Inc. 116 Village Boulevard, Suite 210 Princeton, New Jersey USA Telephone: (+1) 609-874-0416
Sponsor's Global Medical Monitor:	PPD Email: PPD
Sponsor's APAC Medical Monitor:	PPD Email: PPD
Amendment 2:	22 December 2023
Amendment 1:	30 March 2022
Original Protocol:	14 June 2021

Redacted protocol includes redaction of personal identifiable information only.

Confidentiality Statement

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SPONSOR SIGNATURE PAGE

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of KBP-5074, a Mineralocorticoid Receptor Antagonist, in Subjects with Uncontrolled Hypertension Who Have Moderate or Severe (Stage 3b/4) Chronic Kidney Disease
Study Number:	KBP5074-3-001
Amendment 2 Final Date:	22 December 2023

This clinical study protocol amendment 2 was subject to critical review and has been approved by the Sponsor. We, the undersigned, have read this protocol amendment 2 and agree that it contains all necessary information required to conduct the study.

PPD

Date: 12/22/2023 | 12:04 PST

PPD

Date: 12/22/2023 | 12:11 PST

INVESTIGATOR AGREEMENT

Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of KBP-5074, a Mineralocorticoid Receptor Antagonist, in Subjects with Uncontrolled Hypertension Who Have Moderate or Severe (Stage 3b/4) Chronic Kidney Disease
Study Number:	KBP5074-3-001
Amendment 2 Final Date:	22 December 2023

By signing below, I agree that:

I have read this protocol amendment 2. 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 amendment 2 and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol amendment 2 and access to all information furnished by KBP BioSciences PTE. 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 PTE. 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 PTE. 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 International Council for Harmonisation Guidelines for Good Clinical Practices, Food and Drug Administration Regulations, the European Union Clinical Trials Directive 2001/20/EC (EUCTD), Institutional Review Board/Independent Ethics Committee Regulations, and all applicable regulations.

Signed:_____ Date:_____

<enter name and credentials>
<enter title>
<enter affiliation>
<enter address>
<enter phone number>

SYNOPSIS

Sponsor:
KBP BioSciences PTE. Ltd.

Name of Finished Product:
KBP-5074

Name of Active Ingredient:
KBP-5074

Study Title:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of KBP-5074, a Mineralocorticoid Receptor Antagonist, in Subjects with Uncontrolled Hypertension Who Have Moderate or Severe (Stage 3b/4) Chronic Kidney Disease

Study Number:
KBP5074-3-001

Study Phase: 3

Primary Objective:
The primary objective of this study is to evaluate the efficacy and durability of KBP-5074 in reducing systolic blood pressure (SBP).

Secondary Objectives:
The secondary objectives of this study are:

- To evaluate the effect of KBP-5074 on diastolic blood pressure (DBP) and urine albumin:creatinine ratio (UACR);
- To evaluate the safety and tolerability of KBP-5074.

Study Design:
This Phase 3, randomized, double-blind, placebo -controlled, 2-arm, parallel-group-, multicenter study with randomized withdrawal will evaluate the efficacy, safety, and durability of KBP-5074 in adult subjects who have stage 3b/4 chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula [eGFR {EPI}] ≥15 to ≤44 mL/min/1.73 m^2) and uncontrolled hypertension (SBP ≥140 and <180 mm Hg and taking 2 or more antihypertensive medications that have been titrated upward as tolerated to antihypertensive medication target doses per local standard of care [SoC]).

The study will consist of the following periods:

- Pretreatment Phase
  - Prescreening assessment
  - Screening Period of up to 4 weeks
  - 2-week Open-Label Placebo Run-In Period

- A 24-week Double-blind Treatment Period (Randomization to Week 24) that will include:
  - To assess the primary endpoint, an initial 12-week treatment period (Randomization to Week 12) during which
    - Study drug will be titrated
    - Background antihypertensive medications are **not** allowed to change, except for safety reasons
  - A second 12-week treatment period (Week 12 to Week 24) during which
    - Study drug will be titrated
    - Background antihypertensive medications may be changed according to SoC at the Investigator's discretion
- A 24-week Open-Label Treatment Period (Week 24 to Week 48) during which
  - Eligible subjects will receive open-label KBP-5074
  - Background antihypertensive medications
    - Are **not** allowed to change during the initial 6 weeks (Week 24 to Week 30) when study drug is being titrated, except for safety reasons
    - May be changed according to SoC at the Investigator's discretion during the next 14 weeks (Week 30 to Week 44)
    - Are **not** allowed to change during the last 4 weeks (Week 44 to Week 48) in preparation for randomized withdrawal, except for safety reasons
- A 4-week Randomized Double-Blind Withdrawal Period (Week 48 to Week 52) during which eligible subjects will be randomized to continue their current KBP-5074 dose at the end of open-label treatment or receive matching placebo for 4 weeks and during which background antihypertensive medications are **not** allowed to change, except for safety reasons
- A 4-week post-treatment Follow-Up Period (Week 52 to Week 56)

Randomization:
At the beginning of the Double-Blind Treatment Period, eligible subjects will be randomly assigned in a 1:1 ratio to KBP-5074 0.25 mg or matching placebo once daily (QD). Randomization will be stratified to balance enrollment for the following baseline characteristics that may influence safety and/or efficacy evaluations: eGFR (EPI) ($\geq$30 versus <30 mL/min/1.73 m^2), baseline SBP ($\geq$160 versus <160 mm Hg), baseline UACR (<30 versus $\geq$30 mg/g), and geographic region (North America, Asia, and Europe/other).

At the beginning of the Randomized Double-Blind Withdrawal Period, subjects who meet the Randomized Withdrawal Criteria will be randomly assigned in a 1:1 ratio to continue their current KBP-5074 dose at the end of the Open-Label Treatment Period or matching placebo QD.

Study Population:
Adult subjects age ≥18 years with uncontrolled hypertension and Stage 3b/4 CKD (eGFR (EPI) ≥15 and ≤44 mL/min/1.73 m^2) will be enrolled in this study. The study will enroll approximately 600 subjects at approximately 140 study sites globally.

Key Inclusion Criteria:

- Subject must be ≥18 years of age at the Screening Visit (Visit 1).
- Body mass index (BMI) must be ≥19 to <45 kg/m^2 at the Screening Visit (Visit 1).
- Subject must have uncontrolled hypertension defined as meeting both of the following criteria:
  - The subject has a resting seated trough cuff SBP ≥140 mm Hg at the Screening Visit (Visit 1), and at the start (Visit 2) and end (Visit 3) of the Run-In Period.
  - The subject is taking 2 or more antihypertensive medications that have been titrated upward as tolerated to hypertension target doses per local SoC and have been stable (i.e., without any dose adjustments) from 4 weeks before the Screening Visit (Visit 1) through the end of the Run-In Period (Visit 3).
    - The antihypertensive medications must include at least 1 loop, thiazide, or thiazide-like diuretic unless the subject has a documented intolerance to or contraindication for diuretic therapy.
    - A subject on 1 antihypertensive medication that has been titrated upward as tolerated to a hypertension target dose per local SoC and has been stable during the 4 weeks prior to the Screening Visit (Visit 1) may be enrolled in the study if the subject has a documented history of intolerance to multiple antihypertensive medications.
- The subject must have Stage 3b (eGFR [EPI] ≥30 and ≤44 mL/min/1.73 m^2) or Stage 4 (eGFR [EPI] ≥15 and <30 mL/min/1.73 m^2) CKD.

Key Exclusion Criteria:

- Subject has a serum potassium level >4.8 mmol/L according to central laboratory results during the Screening or Run-In Periods.
- Subject has had a serum potassium level >5.6 mmol/L within 2 weeks before the Screening Visit (Visit 1).
- Subject has been hospitalized for hyperkalemia within the 3 months before the Randomization Visit (Visit 3).
- Subject was not compliant with taking placebo during the Run-in Period (defined as taking <80% or >120% of planned placebo doses) or the Investigator determines that the subject was not compliant with background antihypertensive medications during the Run-in Period as assessed at the Randomization Visit (Visit 3).
- Subject has taken a mineralocorticoid receptor antagonist (MRA), a potassium-sparing diuretic, or chronic potassium supplements during the 4 weeks before the Screening Visit (Visit 1).

- Subject has taken potassium binders for the treatment of hyperkalemia during the 3 months before the Screening Visit (Visit 1).
- Subject has taken a strong CYP3A4 inducer or strong CYP3A4 inhibitor during the 7 days before the Randomization Visit (Visit 3).
- Subject has taken a prohibited traditional Chinese medication during the 28 days prior to Screening Visit (Visit 1); see Section 5.6.2.

Test Product, Dose, and Mode of Administration:
0.25- and 0.5-mg strength KBP-5074 tablets administered orally at doses from 0.25 mg to a maximum dose of 0.5 mg QD.

A forced-titration strategy will be used to manage study drug in the Double-Blind and Open-Label Treatment Periods. Initially, eligible subjects will receive KBP-5074 0.25 mg or matching placebo QD. Starting at Week 4 (Visit 5) in Double-Blind and Week 28 (Visit 11) Open-Label Treatment periods, subjects who meet all the Up-Titration Safety Criteria (SBP >120 mm Hg, decrease in SBP from baseline to Week 4 [Visit 5] or from previous visit after Week 4 [Visit 5] is <30 mm Hg, serum potassium ≤4.8 mmol/L, decrease from baseline in eGFR [EPI] is <30%, and no safety concerns) will be up-titrated to the maximum dose of study drug (KBP-5074 0.5 mg or matching placebo).

Subjects who have been up-titrated to the maximum dose of the study drug but who do not tolerate this dose may be down-titrated at any point during the study for safety reasons.

Reference Drug:
Matching placebo tablets administered orally QD

Background Treatment:
Subjects will continue to take their pre-study (background) antihypertensive medications, which have been titrated upward as tolerated to hypertensive target doses per SoC.

Changes to background antihypertensive medications (including adding, discontinuation, or dose adjustment of background antihypertensive medications) may occur as follows:

- No changes to background antihypertensive medications are allowed during the first 12 weeks (Randomization to Week 12) of double-blind treatment except for subject safety (e.g., hypertensive urgency).
- From Week 12 to Week 24 (the end of the Double-Blind Treatment Period), Investigators may change background antihypertensive medications according to SoC.
- No changes in background antihypertensive medications are allowed during the first 6 weeks (Week 24 to Week 30) of Open-Label Treatment Period except for subject safety.
- From Week 30 to Week 44 of the Open-Label Treatment Period, Investigators may change background antihypertensive medications according to SoC.
- No changes to background antihypertensive medications are allowed from Week 44 through Week 48 of the Open-Label Treatment Period or during the Randomized Withdrawal Period (Week 48 to Week 52) except for subject safety.

Duration of Treatment:
The duration of treatment for each subject will be 52 weeks. For subjects who complete the study, the total duration of participation (from the Screening Visit through the Follow-Up Visit) will be approximately 62 weeks.

Efficacy Assessments:
The primary endpoint for efficacy is change in seated trough cuff SBP from baseline to Week 12.

The second key endpoint for durability is change in seated trough cuff SBP from Week 48 to Week 52.

The key secondary efficacy endpoints for the study are:

- Change in seated trough cuff SBP from baseline to Week 24;
- Changes in seated trough cuff DBP from baseline to Week 12 and Week 24;
- Changes in UACR from baseline to Week 12 and Week 24 for subjects with UACR ≥30 mg/g at baseline.

Other secondary efficacy endpoints for the study are:

- Change in seated trough cuff SBP and DBP from baseline to Week 48;
- Percentage changes in UACR from baseline to Week 12 and Week 24 for subjects with UACR ≥30 mg/g at baseline;
- Changes and percentage changes in UACR from baseline to Week 12, Week 24, and Week 48 for subjects with macroalbuminuria (defined as UACR ≥300 mg/g) at baseline;
- Changes and percentage changes in UACR from baseline to Week 12, Week 24, and Week 48 for subjects with microalbuminuria (defined as UACR ≥30 and <300 mg/g) at baseline;
- Change in seated trough cuff DBP from Week 48 to Week 52;
- Change and percentage change in UACR from Week 48 to Week 52 for subjects with UACR ≥30 mg/g at baseline;
- Change and percentage change in UACR from Week 48 to Week 52 for subjects with macroalbuminuria (defined as UACR ≥300 mg/g) at baseline;
- Change and percentage change in UACR from Week 48 to Week 52 for subjects with microalbuminuria (defined as UACR ≥30 and <300 mg/g) at baseline.

Safety Assessments:
Safety assessments include evaluation of adverse events (AEs), vital signs, clinical laboratories findings, 12-lead electrocardiograms (ECGs), and physical examination findings.

Safety endpoints for this study are:

- Incidences of serious adverse events (SAEs), non-serious AEs, AEs leading to discontinuation of study drug, and AEs leading to discontinuation from the study;
- Incidences of AEs of hyperkalemia, hypertension, hypotension, and eGFR decrease;
- Incidences of serum potassium >5.0 to <5.6 mmol/L, ≥5.6 to <6.0 mmol/L, and ≥6.0 mmol/L by central laboratory results;
- Changes in serum potassium levels from baseline to Week 12, Week 24, and Week 48 by central laboratory results;
- Changes in eGFR (EPI) from baseline to Week 12, Week 24, and Week 48 by central laboratory results;
- Incidence of sustained decrease in eGFR (EPI) of ≥30% from baseline by central laboratory results (an eGFR [EPI] decrease of ≥30% from baseline will be considered sustained if the eGFR [EPI] reduction is still ≥30% from baseline at least 4 weeks after the initial measurement);
- Change in serum potassium levels from Week 48 to Week 52 by central laboratory results;
- Change in eGFR (EPI) from Week 48 to Week 52 by central laboratory results.

Statistical Methods:
Analysis Populations:

- The Intent -to-Treat (ITT) Population is defined as all randomized subjects. The ITT Population will be the primary analysis population.
- The UACR population is defined as all randomized subjects who received at least 1 dose of randomized study drug, have a baseline UACR measurement, have UACR ≥30 mg/g at baseline, and have at least 1 post-dose UACR measurement.
- The Safety Population is defined as all randomized subjects who received at least 1 dose of randomized study drug.
- The Pharmacokinetic (PK) Population is defined as all randomized subjects who received at least 1 dose of randomized study drug and have at least 1 measurable plasma concentration of KBP-5074.
- The Pharmacodynamic (PD)/Biomarker Population is defined as all randomized subjects who received at least 1 dose of randomized study drug, have a baseline PD/biomarker measurement, and have at least 1 post-dose PD/biomarker measurement.
- Randomized Withdrawal Population is defined as all randomized subjects who were randomized at the Week 48 Visit into the Randomized Double-Blind Withdrawal Period and have at least 1 SBP measurement after the Week 48 Visit.

Primary Efficacy Analysis at Week 12

The primary estimand will be used for the analysis of the primary efficacy endpoint. The primary efficacy endpoint is the change in seated trough cuff SBP from baseline to Week 12 using the ITT population. The set of intercurrent events for this estimand consists of discontinuation of study treatment up to Week 12, missed study treatment up to Week 12, or a change in background antihypertensive medications after randomization and up to Week 12. The intercurrent events will be handled using a treatment policy strategy where observed data is used regardless of occurrence of these intercurrent events. The absence of a seated trough cuff SBP measurement on or before Week 12 following these subjects' withdrawal, missed study treatment or background antihypertensive medication change will be imputed by multiple imputation and using the information from retrieved dropouts.

The primary efficacy analysis will be based on the ITT Population and employ an analysis of covariance (ANCOVA) model with change in seated trough cuff SBP from baseline at Week 12 as the outcome variable. Treatment, together with baseline eGFR level (≥30 versus <30 mL/min/1.73 m^2), and background antihypertensive medication (3 or more versus fewer than 3) will be factors in the model, and baseline SBP value will be a covariate. Model results will be generated for each completed dataset from PROC MI. The results from these analyses will be combined together for an overall inference using PROC MIANALYZE. This will produce adjusted least squares (LS) mean, standard error, and the two-sided 95% confidence interval (CI) for each treatment group, and the difference between LS-means, and the 95% CI of the difference, and p-values for comparing the KBP-5074 and placebo group.

Analysis of the Second Key Endpoint for Durability at End of Randomized Withdrawal Period

The analysis of the second key endpoint for durability (change in seated trough cuff SBP from Week 48 to Week 52) will be based on the Randomized Withdrawal Population and employ an ANCOVA model with change in seated trough cuff SBP from Week 48 to Week 52 as the outcome variable. Treatment, baseline eGFR level, randomization assignment at the Randomization Withdrawal Week 48 (Visit 15), and background antihypertensive medication will be factors in the model, and baseline SBP value will be a covariate. The LS-means, standard errors, and the two-tailed 95% CIs for each treatment group and the difference of the LS-means, 95% CIs and p-values for comparing the KBP-5074 and placebo groups will be estimated. Missing value impact will be examined by the multiple imputation method; details will be included in the SAP.

Analysis of Secondary Efficacy and Exploratory Endpoints

The effect of treatment on secondary efficacy endpoints will be evaluated by comparing results for the KBP-5074 and placebo groups. Continuous secondary endpoints will be analyzed using methods analogous to the models employed for the primary endpoints. Categorical data will be summarized and analyzed using a logistic regression model with factors such as baseline eGFR group and baseline SBP groups.

For the evaluation of the long-term hypertensive effect of KBP-5074, time to up-titration of study drug or change in background antihypertensive medications will be evaluated over 12 and 24 weeks.

Log transformation will be used for UACR endpoints, which will be analyzed using methods analogous to the model employed for the primary endpoint. Non-parametric methods may also be considered.

For the primary endpoint, second key endpoint for durability, and key secondary endpoints, subgroup analyses will also be performed.

All efficacy endpoints from the Open-Label Treatment Period will be summarized descriptively.

Type 1 Error Control

The overall Type 1 error for the primary endpoint at Week 12 will be controlled at the level of 0.05. The key secondary endpoints during the Double-Blind Treatment Period (Randomization to Week 24) will be tested with same nominal alpha level.

The Type 1 error for the second key endpoint for durability during the Randomized Double-Blind Withdrawal Period (Week 48 to Week 52) will be controlled at the same alpha level of 0.05.

Analysis of Safety

All safety analyses will be conducted using the Safety Population. The assessment of safety will be based primarily on the frequency of subjects with AEs and clinical laboratory abnormalities.

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) not otherwise involved with study conduct will be established to monitor safety during the study. The IDMC will independently review the safety data and determine if it is safe to continue the study according to the protocol.

A formal interim analysis to assess lack of efficacy may be conducted when all subjects complete the Week 12 Visit.

Determination of Sample Size

The primary efficacy endpoint is the change in seated trough cuff SBP from baseline to Week 12. Under the assumption of the submission, the final sample size of 240/240 (or 300/300 at enrollment with 20% dropout rate) will achieve more than 90% power to detect a 6 mm Hg difference in SBP between the KBP-5074 and placebo dose groups, assuming a standard deviation of 20 mm Hg at a target two-sided overall alpha level of 0.05.

The completed phase 2b study showed a treatment difference of approximately 10 mm Hg for KBP-5074 0.5 mg compared to placebo at the end of active treatment, a post-treatment increase in SBP for the KBP-5074 0.5mg group at 28 days after the last dose of study drug of approximately 10 mm Hg, and standard deviations (SDs) for post-treatment increases in SBP in the KBP-5074 and placebo groups of approximately 18 mm Hg.

Based on the data from the phase 2b study, the increase in SBP in subjects randomized to placebo in the Randomized Double-Blind Withdrawal Period 4 weeks after discontinuing treatment with KBP-5074 is expected to be at least 5 mm Hg. Assuming that approximately 400 of the 600 subjects initially enrolled will complete 48 weeks of treatment and be randomized into the Randomized Double-Blind Withdrawal Period and assuming that treatment differences and SDs from the previous phase 2b study hold, the

randomized withdrawal should provide approximately 80% power to detect a difference of at least 5 mm Hg between the KBP-5074 and placebo groups.

Date of Approved Amendment 2: 22 December 2023
Date of Approved Amendment 1: 30 March 2022
Date of Original Approved Protocol: 14 June 2021

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin converting enzyme
ADR	Adverse drug reaction
AE	Adverse event
AHA	American Heart Association
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Ang I	Angiotensin I
Ang II	Angiotensin II
AOBP	Automated office blood pressure
ARB	Angiotensin receptor blockers
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	Area under the concentration-time curve
BMI	Body mass index
CFR	Code of Federal Regulations
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum observed concentration
COVID-19	Coronavirus disease 2019
CRA	Clinical Research Associate
CRO	Clinical research organization
CYP	Cytochrome P450
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
eGFR (EPI)	Estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration formula
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
EQ-5D-5L	EuroQol Group 5-Dimension 5-Level Instrument
ET	Early termination
EUCTD	European Union Clinical Trials Directive 2001/20/EC

FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-treat
KDQOL-36	36-item Kidney Disease Quality of Life Survey
LS	Least squares
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed-model for repeated measures
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonist
PD	Pharmacodynamics
PK	Pharmacokinetics
PRO	Patient-reported outcome
Q1	First quartile
Q3	Third quartile
QD	Once daily
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious drug reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBP	Systolic blood pressure
SD	Standard deviation
SF-12	12-item Short Form Health Survey
SoC	Standard of care
$t_{1/2}$	Terminal elimination half-life

TEAE	Treatment-emergent adverse event
UACR	Urinary albumin:creatinine ratio
ULN	Upper limit of normal
VAS	Visual analog scale
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Women of childbearing potential

1 INTRODUCTION

1.1 Disease Background

Hypertension and chronic kidney disease (CKD) are leading causes of morbidity and mortality worldwide (1). In the United States, 31 to 34 million people had CKD in 2015/2016, and 15 to 18 million of these individuals had evidence of Stage 3b (moderate; estimated glomerular filtration rate [eGFR] ≥30 and ≤44 mL/min/1.73 m^2) to stage 4 (severe; eGFR ≥15 and <30 mL/min/1.73 m^2) CKD (2). Resistant hypertension (defined as blood pressure >130/80 mm Hg despite treatment with 3 or more antihypertensive medications) occurs in about 23% of individuals with CKD (approximately 7.1 to 7.8 million patients with CKD of which approximately 3.5 to 4.1 million patients have stage 3b/4 CKD) (3). Patients with CKD who have hypertension that cannot be controlled are at high risk for stroke, myocardial infarction, heart failure, and worsening kidney function. Hypertension is a major risk factor for renal failure, with a prevalence of 28% in hypertensive patients (4). The risk of death, cardiovascular events, and hospitalizations increased substantially (>3-fold) in patients with stage 3b and stage 4 CKD compared to patients with eGFR ≥60 mL/min/1.73 m^2 (5). The failure to manage hypertension in moderate to severe CKD patients leads to progressive loss of renal function and ultimately the need for dialysis or kidney transplantation.

Antihypertensive therapies most often used in CKD patients include angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, diuretics, and beta blockers. Although these drugs reduced adverse outcomes by lowering blood pressure and, in the case of ACE inhibitors and ARBs, by direct renal protective effects, these agents often failed to reduce blood pressure to target levels in patients with CKD and uncontrolled hypertension (3).

The mineralocorticoid receptor (MR), a member of the steroid receptor family activated through the binding of aldosterone, has been shown to have a major pathophysiological role in the progression of kidney diseases (1,6,7). Inhibition of MR signaling leads to increased sodium excretion, resulting in decreased body fluid, and considerably reduces blood pressure and proteinuria in patients with CKD (1,6,7). Proteinuria is a sign of abnormal kidney function in CKD patients (8). The selective inhibition of MRs is a validated therapeutic approach providing cardiorenal protection and blood pressure control via a mechanism distinct from other antihypertensive agents (9-11).

One challenge with inhibition of this pathway is that the excretion of sodium triggered by MR antagonism typically results in the retention of potassium. In many patients with compromised renal function, retention of potassium results in significant elevations in serum potassium, and therefore, limits the utility of this class of drugs in the patients who are most in need (i.e., patients who have compromised renal function and who are further jeopardized by persistent uncontrolled hypertension). Currently available mineralocorticoid receptor antagonists (MRAs; spironolactone and eplerenone) have strong warnings or are contraindicated for use in the treatment of stage 3b/4 CKD patients due to excessive risk of hyperkalemia. Spironolactone in the AMBER study had 23% of subjects with mean eGFR 36 mL/min/1.73 m^2 discontinue spironolactone due to hyperkalemia and two-thirds of the subjects developed hyperkalemia during the trial (12). Eplerenone in the EPHESUS study

had 24% of subjects with baseline creatinine clearance 31 to 50 mL/min and 32% with baseline creatinine clearance ≤30 mL/min develop serum potassium levels >5.5 mmol/L (13). Because of the risk of hyperkalemia, patients must choose between an inconvenient and/or expensive combination of treatments or, the alternative, live with untreated hypertension, which can lead to additional severe health issues such as progressive renal failure, heart failure, stroke, or myocardial infarction. Supplemental medications (potassium binders) to counteract such risk can lead to a significant additional burden of compliance and cost. These supplemental medications also do not remove risk of hyperkalemia completely. This burden has negatively impacted the rate of adoption of currently available steroidal MRAs to <6% of patients with CKD in the United States, suggesting that few moderate to severe CKD patients with uncontrolled hypertension in the United States have treatment regimens that include MRAs (14).

