Cover Page for Statistical Analysis Plan

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KBP BioSciences PTE. Ltd.

KBP5074-3-001

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

Statistical Analysis Plan

Version: 3.0

Parexel Project Number: 260868

Redacted statistical analysis plan includes redaction of personal identifiable information only.

SPONSOR SIGNATURE PAGE

Approved by: 

4/23/2024
_____
Date

Parexel SIGNATURE PAGE

Signature below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	PPD Project Role: PPD

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	25 May 22	New document
2.0	02 Jan 24	Updates per FDA Advice/Information Request on 11/14/2022 and per Protocol Amendment 2 dated 12/29/23: • ITT Population modified to include all randomized subjects • Removed Per Protocol Population • Analyses of primary and second key efficacy endpoint to be based on retrieved dropout-based multiple imputation with ANCOVA model; • Addition of sensitivity analyses for primary and second key efficacy endpoints using several missing data imputation strategies: MI assuming MAR with ANCOVA analysis model, control-based multiple imputation assuming MNAR with ANCOVA analysis model, and tipping point analysis; • Updated overall Type 1 error rate to be alpha=0.05 for all efficacy analyses • Updated region definition per Protocol Amendment 2 • General updates to programming conventions, definitions and additional SAS coding added for primary efficacy analysis
2.1	18 Apr 24	Updates per FDA Advice/Information Request on 4/5/2024: • Addition of Huber-White sandwich estimator for MMRM analyses • Addition of ethnicity to subgroup analyses
3.0	22 Apr 24	Version changed for consistency with submission cover letter

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
ANCOVA	Analysis of covariance
Ang I	Angiotensin I
Ang II	Angiotensin II
ATC	Anatomic Therapeutic Chemical
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus Disease 2019
CRO	Clinical research organization
CS	Clinically Significant
DAP	Data Analysis Plan
DBP	Diastolic blood pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
EQ-5D-5L	EuroQol Group 5-Dimension 5-Level Instrument
ET	Early termination
GLMM	Generalized Linear Mixed Model
GMR	Geometric mean ratio
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
ITT	Intent-to-treat
KDQOL-36	36-item Kidney Disease Quality of Life Survey
LKAD	Last known assessment date
LLOQ	lower limit of quantification
LS	Least square
MAP	Mean arterial pressure
MAR	Missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed Model with Repeated Measures
MNAR	Missing not at random
MRA	Mineralocorticoid receptor antagonist
NCS	Not Clinically Significant

Abbreviation / Acronym	Definition / Expansion
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
PTAE	Pre-treatment adverse event
PRO	Patient reported outcome
Q1	First quartile
Q3	Third quartile
QD	Once daily
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SoC	Standard of care
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TIA	Transient Ischemic Attack
TLF	Table, Listing, Figure
UACR	Urinary albumin:creatinine ratio
WHO-DD	World Health Organization - Drug Dictionary

1 INTRODUCTION

KBP-5074 is a novel non-steroidal mineralocorticoid receptor antagonist (MRA) being developed for the treatment of uncontrolled hypertension in subjects with Stage 3b (estimated glomerular filtration rate [eGFR] ≥30 and ≤44 mL/min/1.73 m^2) or Stage 4 (eGFR ≥15 and <30 mL/min/1.73 m^2) chronic kidney disease (CKD). This study is designed to evaluate the efficacy and safety for KBP-5074 as well as the durability of its effect in subjects with uncontrolled hypertension who have Stage 3b/4 CKD.

In the Phase 2b study, KBP-5074 was well tolerated and demonstrated statistically significant reductions of systolic blood pressure (SBP) without excessive risk of hyperkalemia in subjects with uncontrolled hypertension and Stage 3b/4 CKD.

This study aims to confirm the unique pharmacological and pharmacokinetic (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.

This study will use a forced titration approach 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. KBP-5074 0.25 mg once daily (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 (refer to protocol, Table 2, Up-Titration Safety Criteria). The KBP-5074 0.5 mg QD dose was chosen as the highest dose for this Phase 3 study to limit the risk of hyperkalemia.

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

This SAP does not include the Table, Listing and Figure (TLF) shells; another document will present them.

The SAP will be finalized and signed prior to database hard lock.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol Amendment 2, Version December 29th, 2023
- electronic Case Report Form (eCRF), Version 6.0 (August 24th, 2023)

2 STUDY OBJECTIVES

2.1 Primary Objectives

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

2.2 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.