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 to meet the significant unmet medical need in treating moderate to severe CKD patients with uncontrolled hypertension.

1.2 KBP-5074

KBP-5074 is a novel non-steroidal MRA being developed for the treatment of uncontrolled hypertension in patients with stage 3b (eGFR ≥30 and ≤44 mL/min/1.73 m^2) or stage 4 (eGFR ≥15 and <30 mL/min/1.73 m^2) CKD.

1.2.1 Summary of Nonclinical Studies

In nonclinical studies, KBP-5074 selectively bound to the MR and blocked the binding of aldosterone with a higher degree of binding affinity, selectivity, and antagonist activity relative to the glucocorticoid receptor, androgen receptor, and progesterone receptor, when compared to the currently available steroidal MRAs, spironolactone and eplerenone. KBP-5074 has also been demonstrated to have better efficacy in lowering blood pressure and renal protection in nonclinical disease models than the benchmark compound eplerenone.

A battery of pharmacology and toxicology studies including safety pharmacology studies, acute toxicity studies and subchronic (4- and 13-week) and chronic (26- and 39-week) repeated-dose toxicity studies in rats and dogs, genotoxicity studies, and reproductive toxicity studies in rats were conducted to support the Investigational New Drug application for conducting clinical trials. These studies demonstrated that KBP-5074 was well tolerated at exposure levels (area under the concentration-time curve [AUC]) that were approximately 90-fold higher in rats (no-observed-adverse-effect level [NOAEL] 20 mg/kg/day) than the estimated clinical exposures for subjects with stage 3b/4 CKD. At these exposures, no adverse histological changes were observed in any organs and no tumors were observed. Histopathological examination demonstrated that adrenal hyperplasia or hypertrophy had occurred in rats and dogs. These findings were reversible in rats, but not in dogs after a 4-week recovery period. Since KBP-5074 is an MRA, these findings were- considered related to the pharmacologic mechanism of KBP-5074 and were not considered pathological.

Further details regarding the non-clinical studies of KBP-5074 can be found in the Investigator's Brochure (IB).

1.2.2 Summary of Clinical Studies

KBP-5074 has been investigated in a total of 9 clinical studies (8 completed Phase 1/2a studies and 1 phase 2b study). A total of 187 subjects with CKD and 139 healthy and non-CKD subjects have been enrolled in the KBP-5074 clinical development program. Overall, 139 healthy and non-CKD subjects have been exposed to KBP-5074 for up to 14 days and 130 subjects with CKD have been exposed to KBP-5074 for up to 84 days.

In phase 1/2a studies, KBP-5074 was safe and generally well tolerated at single doses of from 0.25 to 30 mg, multiple doses of 2.5 and 5.0 mg once daily (QD) for up to 14 days in healthy subjects (including healthy Chinese subjects), and multiple doses of 0.5 and 2.5 mg QD for up to 56 days in subjects with mild to moderate renal impairment (eGFR ≥30 and ≤89 mL/min/1.73 m^2) and proteinuria (urinary albumin:creatinine ratio [UACR] ≥30 and ≤3000 mg/g). Additionally, administration of a single dose of KBP-5074 0.5 mg was well tolerated in subjects with severe CKD (eGFR ≥15 and ≤29 mL/min/1.73 m^2) who were or were not on hemodialysis. Most adverse events (AEs) were mild to moderate intensity. A total of 3 serious adverse events (SAEs; asymptomatic ventricular extrasystoles, hypertensive urgency, and acute cholecystitis/cholelithiasis) were reported across the 8 Phase 1/2a studies; all 3 SAEs were considered unrelated to KBP-5074. There were no deaths or severe AEs and no clinically significant differences in safety and tolerability between the administration groups.

In the recently completed phase 2b (15), randomized, double-blind, placebo-controlled, global, multicenter, dose-finding study in subjects with uncontrolled hypertension who had Stage 3b/4 CKD (eGFR ≥15 and ≤44 mL/min/1.73 m^2), KBP-5074 was well tolerated and demonstrated a clinically and statistically significant improvement in systolic blood pressure (SBP) with a low incidence of hyperkalemia. A total of 162 subjects were randomized in a 1:1:1 ratio to KBP-5074 0.25 mg, KBP-5074 0.5 mg, or placebo QD for 84 days. Overall, 89% of subjects enrolled had treatment-resistant hypertension.

The study met the primary efficacy endpoint for both KBP-5074 dose regimens, demonstrating a clinically meaningful and statistically significant reduction of SBP from baseline to Day 84 in subjects with uncontrolled hypertension who have Stage 3b/4 CKD. The changes in SBP from baseline to Day 84 for subjects in the KBP-5074 0.25- and 0.5-mg dose groups were -11.5 and -15.9 mm Hg, respectively, compared to -5.3 mm Hg for the placebo dose group, representing statistically significant placebo-corrected differences of -7.0 mm Hg (p=0.0399) and -10.2 mm Hg (p=0.0026), respectively. KBP-5074 also demonstrated a clinically meaningful trend in the reduction of UACR, an important measure of kidney disease progression especially among patients with proteinuria.

KBP-5074 was safe and generally well-tolerated. The incidence of subjects experiencing at least 1 treatment-emergent AE (TEAE) was highest in the KBP-5074 0.5-mg dose group (79.6%) but similar in the KBP-5074 0.25-mg (62.7%) and placebo (57.9%) dose groups. Most TEAEs were mild in intensity. The incidences of moderate and severe TEAEs were

higher in the KBP-5074 0.25-mg dose group than the other treatment groups. Seven subjects had severe TEAEs: 3 subjects in the placebo dose group (gout, myocardial infarction, and death of unknown cause), 2 subjects in the KBP-5074 0.25-mg dose group (1 subject with influenza, alanine aminotransferase [ALT] increased, aspartate aminotransferase [AST] increased, and alkaline phosphatase [AP] increased and 1 subject with hypertensive urgency), and 2 subjects in the KBP-5074 0.5-mg dose group (headache and non-Hodgkin's lymphoma). None of the severe TEAEs were considered related to study drug. The incidences of treatment-related TEAEs were higher in the KBP-5074 dose groups compared to placebo with a dose-dependent increase between the KBP-5074 0.25- to 0.5-mg dose groups. Most treatment-related TEAEs were mild in intensity.

The most common TEAE was hyperkalemia with incidences of 50.0%, 29.4%, and 24.6% in the KBP-5074 0.5-mg, KBP-5074 0.25-mg, and placebo dose groups, respectively. Most hyperkalemia events were classified as mild. The next most common TEAEs in any treatment group were glomerular filtration rate (GFR) decreased, CKD, headache, blood creatinine increased, blood potassium increased, hypertensive urgency, and diarrhea, all of which occurred in <10% of subjects in each treatment group. The most common treatment-related TEAEs were hyperkalemia and blood creatinine increased. No severe TEAEs of hyperkalemia and no TEAEs of acute kidney injury occurred during the study. There were no differences in the incidence of TEAEs between subjects with Stage 3b (baseline eGFR ≥30 mL/min/1.73 m^2) and Stage 4 CKD (baseline eGFR <30 mL/min/1.73 m^2).

Two subjects, both in the placebo dose group, died during the study (death of unknown cause and myocardial infarction). A total of 7 subjects (4.3%) had SAEs, with the most SAEs occurring in the placebo dose group (4 subjects [7.0%]). Three subjects in the KBP-5074 dose groups (2.9%) had SAEs: 1 subject in the KBP-5074 0.25-mg dose group had an SAE of cerebrovascular accident, and 2 subjects in the KBP-5074 0.5-mg dose group had 1 SAEs of angina unstable and non-Hodgkin's lymphoma, respectively. All 3 SAEs were considered not related to KBP-5074. No treatment-related SAE occurred during the study, and no subject was hospitalized for hyperkalemia. There were no differences in the incidence of SAEs between subjects with Stage 3b and Stage 4 CKD.

Overall, the incidences of TEAEs of hyperkalemia or blood potassium increased were dose-dependent, with subjects receiving KBP-5074 0.5 mg QD having a higher incidence of AEs of hyperkalemia (50.0%) or blood potassium increased (7.4%) compared to subjects receiving placebo (24.6% and 3.5%, respectively) and KBP-5074 0.25 mg QD (29.4% and 3.9%, respectively), who had similar incidences of AEs of hyperkalemia and blood potassium increased. Based on laboratory results, a dose-dependent increase was observed from KBP-5074 0.25 to 0.5 mg QD in serum potassium levels >5.0 to ≤5.5 mmol/L, but the incidences of serum potassium >5.5 mmol/L were similar between the KBP-5074 dose groups. The incidences of serum potassium levels >5.0 to ≤5.5 mmol/L were similar between the placebo and KBP-5074 0.25 mg dose groups, and the incidences of serum potassium >5.5 mmol/L were low (approximately 11%) and similar across all dose groups. No severe AE, hospitalization, or other SAE due to hyperkalemia occurred during the study.

Further details regarding the clinical studies of KBP-5074 can be found in the IB.

1.2.3 Summary of Clinical Pharmacology

The clinical pharmacokinetics (PK) and pharmacodynamics (PD) of KBP-5074 based on studies in healthy subjects, subjects with moderate hepatic impairment, and subjects with CKD at KBP-5074 doses ranging from 0.25 to 30 mg are summarized below.

Clinical PK data in healthy subjects and subjects with renal impairment show that KBP-5074 was rapidly absorbed with a median time to maximum observed concentration (T_{max}) ranging from 3 to 8 hours and a terminal elimination half-life ($t_{1/2}$) ranging from 52 to 72 hours. Consistent with the $t_{1/2}$ of KBP-5074, steady state was reached about 11 days after the first dose. Steady-state accumulation ratios (maximum observed concentration [C_{max}] and AUC) of approximately 4- to 5-fold were observed following QD dosing. No differences in PK parameters were observed between healthy subjects (including healthy Chinese subjects) and subjects with mild to moderate renal impairment.

A mass balance study showed that KBP-5074-related material was primarily eliminated in feces with approximately 84% of the radioactive dose recovered in feces and 7% recovered in urine.

In the hepatic impairment study, exposure to KBP-5074 was 40% (C_{max}) to 20% (AUC) lower in subjects with moderate hepatic impairment compared to healthy subjects, possibly due to decreased absorption of KBP-5074.

In a drug-drug interaction (DDI) study conducted with a strong cytochrome P450 (CYP) 3A4 inhibitor (itraconazole) and a strong CYP3A4 inducer (rifampin), KBP-5074 exposure was increased approximately 2-fold when co-administered with itraconazole and decreased approximately 80% when co-administered with rifampin.

Population PK analysis showed that combined effects on clearance and bioavailability in severe renal impairment (eGFR≥15 and <30 mL/min/1.73 m^2) were associated with a net decrease in the apparent clearance of KBP-5074 of approximately 34% compared to subjects with normal renal function. Estimated steady state exposures (AUC) for subjects with Stage 3b and Stage 4 CKD were 744.9 and 877.9 h·ng/mL, respectively. Although the population PK analysis suggested that subjects with Stage 4 CKD may have higher exposures to KBP-5074 compared to subjects with Stage 3b CKD, the data from the Phase 2b study indicate that KBP-5074 0.25 and 0.5 mg QD were well tolerated by subjects with Stage 4 CKD and that there were no differences in TEAEs, severe TEAEs, SAEs, events of hyperkalemia, or reduction in eGFR between subjects with Stage 3b and Stage 4 CKD. Based on predicted exposures, exploratory exposure-response analyses, and the observed safety/tolerability profile of KBP-5074, no dose adjustment of KBP-5074 based on the severity of renal impairment of Stage 3b/4 CKD is needed.

Analysis of PD data from the Phase 1/2a studies showed that aldosterone levels increased in a dose-dependent manner after administration of KBP-5074 indicating an effective blockade of the MR.

Further details regarding the clinical pharmacology of KBP-5074 can be found in the IB.

1.3 Study and Dose Rationale

This study is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study with randomized withdrawal to assess the efficacy, safety, and durability of KBP-5074 in subjects with uncontrolled hypertension who have Stage 3b/4 CKD (eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula [eGFR {EPI}] ≥15 to ≤44 mL/min/1.73 m^2). In the Phase 2b study, KBP-5074 was well tolerated and demonstrated statistically significant reductions of SBP without excessive risk of hyperkalemia in subjects with uncontrolled hypertension and Stage 3b/4 CKD. Although the most common AE was mild hyperkalemia, the incidence of subjects with potassium levels >5.5 mmol/L associated with KBP-5074 (approximately 11%) was low and substantially offset by the benefit of a clinically meaningful reduction in the risk of stroke or death due to major cardiovascular events associated with the significant reduction in SBP by KBP-5074.

This study aims to confirm that the unique pharmacological and PK properties of KBP-5074 demonstrated in the Phase 2b study (i.e., greater antihypertensive effectiveness with lower risk of hyperkalemia than reported for other MRAs) and demonstrate the durability of the effect of KBP-5074 on blood pressure. KBP-5074 has the potential to become a novel, selective, non-steroidal MRA drug of choice for addressing one of the most pressing unmet medical needs in subjects with advanced CKD and uncontrolled/resistant hypertension, i.e., achievement of target blood pressure.

The dosing regimens for this study are based on analyses of the available efficacy and safety data from the Phase 2b study, corresponding population PK analyses from clinical studies (including the Phase 2b study and clinical pharmacology studies), and considerations of clinical practice in the treatment of hypertension. As described in Section 1.2.2, the Phase 2b study demonstrated that KBP-5074 0.25 and 0.5 mg QD had favorable benefit/risk profiles. Both KBP-5074 dose regimens produced clinically meaningful and statistically significant placebo-corrected reductions in SBP with no differences observed due to age, baseline eGFR, baseline antihypertensive medications, gender, ethnicity, or diabetic status. KBP-5074 was well tolerated at both doses, with no cases of severe hyperkalemia, acute kidney injury, or hospitalization due to hyperkalemia. Subgroup analyses of TEAEs, SAEs, events of hyperkalemia, and events associated with sustained reductions in eGFR showed no difference in the incidence of these events between subjects with Stage 3b and Stage 4 CKD. As discussed in Section 1.2.3, no dose adjustment of KBP-5074 based on the severity of renal impairment of Stage 3b/4 CKD is needed.

Additionally, no dose adjustments are needed for subjects with mild to moderate hepatic impairment. The hepatic impairment study showed that subjects with moderate hepatic impairment had 41.2% lower C_{max} and 23.5% to 26.6% lower AUC compared to healthy subjects. These results indicate exposure is not expected to increase in subjects with mild or moderate hepatic impairment.

Based on the above considerations, a forced-titration approach is used in this study to balance the need for a consistent dose regimen for the evaluation of efficacy and safety with safety concerns related to potential changes in blood pressure, serum potassium, and renal function (Section 3.1.1). KBP-5074 0.25 mg QD (the lowest dose that has been evaluated), which has

a safety profile similar to placebo, was chosen as the starting dose regimen for the study. After 4 weeks of treatment with KBP-5074 0.25 mg QD, the dose will be up-titrated to KBP-5074 0.5 mg QD unless there are safety concerns (Table 2, Up-Titration Safety Criteria). The KBP-5074 0.5 mg QD dose was chosen as the highest dose for the Phase 3 study to limit the risk of hyperkalemia.

The study will be conducted in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), applicable regulatory requirements, and local and national regulations governing the conduct of human clinical trials.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Endpoint

The primary objective of this study is to evaluate the efficacy and durability of KBP-5074 in reducing SBP.

The primary endpoint for efficacy is the change in seated trough cuff SBP from baseline to Week 12.

The second key endpoint for durability is the change in seated trough cuff SBP from Week 48 to Week 52.

2.2 Secondary Objectives and Endpoints

The secondary objectives of this study are:

- To evaluate the effect of KBP-5074 on diastolic blood pressure (DBP) and UACR;
- To evaluate the safety and tolerability of KBP-5074.

The key secondary efficacy endpoints for the study are:

- Change in seated trough cuff SBP from baseline to Week 24;
- Changes in seated trough cuff DBP from baseline to Week 12 and Week 24;
- Changes in UACR from baseline to Week 12 and Week 24 for subjects with UACR ≥30 mg/g at baseline.

Other secondary efficacy endpoints for the study are:

- Changes in seated trough cuff SBP and DBP from baseline to Week 48;
- Percentage changes in UACR from baseline to Week 12 and Week 24 for subjects with UACR ≥30 mg/g at baseline;
- Changes and percentage changes in UACR from baseline to Week 12, Week 24, and Week 48 for subjects with macroalbuminuria (defined as UACR ≥300 mg/g) at baseline;
- Changes and percentage changes in UACR from baseline to Week 12, Week 24, and Week 48 for subjects with microalbuminuria (defined as UACR ≥30 and <300 mg/g) at baseline;
- Change in seated trough cuff DBP from Week 48 to Week 52;
- Change and percentage change in UACR from Week 48 to Week 52 for subjects with UACR ≥30 mg/g at baseline;

- Change and percentage change in UACR from Week 48 to Week 52 for subjects with macroalbuminuria (defined as UACR ≥300 mg/g) at baseline;
- Change and percentage change in UACR from Week 48 to Week 52 for subjects with microalbuminuria (defined as UACR ≥30 and <300 mg/g) at baseline.

Safety assessments include evaluation of AEs, vital signs, clinical laboratory findings, 12-lead electrocardiograms (ECGs), and physical examination findings.

Safety endpoints for this study are:

- Incidences of SAEs, non-serious AEs, AEs leading to discontinuation of study drug, and AEs leading to discontinuation from the study;
- Incidences of AEs of hyperkalemia, hypertension, hypotension, and eGFR decrease;
- Incidences of serum potassium >5.0 to <5.6 mmol/L, ≥5.6 to <6.0 mmol/L, and ≥6.0 mmol/L by central laboratory results;
- Changes in serum potassium levels from baseline to Week 12, Week 24, and Week 48 by central laboratory results;
- Changes in eGFR (EPI) from baseline to Week 12, Week 24, and Week 48 by central laboratory results;
- Incidence of sustained decreases in eGFR (EPI) of ≥30% from baseline by central laboratory results (an eGFR [EPI] decrease of ≥30% from baseline will be considered sustained if the eGFR [EPI] reduction is still ≥30% from baseline at least 4 weeks after the initial measurement);
- Change in serum potassium levels from Week 48 to Week 52 by central laboratory results;
- Change in eGFR (EPI) from Week 48 to Week 52 by central laboratory results.

2.3 Exploratory Objectives and Endpoints

Exploratory objectives and associated exploratory endpoints for this study are:

- To evaluate changes in SBP and DBP.
  - Changes from baseline to Week 12 in 24-hour mean, daytime mean, and nighttime mean SBP, DBP, mean arterial pressure, and heart rate as measured by ambulatory blood pressure monitoring (ABPM);
  - Proportion of subjects who achieve the target goal of seated trough cuff SBP ≤130 mm Hg or have a decrease from baseline in seated trough cuff SBP ≥10 mm Hg at Week 12, Week 24, and Week 48;

  - Proportion of subjects who achieve the target goal of seated trough cuff SBP ≤130 mm Hg at Week 12, Week 24, and Week 48;
  - Proportion of subjects who have a decrease from baseline in seated trough cuff SBP ≥10 mm Hg at Week 12, Week 24, and Week 48;
  - Changes from baseline to Week 12, Week 24, and Week 48 in seated trough cuff DBP for subjects with DBP ≥90 mm Hg at baseline;
  - Changes from baseline to Week 12, Week 24, and Week 48 in seated trough cuff SBP for subjects with DBP ≥90 mm Hg at baseline;
  - Proportion of subjects who have an increase in seated trough cuff SBP ≥5 mm Hg from Week 48 to Week 52;
  - Proportion of subjects who have an increase in seated trough cuff SBP ≥10 mm Hg from Week 48 to Week 52.

- To evaluate changes in study drug and background antihypertensive medications needed to achieve and maintain target blood pressure.
  - Proportion of subjects who had up-titration in study drug from Day 1 to Week 12, from Week 12 to Week 24, from Week 24 to Week 48, and from Week 48 to Week 52;
  - Proportion of subjects who had down-titration in study drug from Day 1 to Week 12, from Week 12 to Week 24, from Week 24 to Week 48, and from Week 48 to Week 52;
  - Proportion of subjects who had changes in background antihypertensive medications from Day 1 to Week 12, from Week 12 to Week 24, and from Week 24 to Week 48, and from Week 48 to Week 52;
  - Proportion of subjects who achieve the target goal of seated trough cuff SBP ≤130 mm Hg by Week 48:
    - Without study drug titration or change in background antihypertensive medications;
    - Without study drug titration but with change in background antihypertensive;
    - With study drug titration but no change in background antihypertensive medications;
    - With study drug titration and change in background antihypertensive medications.

- To evaluate changes in biomarkers of hypertension, CKD, and inflammation.
  - Biomarkers may include, but are not limited to, the biomarkers listed in Table 13. The panel of biomarkers and time points for analysis will be determined prior to the database lock.

- To evaluate effect of KBP-5074 on subject quality of life.
  - Changes from baseline to Week 24, Week 48, and Week 52 in the EuroQol Group 5-dimension, 5-level Instrument (EQ-5D-5L) scores;
  - Changes from baseline to Week 24, Week 48, and Week 52 in the 36-item Kidney Disease Quality of Life Survey (KDQOL-36) scores.

- To evaluate the PK, PD, and PK/PD relationships of KBP-5074.
  - KBP-5074 plasma concentration at Day 1, and Weeks 4, 6, 12, 24, 28, 30, 48, 52, and 56 (End of Study [EOS]), and unscheduled visits following up- or down-titration and unscheduled Early Termination (ET) and End of Treatment (EOT) visits;
  - The PD variables for this study include changes from baseline to Week 12, Week 24, Week 48, and Week 52 in Triple-A Analysis: serum aldosterone, equilibrium angiotensin I (Ang I), and equilibrium angiotensin II (Ang II).

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This Phase 3, randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multicenter study with randomized withdrawal will evaluate the efficacy, safety, and durability of KBP-5074 in adult subjects who have Stage 3b/4 CKD (eGFR [EPI] ≥15 to ≤44 mL/min/1.73 m^2) and uncontrolled hypertension (SBP ≥140 and <180 mm Hg and taking 2 or more antihypertensive medications that have been titrated upward as tolerated to antihypertensive medication target doses per local standard of care [SoC]). The study will screen approximately 1500 subjects to enroll approximately 600 subjects (300 subjects/arm; see Section 8.11, Determination of Sample Size). Subjects will be recruited, screened, and enrolled at approximately 140 study sites globally.

A diagram of the study design is provided in Figure 1 The Schedule of Study Procedures is provided in Table 10 in Appendix 1.

The study will consist of the following periods:

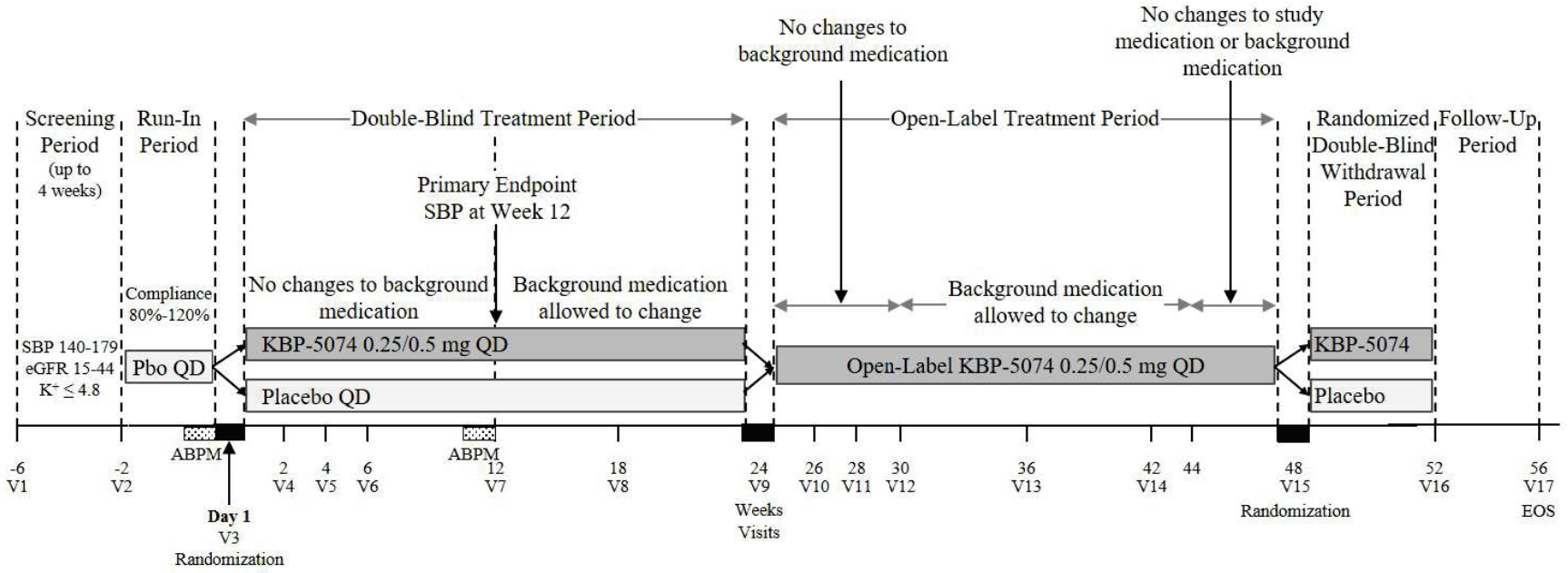
- Pretreatment Phase
  - Prescreening assessment
  - Screening Period of up to 4 weeks
  - 2-week Open-Label Placebo Run-In Period
- A 24-week Double-Blind Treatment Period (Randomization to Week 24) that will include:
  - To assess the primary endpoint, an initial 12-week treatment period (Randomization to Week 12) during which
    - Study drug will be titrated
    - Background antihypertensive medications are **not** allowed to change, except for safety reasons
  - A second 12-week treatment period (Week 12 to Week 24) during which
    - Study drug will be titrated
    - Background antihypertensive medications may be changed according to SoC at the Investigator's discretion
- A 24-week Open-Label Treatment Period (Week 24 to Week 48) during which
  - Eligible subjects will receive open-label KBP-5074
  - Background antihypertensive medications
    - Are **not** allowed to change during the initial 6 weeks (Week 24 to Week 30) when study drug is being titrated, except for safety reasons
    - May be changed according to SoC at the Investigator's discretion during the next 14 weeks (Week 30 to Week 44)

    - Are **not** allowed to change during the last 4 weeks (Week 44 to Week 48) in preparation for randomized withdrawal, except for safety reasons

- A 4-week Randomized Double-Blind Withdrawal Period (Week 48 to Week 52) during which eligible subjects will be randomized to continue their current KBP-5074 dose at the end of open-label treatment or receive matching placebo for 4 weeks and during which background antihypertensive medications are **not** allowed to change, except for safety reasons
- A 4-week post-treatment Follow-Up Period (Week 52 to Week 56)

All assessments of eGFR, including retests, will be performed at both local and central laboratories, and eGFR will be calculated using the CKD-EPI equation (16) by local and central laboratories.