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

2.3 Exploratory Objectives

Exploratory objectives for this study are:

- To evaluate changes in SBP and DBP.
- To evaluate changes in study drug and background antihypertensive medications needed to achieve and maintain target blood pressure.
- To evaluate changes in biomarkers of hypertension, CKD, and inflammation.
- To evaluate the effect of KBP-5074 on subjects' quality of life.
- To evaluate the PK, pharmacodynamics (PD), and PK/PD relationships of KBP-5074.

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 a randomized withdrawal period will evaluate the efficacy, safety, and durability of KBP-5074 in adult subjects who have Stage 3b/4 CKD (estimated glomerular filtration rate [eGFR] ≥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). 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 the protocol Appendix 1.

The study will consist of the following periods:

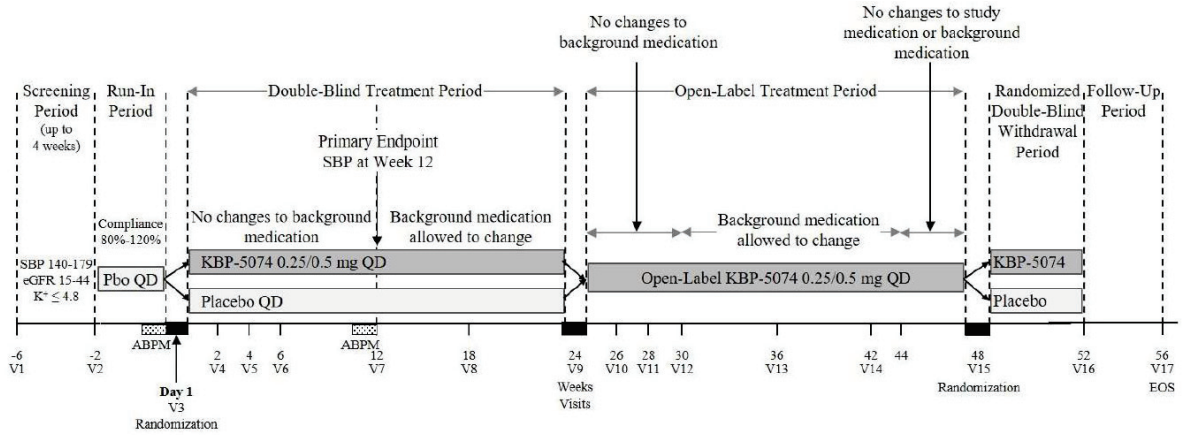
- Pretreatment Phase
  - Prescreening assessment

- Screening Period of up to 4 weeks (full 4 weeks not required if blood pressure, labs, and eligibility are met)
- 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 after Week 4 (Visit 5) (refer to protocol, Table 1, The study drug and background antihypertensive medication titration guidance)
    - 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 (if not already done)
    - 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 at 0.25 mg regardless of study drug dose at the end of the Double-Blind Treatment Period
  - 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 the randomized withdrawal period, 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 to 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 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation 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

3.2 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 QD. Randomization will be stratified to balance enrollment for the following baseline characteristics that may influence safety and/or efficacy evaluations: eGFR (≥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).

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.

3.3 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. After approximately 4 weeks of treatment at the initial dose of study drug, subjects who meet all the Up-Titration Safety Criteria (SBP >120 mm Hg, decrease in SBP from baseline to Week 4 or from previous visit after Week 4 is <30 mm Hg, serum potassium <4.8 mmol/L, decrease

from baseline in eGFR is <30 mL/min/1.73 m2, 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.

3.4 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) not otherwise involved with study conduct will be established to oversee safety and futility evaluation in this study. The IDMC will provide guidance to KBP Biosciences 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. The roles, responsibilities, and membership of the IDMC and study team along with the safety data review schedules will be described in a separate IDMC charter.

3.5 Endpoints

3.5.1 Efficacy Variables

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

A second key endpoint to assess durability of the effect of KBP-5074 is change in seated trough cuff SBP from Week 48 to Week 52.

The key secondary efficacy endpoints 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.

UACR

Urinalysis is assessed 3 times per visit. UACR will be determined 3 times at each visit from first morning void urine samples collected on 3 consecutive days. For the analyses of UACR, the 3 measurements at one visit will be combined. The geometric mean of the available measurements will be used for the analysis.

If a scheduled UACR measurement is missing or invalid and an additional unscheduled measurement was performed instead, this unscheduled measurement will be used to determine the UACR, if the measurement was within 14 days after the last scheduled measurement. If all three scheduled assessments are missing or invalid and unscheduled assessments have been performed, then these will be used for analysis if performed within 1 month before or after the scheduled visit. For the day of last dose of study drug, only unscheduled assessments within 3 days after last study drug intake will be considered. For Visit 1 (Day 1), only measurements known to be taken prior to or within 3 hours of first intake of study drug will be considered.