Figure 1 Study Design Diagram for Study KBP5074-3-001



Abbreviations: ABPM=ambulatory blood pressure monitoring; eGFR=estimated glomerular filtration rate; EOS=end of study; Pbo=placebo; QD=once daily; SBP=systolic blood pressure; SoC=standard of care; V=visit

3.1.1 Titration of Study Drug

A forced-titration strategy will be used to manage study drug in the Double-blind and Open-Label Treatment Periods as indicated in Table 1. Initially eligible subjects will receive KBP-5074 0.25 mg or matching placebo QD. Starting at Week 4 (Visit 5) in the Double-Blind and Week 28 (Visit 11) in the Open-Label Treatment periods, subjects who meet all the Up-Titration Safety Criteria listed in Table 2 will be up-titrated to the maximum dose of study drug. For subjects who are not up-titrated at the Week 4 or Week 28 Visits because they do not meet the Up-Titration Safety Criteria, the Investigator should up-titrate the dose of study drug to KBP-5074 0.5 mg or matching placebo QD at the first opportunity when the subject does meet the Up-Titration Safety Criteria.

The timing of when subjects are up-titrated to the maximum dose of study drug in each study period is described in Table 1 and Section 3.1.3, Study Plan with Forced-Titration.

Subjects who have been up-titrated to the maximum dose of the study drug but who do not tolerate this dose may be down-titrated at any point during the study, including between scheduled visits, if required for safety reasons.

For any changes to study drug, the date and details of the change will be recorded in the subject's source documentation and electronic case report form (eCRF; see Sections 6.15 and 6.16).

After any up or down-titration of study drug, the subject should return for a scheduled or unscheduled visit within 2 weeks (±3 days) of the change to monitor blood pressure, potassium, and renal function as indicated in the Schedule of Study Procedures (Table 10).

Table 1 Study Drug and Background Antihypertensive Medication Titration Guidance

Time Interval on Treatment	Dose Titration of Study Drug	Changes to Background Antihypertensive Medications
Double-Blind Treatment Period		
Visit 3 (Rand) to Visit 5 (Week 4)	No titration or changes allowed except for subject safety [a]	
Visit 5 to Visit 7 (Week 12)	Titration per Investigator discretion if Up-Titration Safety Criteria (Table 2) are met [b]	No changes allowed except for subject safety [a]
Visit 7 to Visit 9 (Week 24)		Changes per Investigator discretion and Local SoC [c]
Open-Label Treatment Period		
Visit 9 to Visit 11 (Week 28)	No titration or changes allowed except for subject safety [a]	
Visit 11 to Visit 12 (Week 30)	Titration per Investigator discretion if Up-Titration Safety Criteria (Table 2) are met [b]	No changes allowed except for subject safety [a]
Visit 12 to <Week 44		Changes per Investigator discretion and Local SoC [c]
≥Week 44 to Visit 15 (Week 48)	No titration or changes allowed except for subject safety [a]	
Randomized Double-Blind Withdrawal Period [d]		
Visit 15 to Visit 16 (Week 52)	No titration or changes allowed except for subject safety [a]	

Abbreviations: Rand=Randomization Visit (Day 1); SoC=standard of care

Notes:

- Subjects who have been up-titrated to the maximum dose of the study drug but who do not tolerate this dose may be down-titrated at any point during the study, including between scheduled visits, if required for safety reasons.
- After any change to study drug or background antihypertensive medications, the Investigator should perform an unscheduled visit within 2 weeks (±3 days) of the change to monitor blood pressure, potassium, and renal function.

[a] If changes to background medication are made for safety reasons, the subject should continue study drug unless the subject meets criteria for study drug discontinuation (Section 3.5.1) or study withdrawal (Section 3.5.2).

[b] Study drug should be up-titrated to the maximum dose of study drug (KBP-5074 0.5 mg or matching placebo QD) at Visit 5 (Week 4) and Visit 11 (Week 28) provided that the subject meets the Up-Titration Safety Criteria (Table 2). For subjects who are not up-titrated at Visit 5 or Visit 11 because they do not meet the Up-Titration Safety Criteria, the Investigator should up-titrate to the maximum dose of study drug at the first opportunity when the subject does meet the Up-Titration Safety Criteria.

[c] Up-titration of study drug should be considered before changing background antihypertensive medications if the subject meets the Up-Titration Safety Criteria (Table 2). Changes to background antihypertensive medications should not occur at the same visit as titration of study drug.

[d] At the beginning of the Randomized Double-Blind Withdrawal Period, eligible subjects will be randomized to continue their current KBP-5074 dose at the end of the Open-Label Treatment Period or receive matching placebo for 4 weeks.

Table 2 Up-Titration Safety Criteria

To be up-titrated to the maximum dose of study drug, a subject must meet all the following criteria:
• The subject's SBP is >120 mm Hg. [a]
• The subject's SBP decrease from baseline is <30 mm Hg (only at Week 4 [Visit 5]), or the subject's SBP decrease from the previous visit is <30 mm Hg (for all visits after Week 4 [Visit 5]).
• The subject's serum potassium (by local laboratory value) is ≤4.8 mmol/L.
• The subject's eGFR (EPI) decrease from baseline (by local laboratory) is <30%. [b]
• There are no safety concerns as determined by the Investigator.

Abbreviations: eGFR (EPI)=estimated glomerular filtration rate calculated using Chronic Kidney Disease Epidemiology Collaboration formula; SBP=systolic blood pressure

[a] SBP calculated as the mean of the second and third consecutive readings of triplicated blood pressure readings collected at 2-minute intervals as described in Section 6.11.1.

[b] For safety management, baseline eGFR (EPI) is the last local eGFR (EPI) result prior to study drug administration at the Randomization Visit (Visit 3; Study Day 1).

3.1.2 Background Antihypertensive Medications

Throughout the study, study treatment will be administered concurrently with the subject's background antihypertensive medications. Subjects' background antihypertensive medications are to be stable (i.e., without any dose adjustments) from 4 weeks before the Screening Visit (Visit 1) to Week 12 (Visit 7).

Background antihypertensive medications may be changed as described in Table 1. Up-titration of study drug should be considered before changing background antihypertensive medication if the subject meets the Up-Titration Safety Criteria (Table 2). Changes to background antihypertensive medications (including adding, discontinuation, or dose adjustment of background antihypertensive medications) are summarized as follows:

- No changes to background antihypertensive medications are allowed during the first 12 weeks of double-blind treatment (i.e., from Visit 3 [Randomization] to Visit 7 [Week 12]) except for subject safety (e.g., hypertensive urgency).
- From Visit 7 (Week 12) to Visit 9 (Week 24, the end of the Double-blind Treatment Period), Investigators may change background antihypertensive medications according to SoC.
- No changes in background antihypertensive medications are allowed during the first 6 weeks of Open-Label Treatment Period (i.e., from Visit 9 [Week 24] to Visit 12 [Week 30]) except for subject safety.
- From Visit 12 (Week 30) to Week 44, Investigators may change background antihypertensive medications according to SoC.
- No changes to background antihypertensive medications are allowed from Week 44 through Visit 15 (Week 48) or during the Randomized Withdrawal Period (Visit 15 [Week 48] to Visit 16 [Week 52]) except for subject safety.

The guidance outlined in Table 1 should be followed; however, changes to background antihypertensive medications will ultimately be at the Investigator's discretion and will depend on the general clinical condition of the individual subject. Up-titration of study drug should be considered before changing background antihypertensive medication if the subject meets the up-titration criteria (Table 2).The dose and/or type of diuretic (e.g., change from thiazide to loop diuretic) may be adjusted based on developing or resolved edema, weight gain or loss, or pulmonary congestion. If changes to background medication are made for safety reasons, the subject should continue study drug unless the subject meets criterion for study drug discontinuation (Section 3.5.1) or study withdrawal (Section 3.5.2). The date and change to background antihypertensive medications will be recorded in the subject's source documentation and eCRF.

After any changes to background antihypertensive medications, the subject should return for a scheduled or unscheduled visit within 2 weeks (±3 days) of the change as indicated in the Schedule of Study Procedures (Table 10) to monitor blood pressure, potassium, and renal function. Additional safety visits can be scheduled for safety reasons.

On days when the subject is not scheduled for a study visit (i.e., non-visit days), the subject will take background antihypertensive medications as usual.

On days when the subject is scheduled for all study visits, (including unplanned visits 2 weeks [±3 days] after titration of study drug or a change to background antihypertensive medication), the subject should do the following:

- If the visit is in the morning, the subject is **not** to take morning doses of background antihypertensive medications until directed to take them during the visit by study personnel; afternoon doses of background antihypertensive medications may be taken as usual after the study visit.
- If the visit is in the afternoon, the subject is to take morning doses of background antihypertensive medications as usual but is **not** to take afternoon doses of background antihypertensive medications until directed to take them during the visit by study personnel.

The intent is to be consistent on timing of medications each visit after the Informed Consent Form (ICF) is signed, but the ultimate decision is at the Investigator's discretion if safety concern on timing of antihypertensive medications for subject.

Subjects will be asked at each visit to confirm if and when they last took their background medications. This information and the dosage, date, and time of dosing of background antihypertensive medications taken on the day of the visit will be recorded in the subject's source documentation and eCRF.

3.1.3 Study Plan with Forced-Titration

The study will have a pretreatment phase, consisting of a prescreening assessment, a Screening Period of up to 4 weeks (full 4 weeks not required if blood pressure, labs, and eligibility are met), and a 2-week Open-Label Placebo Run-In Period. Subjects will be

prescreened based on eGFR (EPI), serum potassium, and SBP (see Section 6.1). Only subjects with an eGFR (EPI) ≥15 to ≤44 mL/min/1.73 m^2 and serum potassium ≤4.8 mmol/L as confirmed by a local laboratory, and SBP ≥140 mm Hg within 3 months prior to Screening will be eligible to enter the Screening Period.

After the Screening Visit (Visit 1), eligible subjects will return to the site at the beginning of the Run-In Period (Visit 2). Subjects who continue to meet the study eligibility criteria at Visit 2 will start the Run-In Period and take placebo QD for 2 weeks. At the end of the Run-In Period, subjects will return to the site for the Randomization Visit (Visit 3) at which eligibility for randomization, including persistence of uncontrolled hypertension and compliance with open-label placebo and background antihypertensive medications during the Run-In Period, will be assessed. If a subject's compliance taking placebo and/or background antihypertensive medications during the Run-In Period is <80% or >120%, the subject will not be eligible for the study.

Subjects who are determined to be ineligible at the Screening Visit (Visit 1), the start of the Run-In Period (Visit 2), or the Randomization Visit (Visit 3) may be rescreened only 1 time if the Investigator believes that the subject's medical condition has changed, and the subject may now meet the eligibility criteria for the study. If a subject is rescreened, a new subject number will be assigned and all the procedures defined in the protocol for the Screening Visit (Visit 1), the Run-In Period (Visit 2), and the Randomization Visit (Visit 3) must be repeated. Subjects who are determined to be ineligible for the study prior to randomization will be considered screen failures.

Subjects who continue to meet the study eligibility criteria at the Randomization Visit (Visit 3) will be randomized in a 1:1 ratio to receive KBP-5074 0.25 mg or matching placebo QD. Randomization will be stratified to balance enrollment for the following baseline characteristics that may influence safety and/or efficacy evaluations: eGFR (EPI) (≥30 versus <30 mL/min/1.73 m^2), baseline SBP (≥160 versus <160 mm Hg), baseline UACR (<30 versus ≥30 mg/g), and geographic region (North America, Asia, and Europe/other). Approximately 30% of subjects enrolled in the study should have eGFR (EPI) ≥15 and <30 mL/min/1.73 m^2.

Subjects will receive their first dose of study drug on-site at the Randomization Visit (Visit 3; defined as Study Day 1) **after** all assessments (except collection of blood for PK analysis) are completed. During the Double-blind Treatment Period, visits for pre- and post-dose assessments, dosing, and study drug accounting and resupply will occur at Weeks 2, 4, 6, 12, 18, and 24 as indicated in the Schedule of Study Procedures (Table 10). At each visit up to Week 24 (Visit 9), vital signs and blood pressure assessment will be completed **before** the administration of study drug.

No changes to study drug are allowed from the first dose of study drug to Week 4 (Visit 5) except for subject safety, and no changes to background antihypertensive medications are allowed from the first dose of study drug to Week 12 (Visit 7) except for subject safety (e.g., hypertensive urgency) as determined by the Investigator.

At the Week 4 (Visit 5), study drug will be up-titrated to KBP-5074 0.5 mg or matching placebo QD provided that the subject meets the Up-Titration Safety Criteria (Table 2). For subjects who are not up-titrated at the Week 4 (Visit 5) because they do not meet the Up-Titration Safety Criteria, the Investigator should up-titrate the dose of study drug to KBP-5074 0.5 mg or matching placebo QD at the first opportunity when the subject does meet the Up-Titration Safety Criteria at any visit from Week 4 (Visit 5) to Week 24 (Visit 9) as indicated in Table 1. From Week 12 (Visit 7) to Week 24 (Visit 9), the Investigator may change background antihypertensive medications according to SoC as indicated in Table 1. Up-titration of study drug should be considered before changing background antihypertensive medications if the subject meets the Up-Titration Safety Criteria.

All subjects who have not discontinued treatment and meet the following Open-Label Treatment Safety Criteria at Week 24 (Visit 9) will continue into the Open-Label Treatment Period:

- SBP is >100 mm Hg (calculated as the mean of the second and third consecutive readings of triplicated blood pressure readings collected at 2-minute intervals as described in Section 6.11.1).
- Subject has >80% and <120% compliance with study drug and background antihypertensive medications between Week 18 (Visit 8) and Week 24 (Visit 9).
- Study drug is not being held for subject safety.
- There are no safety concerns as determined by the Investigator.

Subjects who do not meet the above Open-Label Treatment Safety Criteria at Week 24 (Visit 9) will be discontinued from treatment (Section 3.5.1).

Starting at Week 24 (Visit 9), eligible subjects will be reassigned to open-label KBP-5074 0.25 mg QD regardless of their final treatment regimen at the end of the Double-blind Treatment Period. Subjects will receive their first open-label dose of KBP-5074 0.25 mg on-site at Week 24 (Visit 9) **after** all assessments (except collection of blood for PK analysis) are completed. During the Open-Label Treatment Period, visits for -pre- and post-dose assessments, dosing, and study drug accounting and resupply will occur at Weeks 26, 28, 30, 36, 42, and 48 as indicated- in the Schedule of Study Procedures (Table 10). At each visit, vital signs and blood pressure assessment will be completed **before** the administration of study drug.

No changes to study drug are allowed from the first open-label dose of KBP-5074 0.25 mg QD to Week 28 (Visit- 11) except for subject safety. At Week 28, study drug will be up-titrated to KBP-5074 0.5 mg QD provided that the subject meets the Up-Titration Safety Criteria. For subjects who are not up-titrated at Week 28 because they do not meet the Up-Titration Safety Criteria, the Investigator should up-titrate the dose of study drug to KBP-5074 0.5 mg QD at the first opportunity when the subject does meet the Up-Titration Safety Criteria at any visit from Week 28 to Week 44 as indicated in Table 1. No changes in background antihypertensive medications are allowed from the first dose of open-label study drug at Week 24 (Visit 9) until Week 30 (Visit 12) except for subject safety

(e.g., hypertensive urgency) as determined by the Investigator. From Week 30 to Week 44, the Investigator may change background antihypertensive medications according to SoC as indicated in Table 1. Up-titration of study drug should be considered before changing background antihypertensive medications if the subject meets the Up-Titration Safety Criteria.

No changes to study drug or background antihypertensive medications are allowed from Week 44 to Week 48 (Visit 15) in preparation for the Randomized Withdrawal Period (Table 1).

All subjects who have not discontinued treatment and meet the following Randomized Withdrawal Criteria at Week 48 (Visit 15) will continue into the Randomized Double-Blind Withdrawal Period:

- Subject has >80% and <120% compliance with study drug and background antihypertensive medications between Week 42 (Visit 14) and Week 48 (Visit 15).
- Study drug is not being held for subject safety.
- There are no safety concerns as determined by the Investigator.

Subjects who do not meet the above Randomized Withdrawal Criteria at Week 48 will be discontinued from treatment (Section 3.5.1).

At Week 48, eligible subjects will enter the Randomized Double-Blind Withdrawal Period and be randomized in a 1:1 ratio to continue their current dose of KBP-5074 at the end of the Open-Label Treatment Period or receive matching placebo for 4 weeks. No changes to study drug or background antihypertensive medications are allowed during the Randomized Withdrawal Period except for safety (Table 1).

Subjects who complete the Randomized Double-Blind Withdrawal Period will return 4 weeks after Week 52 (Visit 16) for the Follow-Up EOS Visit (Visit 17) at Week 56.

3.1.4 Biomarker and Pharmacokinetic Sampling

Blood and urine samples for biomarkers will be collected from all subjects pre-dose at the visits indicated in the Schedule of Study Procedures (Table 10). Potential biomarkers may include, but are not limited to, the biomarkers listed in Table 13. See Section 6.13 for details. Biomarker samples collected in this study may be stored for up to 10 years after completion of the study (according to local regulations) for additional research. Samples may be used to understand the effect of KBP-5074 on CKD, cardiovascular disease, or to understand differential drug responders. The research may begin at any time during the study or the post-study storage period. Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers.

Blood samples for PK analyses will be collected from all subjects at the visits and times indicated in the Schedule of Study Procedures (Table 10) and Table 5. See Section 6.12 for details.

3.1.5 Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring will be performed in a subgroup of approximately 120 subjects (60 subjects/treatment group) at specified sites within 1 week before the Randomization Visit (Visit 3; Study Day 1) to collect baseline data and within 1 week before Week 12 (Visit 7). One week is allotted to allow for the collection of ABPM data to provide sufficient time for repeating ABPM if initial results do not meet predefined quality control criteria. See Section 6.11.3 for details.

3.1.6 Data Monitoring and Interim Analyses

An Independent Data Monitoring Committee (IDMC) not otherwise involved with study conduct will be established to monitor this study (see Section 9.8). The IDMC will independently review the safety data (see Section 8.10) and determine if it is safe to continue the study according to the protocol. A formal interim analysis to assess lack of efficacy may be conducted when all subjects complete Week 12.

Subjects, Investigators, and study sites will remain blinded to treatment assignments throughout the study until after database lock.

3.2 Rationale for Study Design

As discussed in the Section 1.1, Disease Background, there is a significant unmet medical need for additional means to control hypertension in patients with Stage 3b/4 CKD that provides a lower risk of hyperkalemia than is reported for available MRAs. The results from the Phase 2b study demonstrate that KBP-5074 was well tolerated and produced clinically meaningful and statistically significant reductions of SBP without excessive risk of hyperkalemia in subjects with uncontrolled hypertension who have Stage 3b/4 CKD. Therefore, a similar population has been selected for the pivotal Phase 3 study.

The Phase 3 study design is based on the Phase 2b study design (15) with input from key opinion leaders in hypertension and kidney disease and advice provided by the Food and Drug Administration (FDA). Rationales for key study design decisions are provided below:

- The primary endpoint for the Phase 3 pivotal study (change in seated trough cuff SBP from baseline to Week 12) was chosen because SBP is a standard endpoint used in studies of hypertension.
- Change in DBP from baseline was selected as a key secondary endpoint because of its importance in the management of patients with hypertension and CKD.
- Change in UACR from baseline was selected as a key secondary endpoint because it is a standard endpoint in studies of moderate to severe CKD studies. Early change in

albuminuria is considered a valid endpoint for kidney disease progression and 6 months is sufficient time to see a change from baseline (17).

- Placebo was chosen as the comparator because no single drug SoC therapy is available.
- The forced-titration scheme for study drug and plan for changes to background antihypertensive medications were chosen to balance the need for a consistent dose regimen for the evaluation of efficacy and safety with safety concerns related to potential changes in blood pressure, serum potassium, and renal function, but still allow evaluation of the primary endpoint and the optimization of background antihypertensive medication in combination with KBP-5074.
- A 12-week evaluation period was chosen for the primary endpoint because treatment with KBP-5074 0.25 and 0.5 mg QD for 12 weeks was sufficient to show reductions in SBP of -11.5 and -15.9 mm Hg, respectively, during the Phase 2b study. The 12-week timepoint was also chosen to provide sufficient time to evaluate an individual subject's response to study drug while minimizing the time during which background antihypertensive agents are not allowed to change except for safety reasons.
- The 12-week period during the Double-Blind Treatment Period when Investigators can change background antihypertension medications (as described in Section 3.1.2) according to SoC was chosen to allow evaluation of the response to KBP-5074 concurrent with SoC treatment and provide comparative safety data (KBP-5074 plus SoC versus SoC versus placebo).
- The study duration (6-month Double-Blind Treatment Period followed by 6-month Open-Label Treatment Period and 1-month Randomized Withdrawal Period) was chosen to minimize the time subjects are on placebo given the severity of disease (Stage 3b/4 CKD with uncontrolled hypertension) and to ensure collection of adequate exposure data to support initial regulatory submissions for KBP-5074.
- The additional 6-month Open-Label Treatment Period was chosen to allow collection of sufficient exposure data to evaluate safety and clinical outcomes in a high- risk population with unmet medical need.
- A Randomized Double-Blind Withdrawal design was chosen to demonstrate durability of the effect of KBP-5074 on SBP as recommended by the FDA. A 4-week Randomized Double-Blind Withdrawal Period will be sufficient to observe an increase in SBP after discontinuation of KBP-5074 treatment based on KBP-5074's 52- to 72-hour half-life and data from the Phase 2b study.

KBP believes that the prospectively defined primary and secondary endpoints proposed for the Phase 3 study are well-documented and appropriate to demonstrate a statistically and clinically meaningful effect of KBP-5074.

3.3 Study Duration

The duration of treatment for each subject will be 52 weeks. For subjects who complete the study, the total duration of participation (from the Screening Visit through the Follow-Up Visit) will be up to 62 weeks.

3.4 Risk Management

3.4.1 Monitoring and Management of Blood Pressure

Blood pressure will be closely monitored throughout this study. Blood pressure will be measured according to the American Heart Association (AHA) recommendations for accurate blood pressure measurement as described in Section 6.11.1.

In general, subjects should not change doses and/or types of the antihypertensive medications they are taking/prescribed except as directed by the Investigator.

The Investigator should not change background antihypertensive medications from the Screening Visit (Visit 1) through the first 12 weeks of treatment as described in Section 3.1.2 and Table 1 unless changes are needed to ensure subject safety. The dose of diuretic may be adjusted based on developing or resolved edema, weight gain or loss, or pulmonary congestion. Starting at Week 12 (Visit 7), background antihypertensive medications may be changed as indicated in Section 3.1.2 and Table 1 and as needed to ensure subject safety. If study drug is discontinued, background antihypertensive medications may be modified as necessary to maintain blood pressure control.

American Heart Association/American College of Cardiology definitions and treatment algorithms for hypertensive emergency and hypertensive urgency/marked elevations in blood pressure are provided in Appendix 2 (18).

If a subject has an event of hypertensive emergency, study drug should be immediately discontinued, and the hypertensive emergency treatment should begin immediately per local SoC guidelines. A documented hypertensive emergency will require discontinuation of study drug (Section 3.5.1).

Events of hypertensive urgency/marked elevations in blood pressure may or may not require discontinuation of study drug as determined by the Investigator but should be recorded as an AE and reviewed with the Sponsor's Medical Monitor. Events of hypertensive urgency/marked elevations in blood pressure may be treated by changes in background antihypertensive medications as determined by the Investigator.