3.5.2 Safety Variables

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

Safety endpoints 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 from baseline to Week 12, Week 24, and Week 48 by central laboratory results;
- Incidence of sustained decreases in eGFR of ≥30% from baseline by central laboratory results (an eGFR decrease of ≥30% from baseline will be considered sustained if the eGFR 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 from Week 48 to Week 52 by central laboratory results.

3.6 Exploratory Variables

Exploratory endpoints 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 (MAP), 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 medications;
    - 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 protocol Table 13. The final 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).

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the Clinical Study Report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

4.2.1 Baseline and Study Day

'First Dosing Date' is defined as the first administration after randomized at Day 1 of the Double-Blind Treatment Period.

'Baseline' is defined as the last non-missing measurement before the first dosing day of study drug unless otherwise stated. In case of an assessment on the same date as the first dosing day (and only the date for that assessment is available), it will be assumed the assessment was done before study drug administration.

'Study Day' will be calculated relative to the date of first dose of study drug. For subjects who have been randomized but not treated with study drug, the randomization date will be used in the calculation.

- When assessment/event date is prior to first dosing date, then Study Day = First Dosing Date – Assessment/Event Date.
- When assessment/event date is equal or after first dosing date, then Study Day = Assessment/Event Date – First Dosing Date + 1.

The baseline for Randomized Double-Blind Withdrawal Period analyses is defined as the last non-missing measurement before the first dosing of Randomized Double-Blind Withdrawal study drug. In most cases, this will be the Week 48 measurement. In case of an assessment on the same date as the first dosing day of the Randomized Double-Blind Withdrawal drug (and only the date for that assessment is available), it will be assumed the assessment was done before study drug administration.

4.2.2 Descriptive Statistics

For descriptive summaries, only observed data will be included, i.e., missing values will not be explicitly imputed unless otherwise specified.

Continuous data will be summarized in terms of the number of observations available, mean, standard deviation (SD), minimum, median, first (Q1) and third (Q3) quartiles and maximum, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean (arithmetic and geometric), median, first quartile, third quartile, and geometric mean ratio (GMR) will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n (the number of observations with non-missing values) as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as '<0.001'.

Confidence intervals (CI) will be presented to one more decimal place than the raw data.

Values in raw data that are in the form "<X", "≤X", ">X", or "≥X" will be converted to the value "X" in the analysis database for analysis purposes.

4.2.3 Presentation of Treatment Groups

All summary tables for most analysis populations during the Double-Blind Treatment Period will be presented by treatment group based on the assignment obtained at randomization (Visit 3) (i.e. KBP-5074-QD or Placebo QD). All summary tables for the Randomized Withdrawal Population during the Randomized Double-Blind Withdrawal Treatment Period will be presented by treatment group based on the assignment obtained at re-randomization (Visit 15). All summaries for the Safety Population during the Double-Blind Treatment Period will be presented by treatment group based on the study drug the subject actually received. In the case a subject received both KBP-5074 QD and Placebo QD during the Double-Blind Treatment Period, then a subject will be associated with the study drug received the most, or in the case of a tie, the treatment they were randomized to.

For summary tables that show data during the Open-Label Treatment Period, a subject will be associated with the treatment sequence from Double-Blind to Open-Label periods and will be displayed as: KBP-5074 QD → KBP-5074-QD and Placebo QD → KBP-5074-QD.

Note that KBP-5074 dose levels will be pooled for analysis, so that regardless of up-titration or down-titration within a treatment group, data collected while a subject received KBP-5074 0.25 mg or KBP-5074 0.5 mg will be summarized in the KBP-5074 treatment group.

4.2.4 Study Analysis Windows

Since the actual visit for a subject may not exactly coincide with their scheduled visit date, the actual visit date is mapped to the study analysis visit as follows based on the type of data. The midpoint between two scheduled visits will determine which scheduled visit the data point will be used for and will be done on a per-parameter basis.

If more than one actual visit (including the unscheduled visits) falls within the same defined window, the visit closest to the target day with non-missing data will be considered for analysis. If two actual visit dates are at the same distance from the target day, the later visit with non-missing data will be considered for analysis. The rules above for selecting a visit from multiple ones within the same visit window are not applicable to retest values of laboratory data. If the laboratory measurement is a retest, the retest value will be chosen.

Note that UACR measurements have specific rules for analysis as described in Section 3.5.1.

4.3 Software

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment.

4.4 Study Subjects

4.4.1 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion.

The following summaries will be provided for the Randomized Population (Section 4.5):

- Subjects screened
- Screen failure and the reason for screen failure
- Subjects enrolled (subjects entered in the Run-In Period)

The following summaries will be provided by treatment group and overall based on all randomized subjects in the Double-Blind Treatment Period:

- Subjects randomized
- Subjects treated/not treated
- Subjects who entered the Open-Label Treatment Period
- Subjects who entered the Randomized Double-Blind Withdrawal Period
- Subjects completed/withdrawn from each study treatment period and the reason for withdrawal; note that adverse events coded to hyperkalemia that lead to withdrawal of study treatment will be displayed
- Subjects who entered the Follow-Up Period
- Subjects completed/withdrawn from study and the reason for withdrawal; note that adverse events coded to hyperkalemia that lead to withdrawal of study will be displayed

Subject disposition may also be summarized by country, and study site, if appropriate. A consort diagram that shows the allocation of study treatment and reasons for discontinuation and exclusion from analysis within each treatment group will be provided.

The following by-subject listings will be provided for the Randomized Population:

- Subjects screened with screen failure flag and the reason for screen failure.
- Withdrawal/Study completion details, including reason for withdrawal.

4.4.2 Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the study design or procedures defined in the protocol. A major 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.

A summary of the number and percentage of subjects with a **major** protocol deviation by treatment group and overall and by type of deviation will be provided for the ITT Population.

A summary of the number and percentage of subjects with a **major** Coronavirus Disease 2019 (COVID-19) related deviation by treatment group and overall and by type of deviation will be provided for the ITT Population.

A by-subject listing of protocol deviations with major/minor categories will be provided for the ITT Population.

4.4.3 Randomization Strata

The following summaries will be generated for randomization into the Double-Blind Treatment Period:

- A summary of the strata based on the randomization system: eGFR (≥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, Europe/Other), by treatment group and overall.
- A cross-tabulation summary of the subject's stratification values based on the eCRF versus the subject's stratification value based on the randomization system, by treatment group and overall.
- A cross-tabulation summary of all strata based on the randomization system: eGFR strata versus baseline SBP strata versus baseline UACR versus geographic region (not done by treatment group).

There will be no summary of randomization strata for the Randomized Double-Blind Withdrawal Period since no factors are used for that randomization.

4.5 Analysis Sets

The study populations 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, had a baseline UACR measurement, had UACR ≥30 mg/g at baseline, and had at least 1 postdose 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 had 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, had a baseline PD/biomarker measurement, and had at least 1 postdose 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 had at least 1 SBP measurement after the Week 48 Visit.

Upon database release, protocol deviation and analysis set outputs will be produced and will be sent to the Sponsor for review. An analysis set classification meeting will be arranged to discuss the outputs and to decide which subjects and/or subject data will be excluded from certain analyses. Decisions made regarding the exclusion of subjects and/or subject data from analyses will be made prior to unblinding and will be documented and approved by the Sponsor.

The following analysis will be provided for the ITT Population:

- A summary of the number and percentage of subjects by treatment group and overall, and corresponding reason of exclusion from each population, for each analysis population.
- A by-subject listing of the Randomized Population and the reason for exclusion from other populations will be provided.

4.6 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by treatment group and overall based on the ITT Population, Safety Population and the Randomized Withdrawal Population. The summaries provided may include the following:

- A summary of demographic variables (age, sex, race, ethnicity and country) by treatment group and overall.
- A summary of baseline characteristics, including height, weight, Body Mass Index (BMI), SBP, DBP, serum potassium, serum creatinine, eGFR, UACR, background antihypertensive medication by treatment group and overall.
- A summary of substance use at Screening, including tobacco and alcohol status, by treatment group and overall.

- A summary of kidney disease and hypertension, including diabetes mellitus, CKD, hypertension, cerebral vascular accident and/or transient ischemic attacks (TIAs), and peripheral vascular disease.

By-subject listings of disposition, discontinuation, demographic, substance use, randomization strata, and kidney disease and hypertension data will be provided.

4.7 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by Preferred Term (PT) and System Organ Class (SOC), treatment group, and overall. Separate summaries will be provided for conditions occurring prior to screening and conditions ongoing at screening.

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

4.8 Concomitant Medication

All medications/therapy will be coded using the World Health Organization Drug Dictionary (WHO-DD) and will be classified by Anatomical Therapeutic Chemical (ATC) Classification. Medication data will be summarized based on Safety Population.

4.8.1 Prior and Concomitant Medication

Prior and concomitant medication start and stop dates will be compared to the date of first dose of study drug to allow medications to be classified as either Prior only or Concomitant only. Medications starting after the study completion/withdrawal date will be listed but will not be classified or summarized.