Symptomatic hypotension or trough seated SBP <90 mm Hg (calculated as the mean of the second and third consecutive readings of triplicated blood pressure readings collected at 2-minute intervals as described in Section 6.11.1) should be reported as an AE. The Investigator should determine, correct, and document any potential reasons that may contribute to hypotension (e.g., dehydration, decreased blood volume, potential overdose of antihypertensive medication [including study drug]). If symptomatic hypotension or a confirmed seated trough cuff SBP <90 mm Hg occurs, Investigators should consider

down-titration of background antihypertensive medications (other than study drug) first. If the symptomatic hypotension or confirmed seated trough cuff SBP <90 mm Hg persists following down-titration of background antihypertensive medications and study drug, the study drug should be discontinued.

3.4.2 Monitoring and Management of Serum Potassium Levels

Hyperkalemia is a frequent event in subjects with severe CKD and one of the main risks identified from previous studies with MRAs. Serum potassium levels will be closely monitored throughout the study. In addition to the clinical laboratory evaluations scheduled in the Schedule of Study Procedures (Table 10), unscheduled assessments of serum potassium levels are recommended under certain situations that may affect a subject's serum electrolyte levels or fluid balance (e.g., vomiting and/or diarrhea for ≥1 day).

All assessments of potassium, including retests, will be performed at both local and central laboratories. Because of potential issues associated with sample preparation and transportation times, falsely elevated serum potassium values (pseudo-hyperkalemia secondary to hemolysis) have been observed in previous studies with KBP-5074. Since the serum potassium levels in locally analyzed samples are not as likely to be affected by hemolysis and results from the local laboratory are available earlier, local laboratory results will be the primary information used to monitor serum potassium levels, management of hyperkalemia, and for dose adjustments to ensure subject safety.

If central laboratory results for serum potassium differ from local laboratory results to such an extent that the Investigator is uncomfortable with the dose adjustment guidance shown in Table 3, assessment of serum potassium may be repeated at the Investigator's discretion at local and central laboratories.

In subjects with serum potassium above the normal laboratory reference range, the Investigator should reinforce dietary restriction for management of elevated potassium and consider local SoC.

Table 3 provides guidance for the laboratory testing, assessment, and management of serum potassium levels >5.0 mmol/L and guidelines for the management of study drug. If serum potassium level is ≤5.0 mmol/L, no action is indicated. If serum potassium level is >5.0 and <5.6 mmol/L, study drug should be continued at the current dose and dietary restriction for management of elevated potassium reinforced; retesting is not required. A serum potassium level ≥5.6 mmol/L requires a hold of study drug and appropriate retesting and intervention. If serum potassium level persists at ≥5.6 mmol/L, the Investigator should continue to hold study drug (as described in Table 3) and continue study visits and safety monitoring. If serum potassium is <5.3 mmol/L after a second or subsequent potassium retests, the Investigator may consider restarting study drug at the same or reduced dose (if titrated) based on the subject's clinical condition.

If serum potassium is >6.5 mmol/L, an ECG should be obtained, and the hyperkalemia and ECG findings (if any) managed per local SoC.

Table 3 Potassium Safety Monitoring and Management of Hyperkalemia

	Alert Local Laboratory Serum Potassium (K^+) Values		
	>5.0 to <5.6 mmol/L	**≥5.6 to <6.0 mmol/L**	**≥6.0 mmol/L**
Following notification of a serum K^+ alert value	Contact subject and reinforce low-K^+ diet.	Contact subject and schedule repeat serum K^+ as soon as possible but no longer than 72 hours after laboratory notification. [a]	Contact subject and schedule repeat serum K^+ as soon as possible but no longer than 72 hours after laboratory notification. [a]
Management [b]	Continue study drug at current dose.	Hold study drug pending retest results. [c]	Hold study drug pending retest results. [c]
Treatment [b]	Reinforce low-K^+ diet.	Reinforce low-K^+ diet; manage hyperkalemia per local SoC.	Reinforce low-K^+ diet; manage hyperkalemia per local SoC (may use K^+ binders).
Management following first serum K^+ retest [d]	Not applicable	If first serum K^+ retest is <5.3 mmol/L, resume study drug at current dose. If first serum K^+ retest is ≥5.3 to <6.0 mmol/L: 1. Continue to hold study drug, 2. Consider higher dose of diuretic, [e] 3. Schedule second serum K^+ retest within 1 week. If first serum K^+ retest is ≥6.0 mmol/L, follow management for ≥6.0 mmol/L. [e]	If first serum K^+ retest is <5.3 mmol/L, resume study drug at current dose. If first serum K^+ retest is ≥5.3 to <6.0 mmol/L: 1. Continue to hold study drug, 2. Consider higher dose of diuretic, [e] 3. Schedule second serum K^+ retest within 1 week. If first serum K^+ retest is ≥6.0 mmol/L, hold study drug [c] and manage hyperkalemia per SoC (e.g., additional binder).
Management following second serum K^+ retest [d]	Not applicable	If second serum K^+ retest is <5.3 mmol/L, resume study drug at current dose. If second serum K^+ retest is ≥5.3 mmol/L, hold study drug. [c]	If second serum K^+ retest is <5.3 mmol/L, resume study drug at current or reduced dose. If second serum K^+ retest is ≥5.3 mmol/L, hold study drug. [c]

Abbreviations: SoC=Standard of care

[a] Study sites should make repeated attempts to contact subjects with high K+ or hyperkalemia to ensure compliance with K+ safety monitoring and required retests.

[b] The Investigator should consider local guidelines and SoC for management of serum K+ levels above the normal laboratory reference range. In all instances, dietary restriction for management of elevated K+ should be reinforced.

[c] If study drug is held, the subject should continue study visits and safety monitoring after second retesting of potassium. More frequent local/central potassium monitoring is acceptable by the Investigator. If serum K+ is <5.3 mmol/L after a second or subsequent potassium retests, the Investigator may consider restarting study drug at the same or reduced dose (if titrated) based on the subject's clinical condition.

[d] 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 72 hours to confirm the value.

[e] Consider use of higher dose of loop, thiazide, or thiazide-like diuretics to manage hyperkalemia.

3.4.3 Safety Management of Renal Function

Estimated GFR (EPI) may decrease, at least temporarily, with the initiation, titration, or adjustments of MRA treatment (19), especially in subjects with more advanced CKD. The change in eGFR (EPI) most likely reflects transient changes in glomerular hemodynamics. Therefore, eGFR (EPI) will be closely monitored throughout the study.

All assessments of eGFR (EPI), including retests, will be performed at both local and central laboratories, and eGFR will be calculated using the CKD-EPI equation (16) by local and central laboratories. Local laboratory results should be used to manage eGFR (EPI) and subject renal safety. If the Investigator suspects a laboratory error, the Investigator may repeat the eGFR (EPI) assessment at the local and central laboratories.

Table 4 provides guidance for the laboratory testing, assessment, and guidelines for the management of study drug if a subject's eGFR (EPI) decreases from baseline. If a subject's eGFR (EPI) decrease from baseline is <30%, no retests are required, study drug can be continued, and titration of study drug to a higher dose is permitted. If a subject's eGFR (EPI) decrease from baseline is ≥30% and <40%, retesting is required within 1 week (±2 days) of notification, study drug can be continued with monitoring of eGFR (EPI) per Schedule of Study Procedures (Table 10), but titration of study drug to a higher dose is not permitted.

If a subject's eGFR (EPI) decrease from baseline is ≥40% and <50%, retesting is required within 1 week (±2 days) of notification; study drug can be continued with weekly monitoring for at least 4 weeks, but titration of study drug to a higher dose is not permitted. If continued testing indicates a sustained eGFR (EPI) decrease from baseline ≥40% for ≥4 weeks from the initial result, study drug should be held but the subject should continue with planned study visits to monitor eGFR (EPI) per Schedule of Study Procedures (Table 10). If a subject has study drug on hold because of a sustained eGFR (EPI) decrease from baseline ≥40% and the subject's eGFR (EPI) decrease from baseline improves to ≤30%, study drug may be restarted at the current or reduced dose (if titrated) at the Investigator's discretion. If study drug is not restarted the subject will be considered discontinued from study treatment (See Section 3.5.1).

If a subject's eGFR (EPI) decrease from baseline is ≥50%, hold study drug and retest within 1 week (±2 days) of notification followed by weekly monitoring for at least 4 weeks. If continued testing indicates a sustained eGFR (EPI) decrease from baseline ≥40% for ≥4 weeks from the initial result, continue to hold study drug. If study drug is held, the subject should continue with planned study visits to monitor eGFR (EPI) per Schedule of Study Procedures (Table 10). If a subject has study drug on hold because of a sustained eGFR (EPI) decrease from baseline ≥40% and the subject's eGFR (EPI) decrease from baseline improves to ≤15%, study drug may be restarted at the current or reduced dose (if titrated) at the Investigator's discretion. If study drug is not restarted the subject will be considered discontinued from study treatment (See Section 3.5.1).

The Investigator should evaluate and document any potential reasons, including pre-renal, post-renal, toxins, or other potential causes, that may contribute to the decrease in eGFR.

Additional visits for testing local and central eGFR may be performed at Investigator discretion.

Table 4 Estimated Glomerular Filtration Rate Safety Monitoring and Management

	Local Alert for eGFR (EPI) Decrease from Baseline [a]			
	<30%	**≥30% and <40%**	**≥40% and <50%**	**≥50% decrease**
Study Drug Management	Continue study drug; Titration to a higher dose permitted if indicated in Table 1	Continue study drug Titration to a higher dose not permitted	Continue study drug Titration to a higher dose not permitted	Hold study drug if eGFR (EPI) decrease from baseline is ≥50%
Retest [b]	Not required	Retest eGFR (EPI) within 1 week (±2 days) of receipt of results and evaluate any potential reasons for decrease in eGFR (EPI) [c]	Retest eGFR (EPI) within 1 week (±2 days) of receipt of results and evaluate any potential reasons for decrease in eGFR (EPI) [c]	Retest eGFR (EPI) within 1 week (±2 days) of receipt of results and evaluate any potential reasons for decrease in eGFR (EPI) [c]
After retesting	Not applicable	If retest eGFR (EPI) decrease from baseline is • <30% or ≥30% and <40%, continue study drug and monitor eGFR (EPI) as scheduled in the Schedule of Study Procedures (Table 10). • If eGFR (EPI) decrease is ≥40% follow guidance for ≥40% and <50% decrease or ≥50% decrease as appropriate. Monitor eGFR (EPI) more frequently if progressive decrease in eGFR (EPI) occurs on repeated testing per SoC.	If retest eGFR (EPI) decrease from baseline is • ≥40% and <50%, continue study drug and monitor eGFR (EPI) weekly for at least 4 weeks then as scheduled in the Schedule of Study Procedures (Table 10). • ≥50% follow guidance for ≥50% decrease. • <40% follow guidance for ≥30% and <40% decrease. Monitor eGFR (EPI) more frequently if progressive decrease in eGFR (EPI) occurs on repeated testing per SoC.	If retest eGFR (EPI) decrease from baseline is • >15%, continue to hold study drug and monitor eGFR (EPI) weekly for at least 4 weeks then as scheduled in the Schedule of Study Procedures (Table 10). • If ≤15% consider restarting study drug as indicated below. Monitor eGFR (EPI) more frequently if progressive decrease in eGFR (EPI) occurs on repeated testing per SoC.
Discontinuation of study drug	Not applicable	Not applicable	If continued testing indicates a sustained eGFR (EPI) decrease from baseline ≥40% for ≥4 weeks from the initial result, study drug should be held but the subject should continue with planned study visits to monitor eGFR (EPI).	If continued testing indicates a sustained eGFR (EPI) decrease from baseline ≥40% for ≥4 weeks from the initial result, continue to hold study drug but the subjects should continue with planned study visits to monitor eGFR (EPI).

Table 4 Estimated Glomerular Filtration Rate Safety Monitoring and Management

	Local Alert for eGFR (EPI) Decrease from Baseline [a]			
	<30%	**≥30% and <40%**	**≥40% and <50%**	**≥50% decrease**
Restart of study drug	Not applicable	Not applicable	If eGFR (EPI) improves and the eGFR (EPI) decrease from baseline is ≤30%, study drug may be restarted at the current or reduced dose (if titrated) at the Investigator's discretion. If study drug is not restarted the subject will be considered discontinued from study treatment.	If eGFR (EPI) improves and the eGFR (EPI) decrease from baseline is ≤15%, study drug may be restarted at the current or reduced dose (if titrated) at the Investigator's discretion. If study drug is not restarted the subject will be considered discontinued from study treatment

Abbreviations: eGFR (EPI)=estimated glomerular filtration rate per Chronic Kidney Disease Epidemiology Collaboration formula; SoC=standard of care

[a] For safety management, baseline eGFR (EPI) is the last local eGFR (EPI) result prior to study drug administration at the Randomization Visit (Visit 3; Study Day 1).

[b] All assessments of eGFR (EPI), including retests, will be performed at both local and central laboratories. Local laboratories should be used to manage eGFR (EPI) and subject renal safety.

[c] The Investigator should evaluate and document any potential reasons for the eGFR decrease, including pre-renal, post-renal, toxins, or other potential causes.

3.4.4 Risk Assessment for Coronavirus Disease Pandemic

There is currently an outbreak of respiratory disease (coronavirus disease 2019 [COVID-19]) caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This new virus has rapidly spread across the globe causing the World Health Organization (WHO) to declare a pandemic situation on March 11, 2020. The countermeasures initiated by national and local governments worldwide and the recommendations issued by the health authorities have impacted current and new clinical studies. As the threat of pandemic burden including new outbreaks, locally or globally, will impact the further conduct of clinical studies, appropriate risk assessments and mitigation measures will need to be taken into consideration in all clinical studies to protect subjects, site staff, and society as a whole.

Both the European Medicines Agency (EMA) (20) and FDA (21), as well as national health authorities in Europe, have issued new guidelines that aim to provide recommendations for the conduct of clinical studies during the COVID-19 pandemic. Because the pandemic situation is evolving, guidelines, recommendations, national laws, and local restrictions may change at a rapid pace. Given the circumstances of potentially relapsing pandemic or epidemic situation regarding the spread of COVID-19, special attention will be paid to protect subjects and study staff participating in the study against infection with SARS-CoV-2 as recommended by FDA, EMA, and WHO guidelines (22).

KBP-5074 is a non-steroidal MRA, and there is no evidence suggesting that KBP-5074 causes immune suppression. Therefore, risk of the subjects exposed to KBP-5074 will be similar to the general population if exposed to SARS-CoV-2 or suffering from COVID-19.

3.5 Discontinuation of Treatment and Discontinuation of Subjects from the Study

3.5.1 Discontinuation of Treatment

A subject must be permanently discontinued from study drug if any of the following occurs:

- Pregnancy
- Subject withdraws consent
- Subject requests discontinuation from the study for any reason
- Hypertensive Emergency (see Section 3.4.1)
- Requires hemodialysis or peritoneal dialysis
- Subject does not meet the Open-Label Treatment Safety Criteria (Section 3.1.3) at Week 24 (Visit 9)
- Subject does not meet the Randomized Withdrawal Criteria (Section 3.1.3) at Week 48 (Visit 15)

Study drug may be discontinued if any of the following occurs:

- Any AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued treatment with study drug is not in the best interest of the subject, including, but not limited to:
  - Persistent symptomatic hypotension or trough seated SBP <90 mm Hg following down-titration of background antihypertensive medications and study drug (see Section 3.4.1)
  - Persistent hyperkalemia (confirmed by a repeated test; see Section 3.4.2)
  - Sustained deterioration of eGFR (EPI) ≥50% from baseline (confirmed by a repeated test; see Section 3.4.3)

The date of and reason for the discontinuation from study drug will be documented in the subject's source documentation and eCRF.

Subjects who temporarily or permanently discontinue treatment should continue with scheduled study visits unless the subject also meets criteria for discontinuation from the study. The Sponsor's Medical Monitor should be notified whenever a subject is temporarily or permanently discontinued from treatment.

All subjects will be asked to continue study visits to the Week 56 EOS Visit (Visit 17) whether they remain on study drug. Subjects who prematurely discontinue study drug are to complete the EOT Visit within approximately 4 weeks of discontinuing treatment as defined in the Schedule of Study Procedures (Table 10). Subjects who prematurely discontinue study drug will continue in the study for all subsequent study visits until study completion and are to complete visit procedures (except for drug dispensing and accountability). In addition, blood and urine samples will be collected for PK analyses and Biomarkers analyses up until 8 weeks after discontinuation of study drug or until the next PK/Biomarker sample collection per study procedures after 8 weeks. For subjects who begin dialysis (which requires permanent discontinuation of study drug), study visits and procedures are to be continued; however, safety management of eGFR and/or potassium are at the discretion of Investigator or provider of dialysis and are not required to follow Table 3 and Table 4.

It is preferred that all visits are conducted in person for subjects who discontinue study drug but remain in study with follow-up visits. However, if the subject who discontinues study drug is unable to attend a visit in person, a telephone visit or other form of follow-up may be performed. The Investigator must document any change to the Schedule of Study Procedures and the level of follow-up that is agreed to by the subject (e.g., in person, by telephone/mail, indirect follow-up through family, friends, and/or healthcare providers, from review of the medical records).

3.5.2 Discontinuation of Subjects from the Study

A subject must be discontinued from the study if the subject withdraws consent or requests discontinuation from the study for any reason.

A subject may be discontinued from the study for any of the following reasons:

- Noncompliance with the protocol (e.g., taking prohibited medication) or inability to comply with protocol procedures
- Any AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by the Sponsor or regulatory authority
- Lost to follow-up

If a subject discontinues from the study early, study staff should make every effort to complete the ET assessments scheduled for the ET Visit in the Schedule of Study Procedures (Table 10) as early as feasible after discontinuation. The date of and reason for the subject's discontinuation from the study will be documented in the subject's source documentation and eCRF.

In the case of a subject who is potentially lost to follow-up, several attempts to contact the subject will be made by site staff and documented in the subject's medical records. The date that the subject is considered lost to follow-up and reason for the subject's subsequent discontinuation from the study (i.e., lost to follow-up) will be documented in the subject's source documentation and eCRF.

The Sponsor's Medical Monitor should be notified whenever a subject is lost to follow-up and/or discontinued from the study.

Subjects who discontinue the study will not be replaced.

4 STUDY POPULATION SELECTION

4.1 Study Population

Adult subjects age ≥18 years with uncontrolled hypertension and Stage 3b/4 CKD will be enrolled in this study. Subject will be prescreened as described in Section 6.1 and must meet all of the inclusion criteria in Section 4.2 and none of the exclusion criteria in Section 4.3 to enroll in the study.

4.2 Inclusion Criteria

Subjects must meet all the following inclusion criteria to be eligible for participation in the study:

1. Subject must provide signed written informed consent before any study-specific procedures are performed and agree to comply with protocol requirements.
2. Subject must be ≥18 years of age at the Screening Visit (Visit 1).
3. Body mass index (BMI) must be ≥19 to <45 kg/m^2 at the Screening Visit (Visit 1).
4. Subject must have uncontrolled hypertension defined as meeting both of the following criteria:
   a. The subject has a resting seated trough cuff SBP ≥140 mm Hg (calculated as the mean of the second and third consecutive readings of triplicated blood pressure readings collected at 2-minute intervals as described in Section 6.11.1) at the Screening Visit (Visit 1), and at the start (Visit 2) and end (Visit 3) of the Run-In Period.
   b. The subject is taking 2 or more antihypertensive medications that have been titrated upward as tolerated to hypertension target doses per local SoC and have been stable (i.e., without any dose adjustments) from 4 weeks before the Screening Visit (Visit 1) through the end of the Run-In Period (Visit 3).
      - The antihypertensive medications must include at least 1 loop, thiazide, or thiazide-like diuretic unless the subject has a documented intolerance to or contraindication for diuretic therapy.
      - A subject on 1 antihypertensive medication that has been titrated upward as tolerated to a hypertension target dose per local SoC and has been stable during the 4 weeks prior to the Screening Visit (Visit 1) may be enrolled in the study if the subject has a documented history of intolerance to multiple antihypertensive medications.
5. The subject must have Stage 3b (eGFR [EPI] ≥30 and ≤44 mL/min/1.73 m^2) or Stage 4 (eGFR [EPI] ≥15 and <30 mL/min/1.73 m^2) CKD according to central laboratory results based on the mean of eGFR (EPI) measured at the Screening Visit (Visit 1) and at the start of the Run-In Period (Visit 2). Estimated GFR will be calculated using the CKD-EPI equation (16). Estimated GFR (EPI) may be retested once at each visit if the Investigator determines the result is a laboratory error or an outlier that is not consistent with the subject's usual eGFR (EPI) range.

6. Female subjects who are women of childbearing potential (WOCBP) must agree to use 2 medically accepted, effective methods of birth control (defined as methods that result in a failure rate <1% per year when used consistently and correctly) during the study and for 90 days after the end of the study.

   Acceptable methods of birth control 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 device, diaphragm, condoms, or spermicides).

   - A WOCBP is defined as a woman who is not surgically or chemically sterilized (e.g., hysterectomy or bilateral oophorectomy; tubal ligation is not acceptable), and who is between menarche and at least 1 year postmenopausal.
   - Postmenopausal is defined as amenorrheic for at least 1 year, AND if aged <60 years, have a serum follicle-stimulating hormone level > 20 mIU/L. Women who are taking hormone replacement therapy do not have to have follicle-stimulating hormone assessments, but the amenorrhea (before starting hormone replacement therapy) must have been naturally (spontaneously) occurring and have been accompanied by an appropriate clinical profile (e.g., age appropriate with a history of vasomotor symptoms).
7. Male subjects with partners who are WOCBP must agree to use condoms plus spermicide and have their female partners use additional contraception (e.g., oral contraceptives or a hormonal or intrauterine device) from the first dose of study drug until at least 90 days after the last dose of study drug. Male subjects must also agree to refrain from donating sperm during the study and for 90 days after the last dose of study drug.

4.3 Exclusion Criteria

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

Blood Pressure

1. Subject has a resting seated trough cuff SBP ≥180 mm Hg (calculated as the mean of the second and third consecutive readings of triplicated blood pressure readings collected at 2-minute intervals as described in Section 6.11.1) at the Screening Visit (Visit 1) or at the start (Visit 2) or end (Visit 3) of the Run-In Period.

Potassium levels

2. Subject has a serum potassium level >4.8 mmol/L according to central laboratory results during the Screening or Run-In Periods. Serum potassium may be retested once at each visit if the Investigator determines the result is a laboratory error.
3. Subject has had a serum potassium level >5.6 mmol/L within 2 weeks before the Screening Visit (Visit 1).

4. Subject has been hospitalization for hyperkalemia within the 3 months before the Randomization Visit (Visit 3).

If central laboratory results for serum potassium differ from local laboratory results to such an extent that the Investigator is uncomfortable with advancing the subject, serum potassium may be retested once at local and central laboratories for each visit at the Investigator's discretion.

Clinical Laboratories

5. Subject has clinically significant abnormal liver function tests at the Screening Visit (Visit 1) or on any subsequent assessment prior to the Randomization Visit (Visit 3), defined as AST or ALT >3× the upper limit of normal (ULN) or total bilirubin >2×ULN. Subjects with a history of Gilbert's syndrome and total bilirubin >2×ULN may be included.
6. Subject has a positive blood screen for human immunodeficiency virus (HIV) at the Screening Visit (Visit 1).
7. Subject has a positive drug screen test (excluding positive results secondary to a prescribed medication from a physician) at the Screening Visit (Visit 1). Drug screen may be retested once before the start of the Run-In Period if the Investigator determines the results from the Screening Visit (Visit 1) were in error. Subjects testing positive for tetrahydrocannabinol (recreational or prescribed) are allowed to enroll in the study.

Medications and Drug-Drug Interactions

8. Subject was not compliant with taking placebo during the Run-in Period (defined as taking <80% or >120% of planned placebo doses) or the Investigator determines that the subject was not compliant with background antihypertensive medications during the Run-in Period as assessed at the Randomization Visit (Visit 3).
9. Subject has taken an MRA, a potassium sparing-diuretic, or chronic potassium supplements during the 4 weeks before the Screening Visit (Visit 1).
10. Subject has taken potassium binders for the treatment of hyperkalemia during the 3 months before the Screening Visit (Visit 1).
11. Subject has taken a strong CYP3A4 inducer or strong CYP3A4 inhibitor (including, but not limited to strong CYP3A4 inducers and inhibitors in Table 12) during the 7 days before the Randomization Visit (Visit 3).
12. Subject has taken a prohibited traditional Chinese medication during the 28 days prior to Screening Visit (Visit 1); see Section 5.6.2.
13. Subject was administered any other investigational product within 4 weeks or 5 half-lives (whichever is longer) prior to the Screening Visit (Visit 1).

Medical History

14. Subject has a history of known or suspected allergy or intolerance to other MRAs or related compounds.
15. Subject has a history of severe renal artery stenosis (>80% luminal narrowing), renovascular hypertension, renal transplant, or if a kidney transplant is anticipated in the next 13 months.
16. Subject had an episode of acute kidney injury or received hemodialysis or peritoneal dialysis within the 3 months before the Screening Visit (Visit 1).
17. Subject has 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 the Screening Visit (Visit 1), or presence of hemodynamically significant valve diseases and/or other hemodynamically significant obstructive lesions of left ventricular outflow tract.
18. Subject had a major cardiac or central nervous system event (including, but not limited to, acute coronary syndrome, myocardial infarction, clinically significant arrhythmia, stroke, and/or transient ischemic attack) within the 3 months before the Screening Visit (Visit 1); major cardiovascular or percutaneous procedures (including cardiac ablation, coronary revascularization, cardioversion, pacemaker and carotid angioplasty) within the 3 months before the Screening Visit (Visit 1); a cardiovascular condition likely to require surgical or percutaneous intervention within the 13 months after the Screening Visit (Visit 1); OR new onset of untreated atrial fibrillation (subjects with asymptomatic, rate-controlled atrial fibrillation on appropriate therapy [which may include anticoagulation] and stable for at least 3 months are permitted to enroll in the study).
19. Subject has a history of cardiac transplant, or is on a heart transplant list, or has a left ventricular assistance device.
20. Subject has a history of severe hepatic impairment (i.e., Class C hepatic impairment per Child-Pugh classification in Table 11).
21. Subject has a history of Addison's disease.
22. Subject has a history of gastrointestinal surgery that might affect absorption or oral bioavailability of KBP-5074 or oral antihypertensive medications.
23. Subject has a history of malignancy within the 2 years before the Screening Visit (Visit 1), 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 prior to the Screening Visit (Visit 1).
24. Subject has a history of prescription drug abuse, illicit drug use, or alcohol abuse according to documented medical history within the 6 months before Randomization (Visit 3).
25. Subject was previously randomized and administered KBP-5074 in a prior KBP-5074 study.

Other

26. Female subject who is known to be pregnant or breastfeeding.
27. Subject is an employee or family member of the Sponsor, Investigator, or study site personnel.
28. Subject is unlikely, in the opinion of the Investigator, to comply with the protocol requirements, instructions, and/or study-related restrictions.
29. Subject has a 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 subject inclusion in the study or a concomitant morbidity of such severity that, in the opinion of the Investigator, the subject is likely to die within 1 year from the Screening Visit (Visit 1).

5 STUDY TREATMENT(S)

5.1 Study Treatments Administered

Subjects will be administered KBP-5074 0.25 mg, KBP-5074 0.5 mg, or matching placebo orally QD during the study:

- During the Open-Label Placebo Run-In Period, all eligible subjects will take placebo orally QD for approximately 2 weeks.
- During the Double-Blind Treatment Period, eligible subjects will be administered KBP-5074 0.25 mg, KBP-5074 0.5 mg, or matching placebo orally QD for up to 24 weeks.
- During the Open-Label Treatment Period, eligible subjects will be administered KBP-5074 0.25 mg or KBP-5074 0.5 mg orally QD for up to 24 weeks.
- During the Randomized Double-Blind Withdrawal Period, eligible subjects will continue their current dose of KBP-5074 at the end of the Open-Label Treatment Period or receive matching placebo orally QD for 4 weeks.

A forced-titration strategy will be used to manage study drug in the Double-Blind and Open-Label Treatment Periods as described in Section 3.1.1.

5.2 Selection and Timing of Dose for Each Patient

At Study Day 1 (Visit 3), eligible subjects will be randomly assigned to KBP-5074 0.25 mg or matching placebo QD as described in Section 5.3. During the Double-Blind Treatment Period (from Study Day 1 [Visit 3] to Week 24 [Visit 9]), study drug will be titrated as described in Section 3.1.1.

At Week 24 (Visit 9), subjects who meet the Open-Label Treatment Safety Criteria will be re-assigned to open-label KBP-5074 0.25 mg QD regardless of their final treatment regimen at the end of the Double-Blind Treatment Period. During the Open-Label Treatment Period (from Week 24 [Visit 9] to Week 48 [Visit 15]), study drug will be titrated as described in Section 3.1.1.

At the beginning of the Randomized Double-Blind Withdrawal Period, subjects who meet the Randomized Withdrawal Criteria will be randomly assigned to continue their current KBP-5074 dose at the end of the Open-Label Treatment Period or receive matching placebo QD for 4 weeks as described in Section 5.3.

On days when the subject is not scheduled for a visit (i.e., non-visit days), subjects will self-administer 1 tablet of study drug each day with water at the same time of day (preferably in the morning). Study drug may be taken on an empty stomach or with food.

On days when the subject is scheduled for a visit (including unplanned visits 2 weeks [±3 days] after titration of study drug), subjects are not to take study drug until directed to take study drug by study personnel after pre-dose assessments have been completed. Subjects will self-administer 1 tablet of study drug at each visit with water under supervision of study personnel. Study drug may be taken on an empty stomach or with food. Subjects should be observed between the time after the first dose of study drug and PK sampling. The date and time of dosing of study drug at visits will be recorded in the subject's source documentation and eCRF.

If a subject misses a scheduled dose of study drug, the subject should be instructed to

- Take the scheduled dose of study drug as soon as possible if there are ≥8 hours before the next scheduled dose.
- Wait and take the next scheduled dose of study drug at the usual time if there are <8 hours before the next scheduled dose.

5.3 Method of Assigning Patients to Treatment Groups

Subject eligibility for randomization will be verified at the end of the Run-In Period (Visit 3; Section 6.5). Eligible subjects will be randomly assigned in a 1:1 ratio to KBP-5074 0.25 mg or matching placebo QD using Interactive Response Technology (IRT; Section 6.6) and a computer-generated randomization schedule. Randomization will be stratified to balance enrollment for the following baseline characteristics that may influence safety and/or efficacy evaluations:

- eGFR (EPI) (≥30 versus <30 mL/min/1.73 m^2) calculated as the mean of eGFR (EPI) at the Screening Visit (Visit 1) and at the start of the Run-In Period (Visit 2) as measured and calculated using the CKD-EPI equation (16) by the central laboratory; approximately 30% of subjects enrolled in the study should have a mean eGFR (EPI) ≥15 and <30 mL/min/1.73 m^2;

- Baseline SBP (≥160 versus <160 mm Hg) calculated as the mean of the second and third consecutive readings of triplicated blood pressure readings collected at 2-minute intervals (as described in Section 6.11.1) at the Randomization Visit (Visit 3);
- Baseline UACR (<30 versus ≥30 mg/g) at the start of the Run-In Period (Visit 2);
- Geographic region (North America, Asia, and Europe/other).

If needed to maintain balanced enrollment, enrollment may be capped for stratification factors as described in the Statistical Analysis Plan (SAP).

At the beginning of the Randomized Double-Blind Withdrawal Period, subjects who meet the Randomized Withdrawal Criteria will be randomly assigned in a 1:1 ratio to continue their current KBP-5074 dose at the end of the Open-Label- Treatment Period or matching placebo QD using IRT (Section 6.6) and a computer-generated randomization schedule.

Computer-generated randomization schedules will be programmed by a qualified statistician or designee (i.e., the randomization statistician) not otherwise involved in the study and provided to the IRT vendor for programming of the IRT system. This study will be double-blinded. To minimize bias and ensure that the study remains blinded, the randomization statistician or IRT vendor will not release the randomization schedule to any personnel directly involved in the conduct of the study until after database lock at the end of the study as outlined in the Study Blinding Plan.

5.4 Blinding

This study will be a double-blinded study. All individuals directly involved in the conduct of the study, including subjects, Investigators, site staff, clinical research organization (CRO) personnel, and Sponsor study personnel, will remain blinded to treatment assignments until all subjects have completed the Week 56 EOS Visit (Visit 17) and the database locked in preparation as described in the Study Blinding Plan. Unblinded individuals such as the randomization statistician, IDMC statistician or statistical programmer, IRT vendor, and packaging and labeling vendor, who will not be otherwise involved in the study, will be identified in the Study Blinding Plan.

Specific measures to ensure blinding include:

- Matching placebo tablets will be identical in appearance to KBP-5074 tablets.
- Packaging and labeling will be designed to maintain the blinding.
- Central randomization using an IRT system will be implemented to maintain the blind when randomizing subjects and dispensing study drug. If there is a medical emergency that requires knowing the treatment status of a subject to determine specific emergency treatment/course of action, the IRT system allows the Investigator, or other responsible person, to identify the subject's treatment assignment in an emergency, without jeopardizing the double-blind integrity of the remainder of the study.

- To minimize bias and ensure that the study remains blinded, the randomization statistician and IRT vendor will not release the randomization schedules to any personnel directly involved in the conduct of the study until authorized to release the randomization scheduled as described in the Study Blinding Plan.

At all times, study personnel will attempt to safeguard the integrity of the blinding to minimize bias in the conduct of the study. If the Investigator, site study staff, or site Investigational Pharmacist becomes aware of a subject's study treatment assignment, efforts should be made to not disclose assignments to other study staff, subjects, or their caregivers.

5.4.1 Breaking of the Blind

Breaking of the blind should not occur except in the case of a medical emergency if specific emergency treatment/course of action would be determined by knowing the treatment assignment of the subject. If possible, the Investigator should discuss the situation with the Sponsor's Medical Monitor before breaking the blind.

If an Investigator needs to know a subject's treatment assignment for a medical emergency, the Investigator may access this information via the IRT system according to the unblinding procedure described in the IRT manual. The Investigator is advised not to reveal the study treatment assignment to site or Sponsor personnel, the subject, or his/her caregivers unless the information is needed to respond to the medical emergency. Study personnel who are aware of a subject's treatment assignment should not disclose the assignment to other study personnel, the subject, or his/her caregivers unless required to respond to the medical emergency.

If the blind is broken for an individual subject, the Sponsor should be informed as soon as possible. The date and reason for the unblinding must be documented in the subject's source documentation and eCRF. Any documentation indicating the subject's treatment assignment must be retained with the subject's source documents in a secure manner (e.g., in a sealed envelope) so as not to unblind the treatment assignment to other site or Sponsor personnel.

If the blind is broken for a subject, the decisions to continue or discontinue study drug and whether the subject is asked to continue or discontinue the study will be based on the nature of the medical emergency by the Investigator in consultation with the Sponsor's Medical Monitor (if possible), and not necessarily because the study blind was broken (although this may be a factor in the decisions).

5.5 Description of Treatment(s)

Subjects will take 1 tablet of either KBP-5074 0.25 mg, KBP-5074 0.5 mg, or matching placebo orally QD. Study drug will be supplied by the Sponsor as KBP-5074 0.25-mg and 0.5-mg strength tablets and matching placebo tablets. The composition of the KBP-5074 and placebo tablets is provided in the IB.

5.5.1 Packaging and Labeling

Study drug tablets will be packaged in high-density polypropylene bottles with polypropylene child-resistant closures and desiccant (drying agent). Each polypropylene bottle will contain 35 tablets of study drug.

The study supplies will be packaged and labeled using the randomization code. Each bottle of study drug will be labeled in English and the language appropriate to the investigational site. Bottle labels will not contain any information that could result in unblinding of subjects, Investigators, or site staff. Label text will be approved according to the Sponsor's agreed procedures.

Each bottle of study drug will be packaged and labeled according to Good Manufacturing Practice (GMP), GCP, and applicable country-specific, local, and regulatory requirements.

For all study drugs, a system of numbering in accordance with GMP requirements 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 Storage and Accountability

Study drug will be shipped to the investigational site. The responsible trained site personnel will verify and confirm receipt of study drug via the IRT system. Upon receipt, study drug will be stored in accordance with GCP and GMP requirements and the instructions provided in the Study Pharmacy Manual. Study drug will be stored in a secure area according to local regulations so that only the Investigator and designated site personnel have access to the study drug. Study drug provided for this study may not be utilized for any other purpose.

All study drug dispensed to subjects must be accurately recorded in the Investigational Product Accountability Log maintained at the study site by the Investigator or trained qualified designee. Subjects will be instructed to return all unused study drug dispensed to them (including empty containers) at each study visit. All investigational product and empty containers will be retained at the site for the site study monitor's verification.

Investigational product accountability and compliance for all investigational products will be performed by the site study monitor at each scheduled study visit starting at the beginning of the Run-In period (Visit 2) through Week 52 (Visit 16) or the EOT or ET Visits. Final reconciliation will be done at the Close-Out Visit.

All unused and/or partially used study drug must be returned, if not authorized by the Sponsor to be destroyed at the site, prior to or upon completion or termination of the study. All study drug returned must be accompanied by the appropriate documentation and be clearly identified. Returned supplies should be in their original containers. Empty bottles may be returned; however, it is the Investigator's responsibility to arrange disposal of all empty containers.

5.6 Concomitant Therapy

A prior therapy is defined as any therapy the subject received with a start date and time prior to the first dose of study drug at the Randomization Visit (Visit 3). Data on prior therapies will be collected as described in Section 6.4.

A concomitant therapy is defined as any therapy the subject receives with a start date and time that is the same as or after the first dose of study drug at the Randomization Visit (Visit 3). Data on concomitant therapies will be collected as described in Section 6.18.

Prior therapies that a subject continues to take after the first dose of study drug (e.g., background antihypertensive medications) may also be concomitant therapies but should be indicated as a prior therapy and a concomitant therapy in the study database.

5.6.1 Permitted Therapies and Management of Comorbidities

Background antihypertensive medications are permitted during the study as described in Section 3.1.2.

Patients who have comorbidities (e.g., diabetes, hyperlipidemia, and cardiovascular disease), should be managed and treated with appropriate therapies as recommended by local SoC and clinical practice guidelines. Medical management and treatment for comorbidities should remain stable from the Screening Visit (Visit 1) to Week 12 (Visit 7). Any additions or adjustments to concomitant medications for the treatment of comorbidities will be recorded in the subject's source documentation and eCRF.

No potassium supplements are permitted, unless clinically indicated to treat hypokalemia on an emergent basis until serum potassium values are within the normal range. If a subject needs a potassium supplement for the treatment of hypokalemia, study drug should be continued, and the potassium supplement discontinued as soon as possible. Subjects should not be maintained on chronic potassium supplements.

Potassium binding-drugs (including, but not limited to, calcium polystyrene sulfonates [e.g., Sorbisterit®, Calcium Resonium®], sodium polystyrene sulfonates [e.g., Kayexalate®, anti-kalium sodium], patiromer [Veltassa®], and sodium zirconium cyclosilicate [Lokelma®]) are permitted as clinically indicated to treat hyperkalemia per local SoC on an emergent basis until serum potassium values are within the normal range. See Section 3.4.2 and Table 3 for guidance on the management of serum potassium levels and hyperkalemia.

5.6.2 Prohibited Therapies

Subjects requiring hemodialysis or peritoneal dialysis during the study will be discontinued from study drug and will be encouraged to continue study visits and procedures for safety as outlined in Section 3.5.2.

The use of MRAs (e.g., eplerenone, spironolactone), renin inhibitor, and potassium sparing-diuretics (e.g., amiloride, triamterene) are not permitted from within 4 weeks before the Screening Visit (Visit 1) through the end of study participation.

The use of strong CYP3A4 inducers and strong CYP3A4 inhibitors (including, but not limited to, the strong CYP3A4 inducers and inhibitors listed in Table 12) are not permitted from 7 days before the Randomization Visit (Visit 3) through the end of study participation. If a subject needs to take CYP3A4 inducers or strong CYP3A4 inhibitors for treatment of an AE, the Investigator should hold study drug during use of CYP3A4 inducers or strong CYP3A4 inhibitors and may restart study drug at least 7 days after completing use of all CYP3A4 inducers or strong CYP3A4 inhibitors.

The use of traditional Chinese medications that potentially increase serum potassium levels and/or cause toxicity to the kidney are not permitted 28 days prior to Screening (Visit 1) and through the end of study participation. The following products are permitted:

Product Name
Corbrin Capsule
Jin Shui Bao Capsule
Niao Du Qing Granules
Shen Shuai Ning Capsule
Shen Shuai Ning Tablet
Shen Shuai Ning Granules
Rhubarb Sodium Bicarbonate Tablet
Hai Kun Shen Xi Capsule

Note: Medical Monitors must review other traditional Chinese medications not listed if Investigator deems necessary.

Injectables can only be used if medically necessary to treat AEs.

All traditional Chinese medications must be listed as a concomitant medication.

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 non-steroidal anti-inflammatory drugs. These medications should be taken only if the Investigator considers these medically necessary. If a subject needs any of these medications, study drug should be continued and serum potassium levels and eGFR (EPI) values monitored closely monitored while the subject is taking these medications.

5.7 Restrictions

5.7.1 Fluid and Food Intake

Hypertension in subjects with CKD is often accompanied by a decrease in the kidney's ability to excrete salt. Addressing this salt sensitivity is critical for the management of hypertension in CKD. Dietary counseling will be conducted at each visit in accordance with the standard practices of the Investigator and should address all the dietary requirements of the subject as appropriate.

Patients will be advised to maintain their normal diet and avoid unhealthy levels of alcohol use and sodium- or potassium-rich foods/drinks during the study period. If a subject experiences elevated serum potassium levels, the Investigator should consider local SoC guideline recommendations for management of serum potassium levels above the normal laboratory reference range and reinforce dietary restriction for management of elevated potassium. See Section 3.4.2 for more details on monitoring and management of elevated serum potassium.

Food and fluid consumption does not impact the absorption or metabolism of KBP-5074. However, grapefruit and grapefruit juice are CYP3A4 inhibitors and prohibited during trial (Table 12).

5.7.2 Patient Activity Restrictions

Strenuous exercise may affect safety laboratory results; for this reason, unusually strenuous exercise (i.e., not part of a subject's regular exercise routine) should be avoided within 72 hours before planned study visits.

5.8 Treatment Compliance

Treatment compliance will be assessed at each study visit indicated in the Schedule of Study Procedures (Table 10). Subjects will be instructed to bring all unused study drug and all empty bottles of study drug and all background antihypertensive medications to each study visit. To assess a subject's compliance with study drug, pill counts of study drug will be performed and trained site personnel will review study drug and background antihypertensive medications with the subject (see Section 6.15). At each visit, study staff will reinforce the importance of compliance with both study drug and background antihypertensive medications during the study.

6 STUDY PROCEDURES

The specific timing of study assessments is provided in Table 10, Schedule of Study Procedures, for KBP5074-3-001 in Appendix 1. Details of study assessments are provided in this section.

6.1 Recruitment and Prescreening

Subjects will be recruited by qualified and trained site personnel according to the Study Recruitment Plan.

Subjects will be prescreened based on eGFR (EPI), serum potassium, and SBP. Only subjects with an eGFR (EPI) ≥15 to ≤44 mL/min/1.73 m^2 (local laboratory), serum potassium ≤4.8 mmol/L (local laboratory), and SBP ≥140 mm Hg within 3 months prior to Screening will be eligible to enter the Screening Period.

If assessments are needed solely for the purpose of prescreening, the Investigator or trained designee must obtain the subject's written informed consent using either the optional prescreening-specific ICF or study's full ICF (see Section 9.4).

If eligibility requirements need to be verified, the Investigator may perform a prescreening visit at any time prior to the Screening Visit (Visit 1) using the provided automated office blood pressure (AOBP) device for triplicate blood pressure testing (see details in the AOBP Site Manual) and local laboratories. It is highly recommended that the prescreening visit incorporates triplicate BP testing using the AOBP device provided, serum potassium, and eGFR (EPI). The Investigator may decide to prescreen for SBP alone if recent serum potassium and eGFR (EPI) results available from the past 3 months are considered stable and acceptable by the Investigator. If the prescreening visit AOBP triplicate result (calculated as the mean of the second and third consecutive readings of triplicated blood pressure readings collected at 2-minute intervals as described in Section 6.11.1) is not in the range for the study, it is not necessary to draw local labs on prescreening visit.

6.2 Informed Consent

Written informed consent for participation in the study will be obtained from all patients before any protocol-specific procedures are performed as described in Section 9.4. The date and time informed consent recorded in the subject's source documentation and eCRF.

If the optional prescreening-specific informed consent was obtained, and the subject is eligible to enter the Screening Period, a full informed consent must be obtained before any further protocol-specific procedures are performed.

6.3 Demographics

Demographic data will be collected at the Screening Visit (Visit 1). Trained site staff will collect and record each subject's demographic data (year of birth, age at time of the Screening Visit, sex, childbearing potential, ethnicity, race, region, smoking habits, and alcohol consumption) in the subject's source documentation and eCRF.

6.4 Medical History and Review of Prior Medications

Each subject's medical history and prior medication data will be collected at the Screening Visit (Visit 1). Trained site staff will record each subject's medical history (i.e., previous conditions, diagnoses, disease, or surgeries) pertaining to kidney disease, hypertension, cardiovascular disease, diabetes, hepatic disease, and conditions otherwise relevant to the study of hypertension and CKD as available to the Investigator in the subject's source documentation and eCRF. The following information will be collected: description of the condition/diagnosis, year (and date if available) of onset, year (and date if available) of resolution, and if the condition is ongoing at the time of the Screening Visit (Visit 1).

In addition, trained site staff will record each subject's prior and ongoing medications (including COVID-19 vaccine, vitamin preparations, and herbal or health supplements) as available to the Investigator in the subject's source documentation and eCRF. The following information will be collected: name or description of the medication, start date, end date or if the medication is ongoing, dosage, frequency, route of administration, the reason/indication that the subject is taking the medication, and if an ongoing medication is considered a background antihypertensive medication. Each medication taken for a previous condition,

diagnosis, disease, or surgery, should have a corresponding entry in the subject's medical history.

To be eligible for enrollment in the study, each subject must be on 2 or more antihypertensive medications that have been titrated upward as tolerated to target doses per local SoC. One of the antihypertensive medications must be a loop, thiazide, or thiazide-like diuretic (except potassium-sparing diuretics) unless the subject has a documented intolerance or contraindication to diuretic therapy. The doses of the antihypertensive medications should be stable (i.e., without dose adjustment) during the 4 weeks prior to the Screening Visit (Visit 1; see Section 4.2, Inclusion Criteria).

6.5 Verification of Study Eligibility

Verification of study eligibility will be performed at the Screening Visit (Visit 1), at the start of the Run-In Period (Visit 2), and prior to Randomization at Visit 3. Subjects must meet all of the inclusion criteria and none of the exclusion criteria at the visits specified in Section 4.2 and Section 4.3, respectively, to enroll in the study.

Subjects who signed the ICF but who do not meet the eligibility requirements for the study will be considered screen failures. Subject eligibility data, including specific reasons for screen failures, will be recorded in the subject's source documentation and eCRF.

6.6 Randomization

Study randomization will occur at the Randomization Visit (Visit 3). After verification of eligibility (Section 6.5), eligible subjects will be randomly assigned in a 1:1 ratio to KBP-5074 0.25 mg QD with optional titration to KBP-5047 0.5 mg QD or matching placebo QD using the IRT system as described in the IRT manual. Individual treatment assignments will be blinded to all individuals directly involved in the conduct of the study including the Sponsor, Investigator, site staff, subjects, and other study personnel directly involved in the study (e.g., CRO, data management) throughout the course of the study.

At Week 48 (Visit 15), subjects who meet all the Randomized Withdrawal Criteria will be randomly assigned in a 1:1 ratio to continue their current KBP-5074 dose at the end of the Open-Label Treatment Period or receive matching placebo using the IRT system as described in the IRT manual. Individual treatment assignments will be blinded to all individuals directly involved in the conduct of the study including the Sponsor, Investigator, site staff, subjects, and other study personnel directly involved in the study (e.g., CRO, data management) throughout the course of the study.

6.7 Physical Examination

The Investigator or a licensed study team member, per local regulations, will perform physical examinations according to the Schedule of Study Procedures (Table 10).

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 subject's source documents. Baseline physical exam findings should be recorded in the subject's source documentation. If a new clinically significant abnormality or clinically significant worsening from baseline of a previous finding is detected after randomization, the finding should be recorded in the subject's source documentation and reported as an AE (if appropriate as determined by the Investigator), and the subject should be considered for further clinical investigations and/or specialist consultation as per the Investigator's medical judgment.

6.8 Height, Weight, Body Mass Index, and Waist Circumference

Height, body weight, BMI, and waist circumference will be measured at the visits indicated in the Schedule of Study Procedures (Table 10) and recorded in the subject's source documentation and eCRF.

Body Mass Index should be calculated as follows:

$$\text{BMI} = \frac{\text{Subject's weight in kg}}{(\text{Subject's height in cm})^2} \times \frac{(10000\ \text{cm}^2)}{\text{m}^2}$$

To measure waist circumference, the subject should be standing, and the tape measure placed around the subject just above the hip bones. The tape measure should be horizontal and snug, but not compressing the skin. Waist circumference should be measured just after the subject breathes out.

6.9 Vital Signs

Vital signs (pulse rate, respiratory rate, and temperature) will be assessed by the Investigator or trained designee prior to study drug administration at the visits indicated in the Schedule of Study Procedures (Table 10) and recorded in the subject's source documentation and eCRF. Heart rate will be measured and recorded with blood pressure as described in Section 6.11.1.

6.10 Electrocardiography

A standard 12-lead ECG will be performed at the visits indicated on the Schedule of Study Procedures (Table 10). In addition, ECG should be obtained if serum potassium >6.5 mmol/L or as indicated for SoC. Patients should be resting in the supine position for at least 10 minutes prior to the assessment. Each ECG tracing should be labeled with the study number, subject number, and date and kept in the source documents at the study site.

ECGs will be interpreted locally by a qualified physician and assessed as normal, abnormal not clinically significant, or abnormal clinically significant and record the data in the subject's source documentation and eCRF. Any clinically significant abnormalities should be documented as an AE/SAE as applicable. Clinically significant abnormalities should be reported as AEs or outcome event as appropriate (e.g., new onset atrial fibrillation) when not

already reported in the medical history or in one of the previous recordings and in case of worsening of previous findings.

6.11 Efficacy Assessments

6.11.1 Blood pressure

Blood pressure and heart rate will be measured in triplicate **prior to the administration of study drug** at the visits indicated on the Schedule of Study Procedures (Table 10) and recorded in the subject's source documentation and eCRF.

Blood pressures will be measured according to the AHA recommendations for accurate blood pressure measurement and should be measured using the same arm throughout the study. Blood pressure measurements will be taken with a validated, digital oscillometric upper-arm blood pressure monitor by the Investigator or trained designee.

At each visit, triplicate blood pressure and heart rate measurements should be taken approximately 2 minutes apart with the subject in the seated position and having rested quietly for at least 5 minutes prior to the blood pressure measurements. No other procedures should be performed during the 5-minute resting period. Subjects should avoid smoking, caffeine, or exercise within 30 minutes before blood pressure measurements. Prior to the blood pressure measurement, subjects should empty his or her bladder.

The blood pressure monitor should be attached to the subject using the correct cuff size with the cuff placed directly on the subject's arm (i.e., not over clothes) at heart level. Blood pressure measurements should be performed on the same arm throughout the study. Once the blood pressure monitor is attached, the subject should sit quietly in a comfortable chair with back and limbs supported for at least 5 minutes before starting blood pressure measurements and remain still during blood pressure measurements. Blood pressures and pulse rates will be measured at the same time.

Blood pressure variability is expected in CKD patients with hypertension. If an outlier greater than 30 mm Hg occurs in triplicate SBP between first-to-second or second-to-third, an additional triplicate reading is required at least 10 minutes after the reading. The second triplicate reading with mean of second and third SBP must be used for management of the subject (i.e., determining eligibility, titration of investigational product (IP) or background medications, withdrawing or discontinuing the subject). No more than two triplicate readings should be performed at a single visit.

6.11.2 Urinary Albumin: Creatinine Ratio

Urine samples for determination of UACR will be collected at the visits indicated in the Schedule of Study Procedures (Table 10). Detailed procedures for collection, preparation, storage, and shipment of urine samples for determination of UACR will be described in the Study Laboratory Manual. The dates and times of urine sample collection will be recorded in the subject's source documentation and eCRF.

For determination of UACR, subjects will be instructed to collect first morning void urine samples as described in the Study Laboratory Manual prior to taking study drug at home on 3 consecutive mornings within 5 days prior to the scheduled visits indicated above and bring the samples to the scheduled visit.

6.11.3 Ambulatory Blood Pressure Monitoring

ABPM will be performed in a subgroup of up to 120 subjects (60 subjects/treatment group) at specified sites within 1 week before the Randomization Visit (Visit 3; Study Day 1) to collect baseline data and within 1 week before Week 12 (Visit 7) as indicated in the Schedule of Study Procedures (Table 10). Sites will have up to 1 week to successfully complete collection of 24 continuous hours of ABPM data. If the APBM data are inadequate, ABPM may be repeated up to 1 time if there is adequate time prior to the scheduled visit. Specific ABPM device specifications and procedures, including downloading the data and determining the adequacy of the data and repeating ABPM, will be specified in the study ABPM manual.

During the 24-hour period, blood pressure and heart rate will be measured every 20 minutes for 16 hours corresponding to awake daytime hours and every 30 minutes for 8 hours corresponding to sleeping nighttime hours.

6.11.4 EuroQol Group 5-Dimension 5-Level Quality-of-Life Instrument

The EQ-5D-5L is a validated patient-reported outcome (PRO) instrument comprised of 5 questions each with 5 levels (e.g., no problems, slight problems, moderate problems, severe problems, and extreme problems) representing five health domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L also includes a visual analog scale (VAS) that records the subject's self-rated health status on a graduated scale that ranges from 0 to 100, with higher scores indicating higher health-related quality-of-life (20-25).

Subjects will complete the EQ-5D-5L before any other procedures are performed at the visits indicated in the Schedule of Study Procedures (Table 10). Trained site staff will review the subject's responses to the EQ-5D-5L immediately after completion by the subject to ensure that all questions, including the VAS, are answered with a single response. Every effort will be made to always use the electronic PRO (ePRO) version on the electronic device provided and for the subject to respond directly on the electronic device. If there is an issue with the electronic device, the approved physical PRO questionnaire form may be used, and this form will be considered as the source document under this circumstance. A subject's written responses recorded at the visit due to issues with electronic system (or other reason) must be transferred by the subject to ePRO once the electronic device is available for use. The subject's written responses should not be transferred on the same visit as a future ePRO procedure is scheduled.

6.11.5 36-item Kidney Disease Quality of Life Survey

The KDQOL-36 is a validated PRO instrument that measures health-related quality-of-life specific for the effects and burden of kidney disease as well as physical and mental health

scores based on the 12-item Short Form Health Survey (SF-12). It is comprised of 5 domains: Physical Component Summary, Mental Component Summary, Burden of Kidney Disease, Symptoms/Problems, and Effects of Kidney Disease (26).

Subjects will complete the KDQOL-36 before any other procedures are performed at the visits indicated in the Schedule of Study Procedures (Table 10). Trained site staff will review the subject's responses to the KDQOL-36 immediately after completion by the subject to ensure that all questions are answered with a single response. Every effort will be made to always use the ePRO version on the electronic device provided and for the subject to respond directly on the electronic device. If there is an issue with the electronic device, the approved physical PRO questionnaire form may be used, and this form will be considered as the source document under this circumstance. A subject's written responses recorded at the visit due to issues with electronic system (or other reason) must be transferred by the subject to ePRO once the electronic device is available for use. The subject's written responses should not be transferred on the same visit as a future ePRO procedure is scheduled.

6.12 Pharmacokinetic Assessments

Blood samples for PK analyses will be collected from all subjects at the visits and times indicated in the Schedule of Study Procedures (Table 10) and Table 5. In addition, blood samples for PK analysis will be collected at any visit at which study drug is up or down-titrated and at unscheduled visits after up or down-titration of study drug. Detailed procedures for the collection, preparation, storage, and shipment of PK blood samples will be described in the Study Laboratory Manual. Subjects who permanently discontinue study drug but continue with study visits should continue to have PK samples obtained for at least 8 weeks or until the next PK sample collection per study procedures after 8 weeks. After that time, PK samples can be removed from study procedures.

The date and time of the last dose of study drug prior to the PK blood sample and the date and time of the PK blood sample will be recorded in the subject's source documentation and eCRF.

Table 5 Collection of Blood Samples for Pharmacokinetic Analyses

Visit	Week	Study Day	Details[a]
3	NA	1	Collect PK sample at least 2 hours following study drug administration as the final assessment of the study visit.
5	4	28	Collect PK sample any time during the study visit (pre- or post-dose).
6	6	42	Collect PK sample any time during the study visit (pre- or post-dose).
7	12	84	Collect PK sample any time during the study visit (pre- or post-dose).
9	24	168	Collect PK sample at least 2 hours following study drug administration as the final assessment of the study visit.
11	28	196	Collect PK sample any time during the study visit (pre- or post-dose).
12	30	210	Collect PK sample any time during the study visit (pre- or post-dose).
15	48	336	Collect PK sample any time during the study visit (pre- or post-dose).
16	52	364	Collect PK sample any time during the study visit (pre- or post-dose).
17 (EOS)	56	392	Collect PK sample any time during the study visit.
Unsch			Collect PK sample any time during the study visit (pre- or post-dose).
EOT			Collect PK sample any time during the study visit.
ET			If the unscheduled visit is following study drug titration, collect PK sample any time during the study visit.

Abbreviations: EOS=end of study; EOT=end of treatment; ET=early termination; NA=not applicable; PK=pharmacokinetics; Unsch=unscheduled

[a] Record the date and time of the most recent dose of study medication prior to collecting the PK sample.

6.13 Pharmacodynamic and Biomarker Assessments

Blood and urine samples for biomarkers will be collected **prior to the administration of study drug** at the visits indicated in the Schedule of Study Procedures (Table 10). Potential biomarkers may include, but are not limited to, the biomarkers listed in Table 13. If subject permanently discontinue study drug but continue with study visits, they should continue to have urine and blood biomarker samples obtained for at least 8 weeks or until the next biomarker sample collection per study procedures after 8 weeks. After that time biomarker samples do not need to be collected.

Detailed procedures for the collection, preparation, storage, and shipment of PD and biomarker blood and urine samples will be described in the Study Laboratory Manual. The date and time of PD and biomarker blood and urine samples will be recorded in the subject's source documentation and eCRF.

Biomarker samples collected in this study may be stored for up to 10 years after completion of the study (according to local regulations) for additional research. Samples may be used to understand the effect of KBP-5074 on CKD, cardiovascular disease, or to understand differential drug responders. The research may begin at any time during the study or the post-

study storage period. Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers.

6.14 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed at each visit indicated in the Schedule of Study Procedures (Table 10). Detailed procedures for the collection, preparation, storage, and shipment of clinical laboratory samples will be described in the Study Laboratory Manual. The date and time of sample collection for clinical laboratory evaluations will be recorded in the subject's source documentation and eCRF. Results for local laboratories will be entered in the subject's eCRF by trained site staff.

All assessments of potassium and eGFR (EPI), including retests, will be performed at both local and central laboratories.

To ensure subject safety, local laboratory results for serum potassium will be the primary information used to monitor serum potassium levels and manage study drug and hyperkalemia as described in Section 3.4.2. Safety monitoring and management of renal function is described in Section 3.4.3.

If central laboratory results for serum potassium or eGFR (EPI) differ from local laboratory results to such an extent that the Investigator is uncomfortable with the dose adjustment guidance shown in Table 3 for serum potassium or Table 4 for eGFR (EPI), local and central testing may be repeated at the Investigator's discretion.

Specific laboratory evaluations are listed in Table 6 .

The Investigator should review and evaluate all laboratory results. Any clinically significant laboratory result should be indicated on the subject's eCRF and rechecked as soon as possible for confirmation. A clinically significant laboratory event may be reported as an AE/SAE if applicable (see Section 6.17).

Table 6 List of Clinical Laboratory Evaluations

Local Laboratory Assessments [a]		
Potassium	Creatinine/eGFR (EPI) [b]	
Central Laboratory Assessments		
Serum Chemistry	**Hematology:**	**Urinalysis:**
Alanine aminotransferase	Hematocrit	Appearance
Albumin	Hemoglobin	Bilirubin
Alkaline phosphatase	Platelet count	Color
Amylase	Red blood cell count	Glucose
Aspartate aminotransferase	White blood cell count with differential	Ketones
Bicarbonate		Leukocyte esterase
Blood urea nitrogen		Nitrite
Calcium	**Coagulation:**	Occult blood

Table 6 List of Clinical Laboratory Evaluations

Chloride	Activated partial thromboplastin time	pH
Creatine kinase	International normalized ratio	Protein
Creatinine	Prothrombin time	Specific gravity
eGFR (EPI) [b]		Urobilinogen
Gamma-glutamyl transferase	**Viral Serology**	Microscopic examination [c]
Glucose	Hepatitis B virus surface antigen	
Lactate dehydrogenase	Hepatitis C virus	
Lipase	Human immunodeficiency virus	
Phosphorus		
Potassium	**Other Evaluations**	
Sodium	UACR (see Section 6.11.2)	
Total bilirubin	Urine drug screen	
Total protein	Follicle stimulating hormone [d]	
Uric acid	Pregnancy testing [e]	

Abbreviations: CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; eGFR (EPI)=estimated glomerular filtration rate calculated using Chronic Kidney Disease Epidemiology Collaboration formula; EOS=end of study; ET=early termination; UACR=urinary albumin:creatinine ratio; WOCBP=women of childbearing potential

[a] All assessments of potassium and eGFR (EPI), including retests, will be performed at both local and central laboratories.
[b] Estimated GFR will be calculated using the CKD-EPI equation (16).
[c] Microscopic examination of urine will be performed only if needed based on positive dipstick test result.
[d] Post-menopausal women only.
[e] Pregnancy tests are required only for WOCBP. Serum pregnancy tests will be performed at the Screening Visit (Visit 1) and at the Week 56 EOS Visit (Visit 17) or ET Visit. A urine pregnancy test will be performed pre-dose on Day 1 (Visit 3) and results verified before the administration of study drug. If required by national and/or institutional regulations, a serum or urine pregnancy test should be performed in subjects of childbearing potential more frequently (e.g., at every visit).

6.15 Study Drug Accountability and Compliance

Subjects will be instructed to bring all unused study drug with their bottles (including empty bottles) and all background antihypertensive medications to each visit.

To assess a subject's compliance with placebo during the Open-Label Run-In Period and with study drug during the Double-Blind and Open-Label Treatment Periods, trained site personnel will perform a pill count as described in the Study Pharmacy Manual to verify how much study drug was taken or lost since the last visit. Trained site personnel will then discuss study drug compliance with the subject to determine if any doses were missed or lost. The pill count and compliance data will be recorded in the subject's source documentation and eCRF as described in the Study Pharmacy Manual.

To assess subject compliance with background antihypertensive medications, trained site personnel will review each of the subject's background antihypertensive medication with the

subject and verify how much of the medication was taken, if any doses were missed or lost, and if the subject has sufficient background antihypertensive medications until the next visit.

Data collected about a subject's compliance with study drug and background antihypertensive medications will be recorded in the subject's source documentation and eCRF.

6.16 Dispensing of Study Drug and On-Site Study Drug Administration

Study drug will be dispensed as indicated in the Schedule of Study Procedures (Table 10), including placebo for the Open-Label Run-In Period, and at any unscheduled visit at which study drug is titrated. Unused study drug will need to be collected and new study drug provided to the subject whenever the dose of study drug is up- or down-titrated.

At each visit, the Investigator or trained designee will determine the amount of study drug to be dispensed according to the Study Pharmacy Manual and use the IRT system to determine the bottle number(s) to be provided to the subject as described in the IRT manual. Subjects will be provided with sufficient study drug until the next scheduled visit and instructed to take 1 tablet QD, preferably in the morning with water and with or without food and to bring all unused study drug (including empty bottles) to the site at the next scheduled visit. The date study drug is dispensed, and the bottle numbers dispensed will be recorded in the subject's source documentation, site Investigational Product Accountability Log, and subject's eCRF.

On-site study drug administration will occur under supervision of qualified site staff. All assessments at the Randomization Visit (Visit 3) and at Week 24 (Visit 9), except collection of the blood sample for PK analysis, will be completed before the administration of study drug. At each subsequent visit, blood pressure and vital signs will be collected prior to the administration of study drug at the visit. The date and time of study drug administration at each visit will be recorded in the subject's source documentation and eCRF.

6.17 Adverse Event Assessments

6.17.1 Performing Adverse Event Assessments

Adverse events, including SAEs, will be collected throughout the study period, beginning from the time the subject signs the Screening ICF until the subject completes the study (i.e., completes all protocol-specified assessments at the Week 56 EOS Visit) or discontinues the study. Adverse events, including SAEs, that occur after a subject completes the study or discontinues from the study will not be reported unless the Investigator determines that there is a reasonable possibility that the AE/SAE is related to study drug or a protocol procedure.

Subjects will be instructed to report any adverse event to the Investigator and/or site staff. Beginning with the Screening Visit, information on AEs and SAEs will be elicited at each visit by asking the subject open-ended questions such as: "Since you were last asked, have you felt unwell or different from usual in any way?" Subject may report AEs spontaneously at any time.

All AEs, which may include observed, elicited, or volunteered problems, complaints, signs, or symptoms, or abnormal clinical laboratory results, are to be recorded on the subject's eCRF. The Investigator is responsible for reporting and evaluating each AE.

The following information will be captured for each AE:

- Description of the AE:
  - A specific diagnosis (e.g., disease or syndrome) rather than individual associated signs and/or 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 diagnosis by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition or event that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as the adverse event, not the procedure.
  - Any medical condition already present at Screening should not be reported as an adverse event unless the medical condition, signs, or symptoms present at baseline change 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 findings (e.g., abnormal ECG) that are detected during the study or are present at Screening and significantly worsen during the study should be reported as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory or other abnormal finding 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.
  - Abnormal laboratory or other abnormal finding (e.g., abnormal ECG) that is determined to be an error should not be reported as an adverse event.
- Date and time of onset of the AE
- Date and time of resolution of the AE
- Severity of the AE (as defined in Section 6.17.3) as determined by the Investigator
- Relationship to study drug (as defined in Section 6.17.4) as determined by the Investigator
  - Investigators will determine the relatedness of an adverse event to study drug based on the temporal relationship to the study drug administration, as well as whether the event is unexpected or unexplained given the subject's clinical course, previous medical conditions, and concomitant medications.
  - If a subject has an adverse event after signing the ICF but before the administration of the first dose of study drug at Visit 3 (i.e., during the Screening and Open-Label Placebo Run-In Periods), the adverse event will be reported as not related to study drug.
- Seriousness criteria (as defined in Section 6.17.5) as determined by the Investigator

- Action taken with study drug (e.g., none, study drug discontinued, study drug interrupted)
  - If study drug is interrupted or discontinued because of an adverse event, study personnel will document the circumstances and data leading to interruption or discontinuation of treatment.
- Subject discontinued or not discontinued from the study
  - If a subject is discontinued from the study because of an adverse event, study personnel will document the circumstances and data leading to discontinuation from the study.
- Treatments administered
  - Any treatments administered because of an AE will be recorded on the concomitant medication page or surgical/medical procedure page of the subject's eCRF as applicable.
- Outcome (e.g., resolved, resolved with sequelae, not resolved, fatal)

All AEs and SAEs will be followed until the event and/or its sequelae resolves, becomes stable, or monitoring is no longer considered needed as determined by the Investigator.

Additional information may be requested for entry into the eCRF for eGFR (EPI) decrease, hypertensive, hypotensive, and hyperkalemia events.

6.17.2 Definitions

Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation subject 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.

Treatment-Emergent Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any AE with an onset during or after administration of the first dose of study drug and before 4 weeks (28 days) after the last dose of study drug or any preexisting AE or medical condition that worsened in severity during or after the administration of first dose of study drug and before 4 weeks (28 days) after the last dose of study drug.

A treatment-emergent SAE is defined as any SAE with an onset during or after administration of the first dose of study drug and before 4 weeks (28 days) after the last dose of study drug or any preexisting AE or medical condition that worsened in severity during or

after the administration of first dose of study drug and before 4 weeks (28 days) after the last dose of study drug.

Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as any noxious and unintended response to a medicinal product related to any dose of the medicinal product. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship could not be ruled out.

Unexpected Adverse Drug Reaction

An unexpected ADR is defined as any ADR, the nature or severity of which is not consistent with the applicable product information, i.e., for the purposes of this study, the IB.

6.17.3 Severity of Adverse Events

The Investigator will assess the severity (intensity) of each adverse event as mild, moderate, or severe using the definitions indicated below:

- Mild: An AE that is easily tolerated and generally not interfering with normal daily activities.
- Moderate: An AE 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.

6.17.4 Relationship of Adverse Events to Study Drug

The Investigator will categorize each adverse event as to its potential relationship to study drug using the following categories:

- Related: An event that followed a reasonable temporal sequence from administration of study drug that follows a known response pattern to the suspected treatment and that was confirmed by improvement on stopping the treatment (dechallenge), and reappearance of the event on repeated exposure (rechallenge).
- Probably Related: An event that followed a reasonable temporal sequence from administration of study drug; that followed a known response pattern to the suspected treatment and that was confirmed by dechallenge and that could not be reasonably explained by the known characteristics of the subject's clinical state.

- Possibly Related: An event that followed a reasonable temporal sequence from administration of study drug that followed a known response pattern to the suspected treatment but that could have been produced by the subject's clinical state or other modes of therapy administered to the patient.
- Unlikely Related: An event that followed a reasonable temporal sequence from administration of the treatment; that did not follow a known response pattern to the suspected treatment but that could not be reasonably explained by the known characteristics of the subject's clinical state.
- Not related: Any event that does not meet the criteria above.

The definition of "related" 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:

- Temporal relationship to 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 and the PK characteristics of the study drug.
- Underlying concomitant or intercurrent disease: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medications: The other medications the subject is taking or the treatment the subject 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 subject 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.

6.17.5 Seriousness of Adverse Events

A serious adverse event (SAE) or serious drug reaction (SAR) is defined as any AE or ADR occurring at any dose that:

- Results in death

- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization but based upon appropriate medical judgment, the event may jeopardize the subject 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 hospitalization, or the development of drug dependency or drug abuse.

The term "life-threatening" in the definition of "serious" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

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 AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

Although the term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction), the event itself may be of relatively minor medical significance (such as a severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations (see Section 6.17.6 for reporting requirements).

6.17.6 Expedited Reporting of Serious Adverse Events

Initial Reports

All SAEs occurring from the time of informed consent until 4 weeks following the last administration of study drug must be reported to Parexel Safety Services within 24 hours of being notified of the event. All SAEs that the Investigator considers related to study drug occurring after 4 weeks following the last administration of study drug must be reported to the Sponsor within 24 hours of being notified of the event.

The primary mechanism for the site to report an SAE will be entry into the electronic data capture (EDC) system within 24 hours of awareness of the SAE. When AE information is initially entered into the EDC system and is marked as serious, an automated SAE alert email (containing all 4 valid criteria for reporting) will be generated to notify Parexel Safety Services.

Note: Enter the AE in the appropriate section (AE page and/or SAE page) of the EDC system, indicate that the event is considered serious, and provide all the details per the eCRF completion guidelines.

Contingency Plan if the EDC is Not Available

If the EDC system is not accessible, contact Parexel Safety Services by email or fax the completed paper SAE form within 24 hours of being notified of the SAE using the following contact information:

- Parexel Safety Services Contact information
  - Email: KBP260868-SAEmailbox@parexel.com
  - Fax Number: NA (Billerica): +1 781-434-5957.

When the EDC system becomes available, the SAE information must be entered in the EDC system within 24 hours.

Follow-Up Reports

The Investigator must continue to follow the subject until the SAE has resolved or until the subject's condition stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receiving follow-up information, the Investigator must update the SAE form electronically in the EDC system and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to Parexel Safety Services via fax or email using the Safety Contact Information above. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs. When the EDC system becomes available, the SAE information must be entered in the EDC system within 24 hours.

Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions (SUSARs) in accordance with ICH E6 GCP, ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, FDA guidelines, European Union Clinical Trials Directive 2001/20/EC (EUCTD), European Commission CT-3 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) policy or local regulations, the Investigator will provide expedited reports to the IRB/IECs.

6.18 Concomitant Medication Assessments

At each visit, trained site staff will review with each subject all medications in addition to the study drug (including vitamin preparations and herbal or health supplements) taken by a subject since the previous visit. Concomitant medications will be recorded in the subject's source documentation and eCRF. The following information will be collected: name or description of the medication, start and stop dates, dosage, frequency, route of administration, the reason/indication for which the subject is taking the medication, and if an ongoing medication is considered a background antihypertensive medication. Medications taken for a previous condition, diagnosis, disease, or surgery, should have a corresponding entry in the subject's medical history.

6.19 Pregnancy Reporting and Follow-up

If a subject or partner of a subject participating in the study becomes pregnant during the study or within 90 days of the last dose of study drug, the Investigator should report the pregnancy to Parexel Safety Services within 24 hours of being notified. Parexel Safety Services will then forward the Exposure-In-Utero Form to the Investigator for completion.

A subject who becomes pregnant while on study drug will be immediately discontinued from study drug and discontinued from the study and ET study procedures will be performed.

The subject or partner of the subject 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 Parexel Safety Services. 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 (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

6.20 Interactive Response Technology Procedures

Subject registration and updates to subject status and data in the IRT system will be performed as described in the IRT manual.

6.21 Appropriateness of Measurements

All efficacy and safety endpoints and their methods of measurement are standard variables/methods in clinical studies and/or clinical practice. They are widely used and generally recognized as reliable, accurate and relevant.

7 QUALITY CONTROL AND ASSURANCE

To ensure compliance with the protocol, GCP, and applicable regulatory requirements, site visits will be conduct at regular intervals in accordance with FDA and ICH guidelines as outlined in the Study Monitoring Plan (see Section 9.6, Study Monitoring). Documented training on the protocol and GCP will be conducted at an Investigator meeting and/or Investigator site initiation visit.

Subject safety and the integrity and quality of subject data will be ensured by providing training and written instructions for IRT operation, ABPM, pharmacy procedures, laboratory procedures, and eCRF completion; and performing quality control checks, conducting ongoing clinical data review (including medical and safety reviews), and performing source data verification and data reconciliation (see Section 9.6, Study Monitoring, and Section 9.9, Data Management).

A central laboratory will be used to ensure consistency of laboratory results across sites and for the final analysis of laboratory data. Local laboratories will be used to monitor serum potassium (Section 3.4.2) and eGFR (EPI) (Section 3.4.3) to ensure subject safety. Local laboratory normal ranges for these assessments will be collected and provided in the clinical study report (CSR).

The Investigator will also permit the Sponsor auditors or designee auditors and IRB/IEC, FDA, or other Regulatory Authority inspectors to review and inspect facilities, procedures, and all records relevant to this study. These records include, but are not limited to: subject signed ICFs, source documentation, regulatory and essential documents, eCRFs, and drug accountability records. If the FDA or other regulatory agency should schedule an inspection, the Investigator should notify the Sponsor’s Medical Monitor immediately.

8 PLANNED STATISTICAL METHODS

This section briefly describes the planned statistical methods for this study. An SAP describing specific statistical methods in detail will be developed and approved by the Sponsor prior to database lock. If there are differences between the protocol and the SAP, the SAP will take precedence over the protocol.

8.1 General Considerations

Statistical analysis will be performed using SAS; the version of SAS used will be specified in the SAP.

All variables will be analyzed by descriptive statistical methods. The number of data available, mean, standard deviation (SD), minimum, median, first (Q1) and third (Q3) quartiles, minimum, and maximum will be calculated for continuous data. The geometric mean, confidence interval (CI), and coefficient of variation may also be provided as appropriate (e.g., for variables with lognormal distributions). Counts and percentages will be provided for categorical data. All data will be provided in by-subject listings.

In general, baseline values will be defined as the last non-missing measurement before the first administration of study drug unless indicated otherwise.

Only data provided by the central laboratory will be used for analyses, values from local laboratories will not be used in the statistical analyses and listed only.

8.2 Analysis Populations

The study populations planned for this study are described below:

- The Intent-to-Treat (ITT) Population is defined as all randomized subjects. The ITT Population will be the primary analysis population.
- The UACR population is defined as all randomized subjects who received at least 1 dose of randomized study drug, have a baseline UACR measurement, had UACR ≥30 mg/g at baseline, and have at least 1 post-dose UACR measurement.
- The Safety Population is defined as all randomized subjects who received at least 1 dose of randomized study drug.
- The PK Population is defined as all randomized subjects who received at least 1 dose of randomized study drug and have at least 1 measurable plasma concentration of KBP-5074.
- The PD/Biomarker Population is defined as all randomized subjects who received at least 1 dose of randomized study drug, have a baseline PD/biomarker measurement, and have at least 1 post-dose PD/biomarker measurement.
- The Randomized Withdrawal Population is defined as all randomized subjects who were randomized at the Week 48 Visit into the Randomized Double-Blind Withdrawal Period and have at least 1 SBP measurement after the Week 48 Visit.

8.3 Disposition, Demographics, and Baseline Characteristics

Patient disposition (e.g., screened, enrolled, randomized, completed the study, and discontinuing study drug and/or the study together with the primary reason for discontinuation) and analysis population data will be tabulated by treatment group and overall. Patient disposition may also be summarized by treatment group, country, and study site. Summary statistics will be provided by treatment group for demographics (e.g., age, sex, race, and ethnicity) and baseline characteristics (e.g., SBP, DBP, serum potassium, eGFR, and UACR).

By-subject listings of disposition, discontinuation, and demographic data will be provided.

8.4 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; Section 9.9) and summarized by MedDRA Primary System Organ Class and Preferred Term, treatment group, and overall.

A by-subject listing of medical history data will be provided.

8.5 Prior and Concomitant Medications

Prior medication/therapy will be coded using the World Health Organization Drug Dictionary (WHO-DD; Section 9.9) and summarized by Anatomic Therapeutic Chemical (ATC) Classification, ATC subclass, Preferred Term, treatment group, and overall.

Concomitant medication/therapy will be coded using the WHO-DD (Section 9.9) and summarized by ATC Classification, ATC subclass, Preferred Term, and treatment group.

In addition, background antihypertensive medications will be summarized by ATC Classification, ATC subclass, Preferred Term, and treatment group.

By-subject listings of prior, concomitant, and background antihypertensive medications will be provided.

8.6 Treatment Duration, Titration Status, Exposure, and Compliance

Treatment duration will be summarized using descriptive statistics by treatment group, dose, and overall. In general, treatment duration for each dose and overall will be calculated as follows:

Treatment duration = (last date of study drug) – (date of first dose) + 1.

Further specification for calculating treatment duration will be provided in the SAP.

The titration status (yes/no, up- or down-titration), regardless of actual or sham titration, will be summarized by treatment group, visit, and overall.

The extent of exposure to study drug will be summarized using descriptive statistics by treatment group and dose.

Overall compliance to study drug will be calculated as a percentage of doses taken relative to planned doses as follows:

Compliance (%) = (number of tablets taken) / (number of planned tablets) × 100.

The number of planned tablets will be calculated as follows:

Planned tablets = (treatment duration in days) × (planned tablets per day).

The compliance will be summarized descriptively by treatment group, dose, and overall.

8.7 Analysis of Efficacy

8.7.1 Analysis of the Primary Efficacy Endpoint at Week 12

Primary Efficacy Endpoint and Estimand

The primary estimand is the mean difference between KBP-5074 0.25 to 0.5 mg and the placebo group in change in seated trough cuff SBP from baseline to Week 12 in subjects with uncontrolled hypertension who have moderate or severe (Stage 3b/4) CKD, regardless of study treatment discontinuation, missed study treatment, or a change in background antihypertensive medication. The primary estimand will be used for the analysis of the primary efficacy endpoint. The primary efficacy endpoint is the change in seated trough cuff SBP from baseline to Week 12 using the ITT population. The set of intercurrent events for this estimand consists of discontinuation of study treatment up to Week 12, missed study treatment up to Week 12, or a change in background antihypertensive medications after randomization and up to Week 12 (Table 7). The intercurrent events will be handled using a treatment policy strategy where observed data is used regardless of occurrence of these intercurrent events. The absence of a seated trough cuff SBP measurement on or before Week 12 following these subjects' withdrawal, missed study treatment or background antihypertensive medication change will be imputed by multiple imputation and using the information from retrieved dropouts (See SAP for details).

Table 7 Intercurrent Event Strategy for Primary Endpoint

Intercurrent Event	Strategy for Primary Endpoint
Discontinuation of study treatment up to Week 12	Treatment policy
Change in background antihypertensive medications prior to Week 12	Treatment policy

The primary efficacy analysis will be based on the ITT Population and employ an analysis of covariance (ANCOVA) model with change in seated trough cuff SBP from baseline at Week

12 as the outcome variable. Treatment, together with baseline eGFR level (≥30 versus <30 mL/min/1.73 m^2), and background antihypertensive medication (3 or more versus fewer than 3) will be factors in the model and baseline SBP value will be a covariate. Model results will be generated for each completed dataset from PROC MI. The results from these analyses will be combined together for an overall inference using PROC MIANALYZE. This will produce adjusted least squares (LS) mean, standard error, and the two-sided 95% CI for each treatment group, and the difference between LS-means, and the 95% CI of the difference, and p-values for comparing the KBP-5074 and placebo group.

Other imputation methods for the primary efficacy endpoint at Week 12 may also be explored as described in the SAP.

8.7.2 Analysis of Second Key Endpoint for Durability at End of Randomized Withdrawal Period

The second key endpoint for durability at the end of the Randomized Withdrawal Period is the change in seated trough cuff SBP from Week 48 to Week 52. If a subject had a change of background antihypertensive medications because of an AE (e.g., hypertensive urgency) between the Week 48 and Week 52 Visits, the last SBP measurement collected before the change of medications will be used. The effect of randomized withdrawal will be evaluated by comparing results for KBP-5074 and placebo.

The analysis of the second key endpoint for durability will be based on the Randomized Withdrawal Population and employ an ANCOVA model with change in seated trough cuff SBP from Week 48 to Week 52 as the outcome variable. Treatment, baseline eGFR (EPI) level (≥30 versus <30 mL/min/1.73 m^2), randomization assignment at the Randomization Withdrawal Week 48 (Visit 15), and background antihypertensive medication (3 or more versus fewer than 3) will be factors in the model, and baseline SBP value will be a covariate. The LS-means, standard errors, and the two-tailed 95% CI for each treatment group and the difference of the LS-means, 95% CIs, and p-values for comparing the KBP-5074 and placebo groups will be estimated. Missing value impact will be examined by the multiple imputation method; details will be included in the SAP.

8.7.3 Analyses for Secondary and Exploratory Efficacy Endpoints

The effect of treatment on secondary and exploratory efficacy endpoints will be evaluated by comparing results for KBP-5074 and placebo.

Continuous secondary endpoints, such as change in seated trough cuff SBP from baseline to Week 24 and changes in seated trough cuff DBP from baseline to Week 12 and Week 24, will be analyzed using methods analogous to the models employed for the primary endpoints. Categorical data (e.g., the percentage of subjects who achieve the target goal of SBP ≤130 mm Hg or have a decrease from baseline ≥10 mm Hg at Week 12 and Week 24) will be summarized and analyzed using a logistic regression model with factors such as baseline eGFR group and baseline SBP groups.

For the evaluation of the long-term hypertensive effect of KBP-5074, time to up-titration of study drug or change in background antihypertensive medications will be evaluated over 12 and 24 weeks.

Log transformation will be used for UACR endpoints, which will be analyzed using methods analogous to the model employed for the primary endpoint. Non-parametric methods may also be considered.

For the primary endpoint, second key endpoint for durability, and key secondary endpoints, subgroup analysis will also be performed. The specific analyses for secondary and exploratory efficacy endpoints will be provided in the SAP.

8.7.4 Analysis of Efficacy Endpoints from the Open-Label Treatment Period

All efficacy endpoints from the Open-Label Treatment Period (from Week 24 to Week 48), such as change in seated trough cuff SBP, DBP, and UACR from baseline to Week 48 and the percentage of subjects who achieve the target goal of SBP ≤130 mm Hg or have a decrease in SBP from baseline ≥10 mm Hg at Week 48, will be summarized descriptively.

8.7.5 Type 1 Error Control

The overall Type 1 error for the Double-Blind Treatment Period (baseline to Week 24 including primary endpoint at Week 12) will be controlled at the level of 0.05. For the Week 12 primary endpoint and key secondary endpoint analyses, the following test procedure will be used:

- The primary endpoint of change in seated trough cuff SBP from baseline to Week 12 will be tested at 0.05.
- The following key secondary endpoints will be tested with same nominal alpha level:
  - Change in seated trough cuff SBP from baseline to Week 24
  - Changes in seated trough cuff DBP from baseline to Week 12 and Week 24
  - Change in UACR from baseline to Week 12 and Week 24 for subjects with UACR >30 mg/g at baseline

The overall Type 1 error for the second key endpoint for durability during the Randomized Double-Blind Withdrawal Period (Week 48 to Week 52) will also focus on the full Randomized Withdrawal Population and be controlled at the same alpha level of 0.05.

8.7.6 Subgroup Analyses

The following subgroups will be considered for the descriptive and exploratory analysis of the primary endpoints:

- Age (18 to 45 years, >45 to ≤65 years, >65 to ≤75 years, and >75 years)
- Region (Europe, North America, Asia, China/Hong Kong/Taiwan, others)

- Gender (male, female)
- Race (white, black, Asian, other)
- Baseline BMI (≤30 kg/m^2, >30 kg/m^2)
- Baseline serum potassium value (≤4.5 mmol/L and >4.5 mmol/L)
- Baseline eGFR values (30 to ≤44 mL/min/1.73 m^2, 15-29 mL/min/1.73 m^2)
- Baseline proteinuria (UACR <30 mg/g, UACR ≥30 to ≤300 mg/g, UACR>300 mg/g)
- Baseline systolic blood pressure (≥160 mm Hg or < 160 mm Hg)
- Diabetic (Yes/No)
- Background antihypertensive medication change (Yes/No)
- Number of background antihypertensive medications

If the total number of subjects in a subgroup is less than 15, the analysis for that subgroup will not be performed. Additional subgroups defined for descriptive summaries will be specified in the SAP.

8.8 Analysis of Safety

All safety analyses will be conducted using the Safety Population. The assessment of safety will be based primarily on the frequency of subjects with AEs and clinical laboratory abnormalities. Other safety data will be summarized as appropriate. All AEs will be coded using the MedDRA.

For serum potassium and related hyperkalemia events:

- TEAEs of hyperkalemia will be summarized by treatment group, severity, and eGFR status at baseline.
- Serum potassium >5.0 and <5.6 mmol/L, ≥5.6 and <6.0 mmol/L, and ≥6.0 mmol/L by central laboratory results will be summarized by treatment group and eGFR status at baseline.
- On treatment change from baseline of serum potassium will be evaluated over time.

For eGFR (EPI) values and related renal events:

- TEAEs related to decreases in eGFR (EPI) will be summarized by treatment group, severity, and eGFR (EPI) status at baseline.

- Sustained eGFR (EPI) decreases from baseline ≥30% will be summarized by treatment group and eGFR (EPI) status at baseline.
- On treatment change from baseline of eGFR (EPI) will be evaluated over time.

8.9 Pharmacokinetic and Pharmacodynamic Analyses

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 PK Population. Different PK models will be attempted to fit the PK concentration time data.

After the population PK modeling, a population PD approach may be used to explore the concentration-effect relationships. Different PD models may be attempted to fit the concentration-effect data. All PD exploration will be based on the ITT Population.

8.10 Interim Analysis

An IDMC not otherwise involved with study conduct will be established to oversee safety and futility evaluation in Study KBP5074-3-001 (see Section 9.8). The IDMC will provide guidance to KBP Biosciences, as deemed necessary, for the continued protection of enrolled subjects and those yet to be recruited to the trial. The IDMC will independently review the safety data and determine if it is safe to continue the study according to the protocol. Blinded summaries of all AEs and SAEs will be provided every 4 weeks to the IDMC. The committee will meet at the following milestones listed in Table 8.

Table 8 IDMC Meetings

Time Point	Evaluation
10% of subjects enrolled	Baseline Demographics
25% of subjects complete Week 12 (Visit 7)	Safety
50% of subjects complete Week 12 (Visit 7)	Safety
75% of subjects complete Week 12 (Visit 7)	Safety
100% of subjects complete Week 12 (Visit 7) or have discontinued from the study	Safety and Efficacy
50% of subjects complete Week 24 (Visit 9)	Safety
100% of subjects complete or discontinue the study	Safety and Efficacy

Formal Interim Analysis for Assessment of Lack of Efficacy (Futility)

A formal interim analysis to assess lack of efficacy may be performed when all subjects complete the Week 12 (Visit 7). The data collected at this time will be cleaned, locked,

unblinded, and analyzed for the primary analysis as specified in Section 8.7.1. The study will be considered futile if the p-value for the primary analysis test is ≥0.05 or the model-adjusted SBP reduction in treatment group compared to placebo is less than 5 mm Hg. The IDMC Chairman will notify KBP Biosciences PTE. Ltd. whether any of above efficacy futility criteria are met. KBP Bioscience Chief Development Officer may decide to terminate the study early due to lack of efficacy.

8.11 Determination of Sample Size

The primary efficacy endpoint is the change in seated trough cuff SBP from baseline to Week 12. Under the assumption of the submission, the final sample size of 240/240 (or 300/300 at enrollment with 20% dropout rate) will achieve more than 90% power to detect a 6 mm Hg difference in SBP between the KBP-5074 and placebo dose groups, assuming a standard deviation of 20 mm Hg at a target two-sided overall alpha level of 0.05.

Additional sample size calculations are provided in Table 9.

Table 9 Sample Size Estimates

	Treatment Difference: KBP-5074 versus Placebo			
Power of Study	**5 mm Hg**	**6 mm Hg**	**7 mm Hg**	**8 mm Hg**
80%	506	352	260	200
85%	578	402	296	228
90%	676	470	346	266

As discussed in Section 1.2.2, the completed Phase 2b study showed a treatment difference of approximately 10 mm Hg for KBP-5074 0.5 mg compared to placebo at the end of active treatment. In addition, the post-treatment increase in SBP for the KBP-5074 0.5-mg group at 28 days after the last dose of study drug was approximately 10 mm Hg, and the SDs of the post-treatment increase in SBP in subjects randomized to the placebo group and the KBP-5074 groups were approximately 18 mm Hg.

For this Phase 3 study, approximately 400 of the 600 subjects initially enrolled are expected to complete 48 weeks of treatment and be randomized into the Randomized Double-Blind Withdrawal Period. Additionally, approximately 50% of these subjects are expected to have changes of background antihypertensive medications during the Double-Blind or Open-Label Treatment Periods. Based on the data from the Phase 2b study, the increase in SBP in subjects randomized to placebo in the Randomized Double-Blind Withdrawal Period 4 weeks after discontinuing treatment with KBP-5074 is expected to be at least 5 mm Hg. Based on these assumptions and assuming that the treatment differences and SDs from the previous Phase 2b study hold, 400 subjects randomized into the Randomized Double-Blind Withdrawal Period should provide approximately 80% power to detect a difference of at least 5 mm Hg between the KBP-5074 and placebo groups.

9 ADMINISTRATIVE CONSIDERATIONS

9.1 Ethical Conduct of the Study

The study will be conducted in accordance with United States FDA regulations, ICH E6 guidelines for GCP, the Declaration of Helsinki, and IRB/IEC requirements. The study will also be conducted in accordance with the EUCTD for sites in the European Union and all other applicable local and national laws and regulations governing the conduct of human clinical studies.

GCP is an international ethical and scientific quality standard for the design, conduct, documentation, and reporting of studies that involve human subjects. 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.

The Investigator is responsible for ensuring that the study is conducted in accordance with the protocol, ICH GCP guidelines, Declaration of Helsinki, current local and national regulations, and other applicable requirements governing the conduct of human clinical trials.

9.2 Institutional Review Board or Independent Ethics Committee Approval

To safeguard the rights, safety, and well-being of study subjects, an IRB or IEC must review all appropriate study documentation in accordance with GCP and local regulatory requirements. The study will only be conducted at sites where IRB/IEC approval has been obtained. The Investigator is responsible for submitting the study protocol, any protocol amendments, site-specific ICFs (local language and English versions), participant education and recruitment materials, and any other requested documents (and subsequent modifications) to the applicable IRB/IEC for review and approval. Upon approval by the IRB/IEC, the approval letter from the IRB/IEC will be filed at the site and an official copy forwarded to the Sponsor. No drug will be released to the site until written IRB/IEC authorization has been received by the Sponsor.

After initial IRB/IEC review and approval, the Investigator is responsible for submitting safety and progress reports to the IRBs/ECs at least annually and within 3 months of study termination or completion of the study at the Investigator's site in accordance with the regulatory requirements and IRB/IEC policies and procedures. Copies of the Investigator's annual report and other required reports to the IRB/IEC and copies of the IRB/IEC continuance of approval must be provided to the Sponsor. The Investigator must also inform the IRB/IEC of any protocol changes or amendments, changes to the IB, expedited reports of SAEs submitted to regulatory authorities, and other significant safety concerns according to the IRB/IEC policy. After completion or termination of the study, Investigators will notify their IRB/IECs. The Investigator will comply with all IRB/IEC policies throughout the duration of the study.

9.3 Changes to the Protocol, Protocol Amendments, and Protocol Deviations

The Investigator will not deviate from the protocol without prior written approval from the Sponsor, except in medical emergencies. In the event of a medical emergency, the Investigator must notify the Sponsor's Medical Monitor as soon as possible.

The Investigator may also implement a deviation from or change to the protocol to eliminate an immediate hazard to study subjects without prior Sponsor or IRB/IEC approval, but must report the implemented deviation or change and the reasons for it to the Sponsor's Medical Monitor as soon as possible, and to IRB/IEC in accordance with IRB/IEC policies.

Deviations from the protocol will be recorded in the eCRF. A protocol deviation is defined as any change, divergence, or departure from the study design or procedures defined in the protocol. A major (or important) protocol deviation is defined as a protocol deviation that could significantly impact the completeness, accuracy, and/or reliability of the study data or that could significantly affect a subject's rights, safety, or well-being. After completion of the study and prior to database lock, protocol deviations will be classified as major or minor as outlined in the Protocol Deviation Plan.

Any modifications to the protocol that affect the potential benefit to or safety of subjects or impact the conduct of the study, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Any amendments to the study protocol will be communicated to Investigators by the Sponsor or the Sponsor's designee. Modifications to the study protocol at individual sites will not be implemented by either the Sponsor or the Investigator without agreement by both parties. All protocol amendments will undergo the same review and approval process as the original protocol. Written documentation of IRB/IEC approval of protocol amendments must be received before a protocol amendment is implemented, and the approval letter filed at the site with an official copy forwarded to the Sponsor.

Health authorities should be notified of protocol amendments in accordance with local regulations.

Administrative changes to the protocol are minor corrections and/or clarifications that have no effect on the conduct of the study. These administrative changes will be and documented in a memorandum (e.g., Protocol Clarification Letter) communicated to Investigators by the Sponsor or the Sponsor's designee. The IRB/IEC may be notified of administrative changes at the discretion of the Investigator.

9.4 Informed Consent

The ICF and any participant education and recruitment materials and any changes to the ICF or any participant education and recruitment materials made during the study must follow all ICH GCP, local regulatory, and legal requirements and must be agreed to by the Sponsor and Investigator and approved by the IRB/IEC prior to their use.

Written informed consent must be obtained from each subject before any study-specific activity is performed. The Investigator or trained designee will explain the nature, purpose, procedures, and possible risks of the study with each subject (and his/her representative) and that the subject's free and voluntary consent will be requested. The subject (and his/her representative) must be informed that the subject's participation is voluntary and that the subject may withdraw at any time without any consequences. The subject (and his/her representative) must also be informed that the Sponsor, their representatives, and the responsible authorities will have access to the clinical data. The subject (and his/her representative) will then be provided with the ICF and any participant education materials and allowed ample time to read and understand the ICF and other materials so that the subject can have an informed discussion about the study with the Investigator or trained designee.

Prior to obtaining the subject's signature, the Investigator or trained designee must ensure that each subject understands and is fully informed about the nature, objectives, and possible risks associated with participation in the study, that the subject has had the opportunity to ask questions and that they have been properly answered, and that the subject has been informed of his/her rights to privacy. The Investigator or trained designee will then obtain written informed consent from each subject before any study-specific activity is performed and should document that informed consent was obtained prior to enrollment in the study in the subject's source documentation. The original signed copy of the ICF must be signed by the subject and the Investigator or trained designee and maintained by the Investigator in the site's files. A copy of the signed ICF will be given to the subject. The signed ICF should be filed at the site and available for inspection by the Sponsor or Sponsor representatives, auditors, the IRB/IEC, and/or regulatory agencies.

For subjects who require additional local laboratory assessment solely for the purpose of prescreening, the Investigator or trained designee must obtain the subject's written informed consent using either the optional prescreening-specific or study's full ICF. If the optional prescreening-specific informed consent is obtained, and the subject is eligible to enter the Screening Period, full informed consent must be obtained before screening is initiated.

For subjects agreeing to participate in ABPM, the Investigator or trained designee must obtain the subject's written informed consent using the ABPM ICF before ABPM is initiated.

The same informed consent process used for the study's full informed consent will be followed for the prescreening-specific and ABPM informed consents. A copy of each signed ICF will be given to the subject. The signed ICFs should be filed at the site and available for inspection by the Sponsor or Sponsor representatives, auditors, the IRB/IEC, and/or regulatory agencies.

Subjects will need to be re-consented if there are any changes to the ICF because of changes to the risk-benefit profile due to new safety information, changes to the IB, or protocol amendments.

9.5 Patient Information and Confidentiality

Individual subject's medical information obtained because of participation in this study is considered confidential and disclosure to unauthorized parties is prohibited. All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access.

To maintain subject confidentiality, all laboratory specimens, reports, data collection, processes, and administrative forms will be identified by a coded identification (ID) number only. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link subject ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

All HIV test results will be kept strictly confidential, all counseling and blood draws will be conducted in private rooms, and study staff will be required to sign agreements to preserve the confidentiality of all participants. In the United States, the ICF may include authorization allowing the institution, Investigator, and Sponsor to use and disclose personal health information in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Subjects' study information will not be released outside of the study without the written permission of the subject, except as necessary for monitoring or auditing by the Sponsor or Sponsor representatives, the IRB/IEC, and/or regulatory agencies.

If results of this study are reported in medical journals or at meetings, the subject's identity will not be disclosed. With the subject's authorization, medical information may be provided to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare.

9.6 Study Monitoring

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.

Before the enrollment of any patient in this study, the Sponsor or their designee will review the following documents with the Investigator and site personnel: protocol, IB, eCRFs and procedures for their completion, informed consent process, monitoring plan, and the procedure for reporting SAEs.

To ensure compliance with the protocol, GCP, and applicable regulatory requirements, site visits will be conducted at regular intervals in accordance with FDA and ICH guidelines as

outlined in the Study Monitoring Plan. The Sponsor or designee will monitor site activity to verify that:

- The rights and well-being of human subjects are protected.
- The reported trial data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol/amendment, with study agreements, with GCP, and with the applicable regulatory requirements.

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.

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.

9.7 Steering Committee

A Steering Committee will be established for this study. The Steering Committee will be blinded to the study data while the trial is ongoing. Their main responsibilities are as follows:

- Provide input to protocol-related issues and protocol amendments that may arise during of the study,
- Oversee study progress and provide recommendations to Sponsor's study team regarding any necessary modifications that may be required in study conduct or study monitoring,
- Serve as resource for scientific review of substudies, publications, presentations and/or educational material as applicable.

9.8 Data Monitoring Committee

An IDMC will be established to independently review safety data and determine if it is safe to continue the study according to the protocol. The committee will consist of members external to the Sponsor who are completely uninvolved in the running of the study and who cannot be unfairly influenced (either directly or indirectly) by people or institutions involved in the study. An IDMC charter will be developed, and the approved IDMC charter will be on file and available for inspection.

The IDMC Charter will include a description of the scope of planned reviews. A blinded summary of all AEs and SAEs will be provided every 4 weeks to the IDMC. The committee will meet at the study milestones indicated in Table 8.

When reviewing data, the IDMC may be unblinded to treatment assignments. Unblinded data will be provided to the IDMC by an independent statistical center not otherwise involved in the study and will not be available to site, CRO, or Sponsor personnel, or other persons involved in the conduct of the study. The IDMC will advise the Steering Committee regarding the need for changes in the conduct of the study as outlined in the charter.

9.9 Data Management

Data management will be performed by a qualified CRO using validated computer systems conforming to regulatory requirements. Data will be recorded while the study is in progress using an EDC system and Sponsor-approved eCRF (see Section 9.10). Data entry and access to the study data will be restricted and controlled by procedures compliant with Title 21 of the Code of Federal Regulations Part 11 (21 CFR Part 11) and other appropriate international regulation. All passwords will be strictly confidential.

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 to ensure accurate, consistent, and reliable data entry. These checks may be used to:

- Identify missing data, inconsistent data, data outliers, unexpected lack of variability, and protocol deviations.
- Examine data trends such as the range, consistency, and variability of data within and across sites.
- Evaluate for systematic or significant errors in data collection and reporting at a site or across sites, potential data manipulation, or data integrity problems.

Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

Medical history and AE terms will be coded by the CRO using the MedDRA and reviewed by the Sponsor's Medical Monitor before database lock. Background antihypertensive medications, prior medications, and concomitant medications will be coded by the CRO using the WHO-DD and reviewed by the Sponsor's Medical Monitor before database lock.

Details regarding data management are documented in the study Data Management Plan.

9.10 Case Report Forms

All protocol-required information to be included in the study database will be entered into a source document and an eCRF created by the Sponsor or designated CRO and approved by the Sponsor using the EDC system. Data reported on the eCRF should be derived and consistent with source documents or the discrepancies should be explained. An explanation should be given for all missing data.

Data will be recorded at the site on eCRFs and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRAs will verify that:

- The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
- Any dose and/or therapy modifications are well documented for each of the trial subjects.
- Adverse events, concomitant medications, and intercurrent illnesses are reported in accordance with the protocol on the CRFs.
- Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
- All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

All corrections or changes made to any study data must be documented in source documents and appropriately tracked in an audit trail in the EDC system. The audit trail will contain the original data value, new data value, date changed, the user who made the change, and the reason(s) for the change. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

All eCRF data and query resolutions must be completed only by the site personnel designated by the Investigator. Designated site staff will have proper training prior to accessing the EDC system and must log into the system using their secure username and password to enter, review, or correct study data. All passwords will be strictly confidential.

Data entry into the eCRF should be completed in a timely manner to support the study timeline (i.e., the site should not wait for a monitoring visit before entering data into the eCRF).

The Investigator is responsible for ensuring the accuracy, completeness, and timeliness of the data reported on each subject's eCRF. Each subject's eCRF must be reviewed and electronically signed by the Investigator.

9.11 Study Records and Access to Source Documentation

Subject records, 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 including case histories, progress notes of the physician, nurses' notes, medical records, hospital records, clinical and office charts,

laboratory notes, memoranda, or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, records kept at the pharmacy or laboratories, and subject logs). Examples of source data include clinical findings, observations, enrollment summary information and ICF procedures, assessment of clinical significance for laboratory results, AE severity and seriousness, and Investigator's opinion of AE relatedness to study drug.

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. The Investigator and/or associated institutions must provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspections by the Sponsor or their designee, applicable regulatory authorities (e.g., FDA, European Medicines Agency, Pharmaceuticals and Medical Devices Agency), and IRBs/IECs.

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.

9.12 Retention of Data

To enable inspections from regulatory authorities or evaluations and/or audits from the Sponsor, the Investigator will keep records, including the identity of all participating patients (sufficient information to link records, e.g., 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/clinical site must retain essential documents (as defined in ICH E6, Guideline for GCP E6[R2]) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

The Investigator will notify the Sponsor in writing of relocation of any study records away from the research facility after study closure. 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.

The Investigator must contact the Sponsor in writing prior to the destruction of any study records, or in the event of loss of any study records. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

9.13 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.

9.14 Publication and Disclosure Policy

Patient medical information obtained during the study is confidential and disclosure to third parties, except as indicated in Section 9.11, is prohibited.

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.

As required by local regulation and law, the study results will also be published in clinical trials registries in all applicable countries and regions (e.g., EudraCT, Clinicaltrialsregister.eu, clinicaltrials.gov, chinadrugtrials.org.cn).

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Appendix 1 Schedule of Events

Table 10 Schedule of Study Procedures for KBP5074-3-001

Study Period	Screening [a]	Run-In	Double-Blind Treatment							Open-Label Treatment						Randomized Withdrawal	Follow-Up			
Visit	1	2	3 [b]	4	5	6	7	8	9 [b]	10	11	12	13	14	15 [b]	16	EOS 17	Unsch [c]	EOT [d]	ET [e]
Study Week	-6 to -2	-2 to -1	NA	2	4	6	12	18	24	26	28	30	36	42	48	52	56			
Study Day	-42 to -15	-14 [f]	1 [g]	14	28	42	84	126	168	182	196	210	252	294	336	364	392			
Procedure Visit Window	NA	-7/+2	NA	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	+4	±4			
Sign Informed Consents [h]	X																			
Demographic Information	X																			
Medical History	X																			
Review Prior Medications	X																			
Inclusion/Exclusion Criteria	X	X	X																	
Randomization			X [i]												X					
Open-Label Safety Criteria									X											
Randomized Withdrawal Safety Criteria															X					
Physical Examination	X		X				X		X								X			X
Height (cm)	X																			
Body Weight (kg)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Mass Index (kg/m^2) and Waist Circumference (cm)	X						X		X								X			X
Vital Signs (pulse rate, respiratory rate, and temperature) [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG [k]	X		X				X		X						X		X		X	X
Efficacy Assessments																				
Blood Pressure [l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
UACR [m]		X	X		X		X		X						X	X	X		X	X
24-hour ABPM Device Placement [n]			X				X													
EQ-5D-5L			X						X						X	X				X
KDQOL-36			X						X						X	X				X
Blood samples for Pharmacokinetic Analyses [o]			X		X	X	X		X		X	X			X	X	X	X [p]	X	X
Blood and Urine samples for Biomarkers [q]			X				X		X						X	X	X		X	X
Clinical Laboratory Evaluations																				
Local Laboratory Evaluations (Serum potassium and eGFR [EPI])	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 10 Schedule of Study Procedures for KBP5074-3-001

Study Period	Screening [a]	Run-In	Double-Blind Treatment							Open-Label Treatment						Randomized Withdrawal	Follow-Up			
Visit	1	2	3 [b]	4	5	6	7	8	9 [b]	10	11	12	13	14	15 [b]	16	EOS 17	Unsch [c]	EOT [d]	ET [e]
Study Week	-6 to -2	-2 to -1	NA	2	4	6	12	18	24	26	28	30	36	42	48	52	56			
Study Day	-42 to -15	-14 [f]	1 [g]	14	28	42	84	126	168	182	196	210	252	294	336	364	392			
Procedure Visit Window	NA	-7/+2	NA	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	+4	±4			
Central Laboratory Evaluations																				
Serum Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [r]	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Coagulation	X		X				X		X						X	X	X		X	X
Viral Serology	X																			
Urine Drug Screen	X	X [s]																		
Follicle Stimulating Hormone [t]	X																			
Pregnancy Testing [u]	X		X														X			X
Discuss/Review control of dietary sodium and potassium intake	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		
Study Placebo Run-In Instructions and Dispensing		X																		
Study Drug Accountability and Compliance		X	X [i]	X	X	X	X	X	X [v]	X	X	X	X	X	X	X			X	X
Study Drug Dispensing		X	X [i]	X	X	X	X	X	X [v]	X	X	X	X	X	X					
Study Drug Administration at Visit [w]		X	X [i]	X	X	X	X	X	X [v]	X	X	X	X	X	X					
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: ABPM=ambulatory blood pressure monitoring; ECG=electrocardiogram; eGFR (EPI)=estimated glomerular filtration rate calculated using Chronic Kidney Disease Epidemiology Collaboration formula; EOS=end of study; EOT=end of treatment; EQ-5D-5L=EuroQol 5-Dimension 5-Level Quality of Life Instrument; ET=early termination; KDQOL=Kidney Disease Quality of Life Instrument; NA=not applicable; PK=pharmacokinetics; QD=once daily; SBP=systolic blood pressure; UACR=urine albumin:creatinine ratio; Unsch=unscheduled; WOCBP=women of childbearing potential

Note:

- All visits should be performed within the visit windows specified in the table which is calculated from the day of initial randomization and not based on date of prior visit. Every attempt should be made to have the subject attend each visit as scheduled. The investigational site will make a reminder phone call to the subject approximately 2 to 3 days before each scheduled visit. However, if a subject is unable to attend a visit within the specified window, the visit should be scheduled as closely as possible to the window. A subject should not skip a protocol-specified visit due to scheduling difficulties.

[a] The study will have a pretreatment phase, consisting of a prescreening assessment, a Screening Period of up to 4 weeks (full 4 weeks not required if blood pressure, labs, and eligibility are met), and a 2-week Open-Label Placebo Run-In Period. Subjects will be prescreened based on eGFR (EPI), serum

Table 10 Schedule of Study Procedures for KBP5074-3-001

Study Period	Screening [a]	Run-In	Double-Blind Treatment							Open-Label Treatment						Randomized Withdrawal	Follow-Up			
Visit	1	2	3 [b]	4	5	6	7	8	9 [b]	10	11	12	13	14	15 [b]	16	EOS 17	Unsch [c]	EOT [d]	ET [e]
Study Week	-6 to -2	-2 to -1	NA	2	4	6	12	18	24	26	28	30	36	42	48	52	56			
Study Day	-42 to -15	-14 [f]	1 [g]	14	28	42	84	126	168	182	196	210	252	294	336	364	392			
Procedure / Visit Window	NA	-7/+2	NA	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	+4	±4			

potassium, and SBP. Only subjects with an eGFR (EPI) ≥15 to ≤44 mL/min/1.73 m^2, serum potassium ≤4.8 mmol/L as confirmed by a local laboratory, and SBP ≥140 mm Hg within 3 months prior to Screening will be eligible to enter the Screening Period.

[b] All assessments at the Randomization Visit (Visit 3) and Week 24 (Visit 9), except collection of the blood sample for PK analysis, will be completed **before** the administration of study drug.

[c] After any change to study drug or background antihypertensive medications, the Investigator should perform an unscheduled visit within 2 weeks (±3 days) of the change to monitor blood pressure, potassium, and renal function.

[d] For subjects who discontinue study drug prematurely, an EOT Visit should be performed within approximately 4 weeks of discontinuing treatment. Subjects who prematurely discontinue study drug will continue in the study for all subsequent study visits until study completion and are to complete visit procedures (except for drug dispensing and accountability).

[e] For subjects who discontinue the study prematurely, an ET Visit should be scheduled as early as feasible after discontinuation to perform final assessments.

[f] The Run-In Visit must occur after the Screening Visit (Visit 1) and may occur any time between 21 and 12 days before first dose of study drug on Day 1.

[g] The target day for each visit after randomization will be calculated relative to the date of the first administration of study drug at the Randomization Visit (Visit 3) and not relative to the date of the previous visit.

[h] For subjects who require additional local laboratory assessments or AOBP measurements solely for the purpose of prescreening, either the optional prescreening-specific or full informed consent must be obtained before collecting clinical laboratory samples or AOBP measurements. If an optional prescreening specific informed consent is obtained and the subject is eligible to enter the Screening Period, the full informed consent must be obtained before screening is initiated.

[i] If a subject's compliance to medications during the Open-Label Placebo Run-In Period (including both placebo and background antihypertensive medications) is not within the acceptable parameters as defined in Section 3.1.3, the subject will not be eligible for the study.

[j] Vital signs will be collected before the administration of study drug at the visit.

[k] Standard 12-lead ECGs will be collected. Subjects should be resting in a supine position for at least 10 minutes before collection of the ECGs.

[l] Blood pressure will be measured before the administration of study drug at the visit. Triplicate blood pressure measurements should be collected approximately 2 minutes apart after the subject has rested in the seated position for at least 5 minutes as described in Section 6.11.1. If an outlier greater than 30 mm Hg occurs in triplicate SBP between first-to-second or second-to-third, an additional triplicate reading is required at least 10 minutes after the initial reading. The second triplicate reading with mean of second and third SBP must be used for data analysis and management.

[m] For UACR, subjects will collect first morning void urine samples prior to taking study drug at home on 3 consecutive mornings within 5 days prior to the scheduled visit and bring the samples to the scheduled visit.

Table 10 Schedule of Study Procedures for KBP5074-3-001

Study Period	Screening [a]	Run-In	Double-Blind Treatment							Open-Label Treatment						Randomized Withdrawal	Follow-Up			
Visit	1	2	3 [b]	4	5	6	7	8	9 [b]	10	11	12	13	14	15 [b]	16	EOS 17	Unsch [c]	EOT [d]	ET [e]
Study Week	-6 to -2	-2 to -1	NA	2	4	6	12	18	24	26	28	30	36	42	48	52	56			
Study Day	-42 to -15	-14 [f]	1 [g]	14	28	42	84	126	168	182	196	210	252	294	336	364	392			
Procedure / Visit Window	NA	-7/+2	NA	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	+4	±4			

[n] ABPM will be performed on a subset of subjects at selected sites who agree to ABPM as described in Section 6.11.3.

[o] See Table 5 for details of collecting PK samples. Note: Subjects who permanently discontinue study drug but continue with study visits should continue to have PK samples obtained for at least 8 weeks or until the next PK sample collection per study procedures after 8 weeks. After that time, PK samples can be removed from study procedures.

[p] Blood samples for PK analysis are only to be collected if the visit is scheduled because of an up or down-titration of study drug.

[q] Blood and urine samples for biomarker analyses will be collected before the administration of the study drug at the site. The materials and methods for collecting and processing biomarker samples are provided in the Study Laboratory Manual. If subject permanently discontinue study drug but continue with study visits, they should continue to have urine and blood biomarker samples obtained for at least 8 weeks or until the next biomarker sample collection per study procedures after 8 weeks. After that time biomarker samples do not need to be collected.

[r] Only serum potassium and eGFR (EPI) need to be assessed by the central laboratory at unscheduled visits after any change to study drug or background antihypertensive medications unless otherwise indicated as determined by the Investigator. As reminder, all testing of labs should include both central and local labs.

[s] The urine drug screen may be repeated once before the start of the Run-In Period at Visit 2 to verify eligibility requirements if the Investigator determines the results from the Screening Visit (Visit 1) were in error.

[t] Post-menopausal women only.

[u] WOCBP only. Serum pregnancy tests will be performed at the Screening Visit (Visit 1) and at the Week 56 EOS Visit (Visit 17) or ET Visit. A urine pregnancy test will be performed pre-dose on Day 1 (Visit 3) and results verified before the administration of study drug. If required by national and/or institutional regulations, a serum or urine pregnancy test should be performed in subjects of childbearing potential more frequently (e.g., at every visit or monthly).

[v] Starting at Week 24 (Visit 9), subjects will be reassigned to open-label KBP-5074 0.25 mg QD regardless of the subjects' final treatment regimen at the end of the Double-Blind Treatment Period, as indicated in Table 1.

[w] On days when the subject is scheduled for a visit (including unplanned visits 2 weeks [±3 days] after titration of study drug), subjects are not to take study drug at home, but wait until directed to take study drug on-site by study personnel after pre-dose assessments have been completed.

Appendix 2 Definition and Management of Hypertensive Emergency and Hypertensive Urgency/Markedly Elevated Blood Pressure

Hypertensive Emergency

A hypertensive emergency is defined as severe elevation in systolic blood pressure (SBP) >180 mm Hg and/or diastolic blood pressure (DBP) >120 mm Hg (based on the mean of 2 or more consecutive blood pressures readings) in conjunction with new or progressive target organ damage (e.g., Grade III or IV), neurologic, or cardiac symptoms. This definition of hypertensive emergency is consistent with the definition proposed in Figure 2).

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

Hypertensive emergencies in subjects presenting with acute intracranial hemorrhage and/or acute ischemic stroke require particularly close management. Local guidelines for these subjects should be followed.

Documented hypertensive emergency will require termination of the study drug.

Hypertensive Urgency or Markedly Elevated Blood Pressure

Blood pressures where SBP >180 mm Hg and/or DBP >120 mm Hg (based on the mean of 2 or more consecutive blood pressures readings) 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 subjects with severe uncontrolled hypertension, with the subject resting in a quiet, comfortable environment to confirm the elevated blood pressure, and to minimize white coat effect, anxiety, stress, pain, etc.

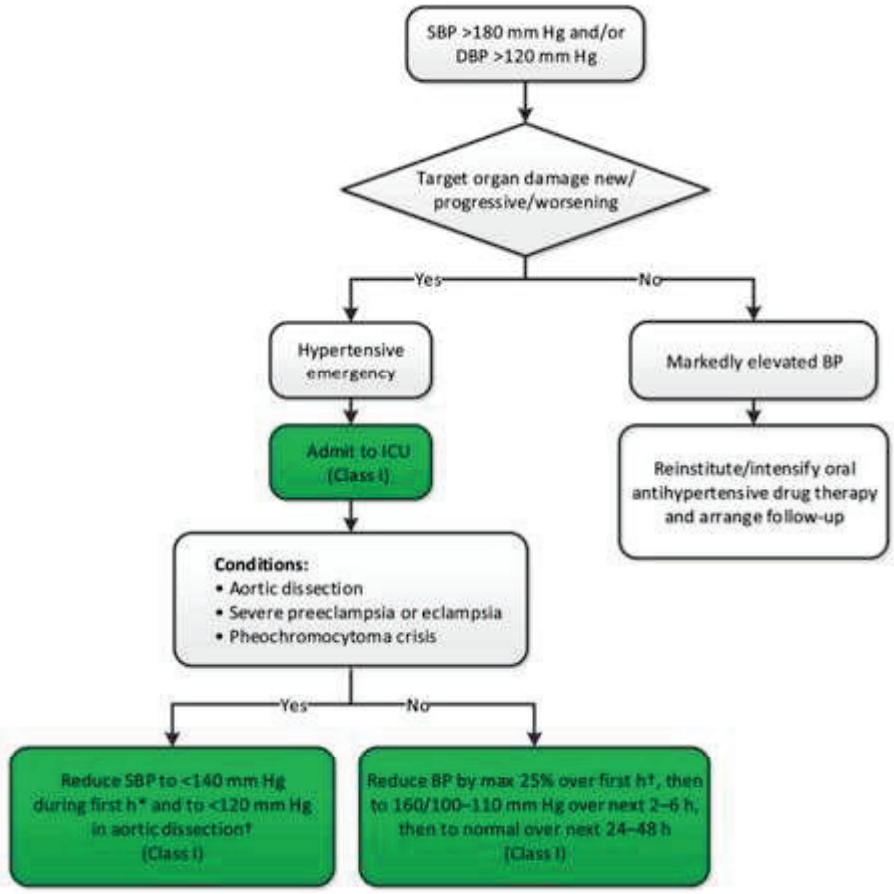
Hypertensive urgencies are situations associated with severe blood pressure elevation in otherwise stable subjects without acute or impending change in target organ damage or

dysfunction. Many of these subjects have withdrawn from or are noncompliant with antihypertensive therapy and do not have clinical or laboratory evidence of acute target organ damage.

These subjects should not be considered as having a hypertensive emergency and, instead, should be treated by reinstitution or intensification of antihypertensive drug therapy and treatment of anxiety as applicable. Hypertensive urgency does not require referral to the emergency department for immediate reduction in blood pressure in the emergency department or hospitalization.

A documented episode of hypertensive urgency or severe uncontrolled hypertension, pending response to drug therapy, may or may not require discontinuation 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; max=maximum; SBP=systolic blood pressure

* Use drug(s) specified in Table 19 of Whelton et al. 2018 (18).

† If other comorbidities are present, select a drug specified in Table 20 of Whelton et al. 2018 (18).

Source: Whelton et al. 2018 (18) Figure 11.

Appendix 3 Child-Pugh Grading of Severity of Liver Disease

Table 11 Child-Pugh Grading of Severity of Liver Disease

	Score		
	+1	**+2**	**+3**
Factor			
Hepatic Encephalopathy Grade [a]	0	1 or 2	3 or 4
Ascites [b]	Absent	Slight	Moderate to Severe
Serum Bilirubin (mg/dL)	<2	2 to 3	>3
Serum Albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
International Normalized Ratio	<1.7	1.7 to 2.3	>2.3
Child-Pugh Classification			
Points [c]	5 to 6	7 to 9	10 to 15
Classification	A	B	C

[a] Hepatic Encephalopathy Grade:
- Grade 0: Normal consciousness, personality, neurological examination, or electroencephalogram
- Grade 1: Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, or 5 cycles per second (cps) waves
- Grade 2: Lethargic, time disoriented, inappropriate, asterixis, ataxia, or slow triphasic waves
- Grade 3: Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, or slower waves
- Grade 4: Unarousable coma, no personality behavior, decerebrate, or slow 2 to 3 cps delta activity

[b] Ascites classifications:
- Absent: No ascites is detectable by manual examination or by ultrasound (if performed)
- Slight: Ascites palpation doubtful, but ascites measurable by ultrasound (if performed)
- Moderate: Ascites detectable by palpation and by ultrasound (if performed)
- Severe: Necessity of paracentesis; does not respond to medication treatment

[c] Child-Pugh Classification is obtained by adding the scores from the 5 individual factors listed above.

Appendix 4 Prohibited Concomitant Medications

Table 12 Prohibited CYP3A4 Inhibitors and Inducers

CYP3A4 Inducers	CYP3A4 Inhibitors
Avasimibe	Amprenavir
Bosentan	Atazanavir and other inhibitors of human HIV protease
Carbamazepin	Boceprevir
Efavirenz	Clarithromycin
Enzalutamide	Cobicistat
Etravirine	Conivaptan >20 mg
Fosphenytoin	Crizotinib
Hypericum Perforatum/St John's Wort	Danoprevir
Lersivirine	Darunavir
Mephenytoin	Delavirdine
Methylphenobarbital	Diltiazem
Mitotane	Dronedarone
Modafinil	Elvitegravir
Nafcillin	Erythromycin
Nevirapine	Fluconazole >200 mg
Oxcarbazepine	Fosamprenavir
Phenobarbital	Grapefruit and Grapefruit Juice
Phenytoin	Idealisib
Primidone	Indinavir
Rifabutin	Itraconazole
Rifampicin	Ketoconazole
Semagacestat	Lopinavir
Talviraline	Miconazole
Thioridazine	Nefazodone
Troglitazone	Nelfinavir
Vemurafenib	Posaconazole
	Ritonavir
	Nirmatrelvir/Ritonavir/(Paxlovid)
	Saquinavir
	Telaprevir
	Telithromycin
	Tipranavir
	Troleandomycin
	Voriconazole

Abbreviation: HIV=human immunodeficiency virus
Note: Any concomitant medication that is prescribed under emergency use and/or does not have a drug-drug interaction profile it is recommended to have a discussion with a Medical Monitor. This includes but is not limited to antiviral medications for COVID-19 Molnupiravir (Lagevrio) and Remdesivir (Veklury).

Appendix 5 Potential Biomarkers

Table 13 Potential Biomarkers

Biomarker	Mechanism	Rationale for Assessing This Biomarker
Cystatin C	Biomarker for kidney function not impacted by inflammation	Important association with mortality across the eGFR range and now studied as part of new onset cardiovascular decline.
Galectin-3 (Gal-3)	Cardiac biomarker for fibroblast and cardiomyocyte stress	Serum Gal-3 predicts short-, mid-, and long-term mortality and heart failure-associated hospitalization in early and late stage HFpEF and HFrEF.
Interleukin-6 (IL-6)	Acts as both a pro-inflammatory cytokine and an anti-inflammatory- myokine	
Kidney Injury Molecule-1 (KIM-1)	Renal tubular cell injury	Increased level indicates progressive renal damage in CKD.
N-terminal Pro-b-type Natriuretic Peptide (NT-proBNP)	Myocardial pressure volume overload	Increased in CKD and increased in subjects with asymptomatic or symptomatic LV dysfunction. Can be associated with coronary artery disease and myocardial ischemia.
Triple-A Analysis	Response to MRA and detection of primary aldosteronism	Triple-A analysis: serum aldosterone, equilibrium angiotensin I (Ang I), and equilibrium angiotensin I (Ang II).
Procollagen III Amino Terminal Propeptide (PIIINP)	Fibrosis marker	
Soluble Urokinase-type Plasminogen Activator Receptor (SuPAR)	Cell surface receptor implicated in inflammation	Prognosis and mortality marker for inflammation
Tumor Necrosis Factor Receptor 1 (TNFR1)	Inflammatory biomarker	Serum TNFR levels are positively associated with albuminuria and negatively associated with eGFR, while circulating levels of TNFRs exhibited an independent effect on all-cause mortality and eGFR decline.

Abbreviations: CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; HFpEF= heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; LV=left ventricle; MRA=mineralocorticoid receptor antagonist; TNFR=tumor necrosis factor receptor.