Medications that stop prior to the date of first dose of study drug will be classified as 'Prior' only. Medications will be classified as Concomitant if they have a start date on or after the date of first dose of study medication. In addition, medications start prior to first dose of study drug and stop after first dosing date are classified as Concomitant medication as well. Imputation of partial dates of medication records for classification of 'prior' and 'concomitant' is described in Appendix 1, Section 6.2.1.

The summaries provided may include the following:

- Prior medication/therapy and concomitant medications/therapy will be summarized by Anatomical Therapeutic Chemical (ATC) classification level 4 and preferred term by treatment group and overall. Additionally, a summary table by each period will be provided. If the ATC level 4 coding is not available for a PT, the next available lower level ATC code will be used.

By-subject listings of all medication/therapy will be provided with flag of 'prior' or 'concomitant'.

4.8.2 Background antihypertensive medications

Imputation of partial dates of background antihypertensive medications records for classification of each interested period is described in Appendix 1, Section 6.2.2.

- Background antihypertensive medications will be summarized by ATC level 4 and preferred term by treatment group and overall.

- Background antihypertensive medications will be summarized by ATC level 4 and preferred term at several periods (during Run-In Period, 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) by treatment group and overall.
- One of the Exploratory Endpoints is the proportion of subjects who had changes in background antihypertensive medications at period of interest (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).

  Any change of background antihypertensive medications will include decrease or increase in dosing, discontinuation or start of new medications. The baseline background antihypertensive medications change will be defined as the data collected during Run-In Period.
- A by-subject listing of all background antihypertensive medications will be provided.

4.9 Treatment Compliance

Compliance data will be summarized and listed for the Safety Population and the Intent-to-Treat Population. If needed, the summary of compliance data for each study treatment period (Run-In Period, Day 1 to Week 12, Double-Blind Treatment Period, Open-Label Treatment Period, Randomized Double-Blind Withdrawal Period, and Overall Period) will be provided separately.

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).

Treatment duration is defined from first dosing date to end of treatment/discontinuation of treatment; the same rule will used to define treatment duration by study treatment period.

The summaries provided may include the following:

- The compliance will be summarized descriptively by treatment group, dose, and overall.
- A summary of the number and percentage of subjects with category of compliance ‘<80%’, ‘80%-120%’ and ‘>120%’ by treatment group, period and overall will be provided.
- A by-subject listing of treatment compliance will be provided.

4.10 Efficacy Evaluation

4.10.1 Analysis and Data Conventions

This study is designed to test for superiority of KBP-5074 compared to placebo. The null hypothesis for the treatment comparison is that there is no difference between KBP-5074 QD and placebo QD in change of seated trough cuff SBP from baseline to Week 12. The alternative hypothesis is there is a difference. Symbolically, this is expressed as follows:

H(0): μ(KBP-5074) = μ(placebo)

H(1): μ(KBP-5074) $\neq$ μ(placebo)

4.10.1.1 Multi-center Studies

For the summaries and analyses, the term 'Center' will be used to define each investigator site. The data from all centers will be pooled together for analyses and summary statistics.

4.10.1.2 Type 1 Error Rate Control

The overall Type 1 error rate 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 using a gatekeeping procedure.

For the 12 week 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.
- If the null hypothesis for the primary endpoint is rejected, then the **key endpoint** for durability of change in seated trough cuff SBP from Week 48 to Week 52 on the full Randomized Withdrawal Population will be tested at the level of 0.05.

For **the key secondary endpoint** analyses, the following test procedure will be tested with same nominal alpha level (0.05), and will be tested in the following order:

- 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

With the gatekeeping procedure, the secondary endpoints will be tested in a sequential manner and the tests for subsequent secondary endpoints will be performed only if the test for the previous endpoint is significant.

4.10.1.3 Adjustments for Covariates

The primary efficacy analysis will be adjusted for the following baseline covariates:

- Baseline eGFR (≥30 versus <30 mL/min/1.73 m^2) which is calculated as the mean of eGFR at the Screening Visit (Visit 1) and at the start of the Run-In Period (Visit 2) (stratification variable)
- Background antihypertensive medications (3 or more versus fewer than 3)
- Baseline measure of seated trough cuff SBP value

4.10.1.4 Analysis of Covariance (ANCOVA)

An Analysis of Covariance analysis (ANCOVA) will be used to evaluate the primary efficacy endpoint of change from baseline at Week 12 in seated trough cuff SBP and the second key efficacy endpoint of change from Week 48 to Week 52 in seated trough cuff SBP. The change in seated trough cuff SBP will be the outcome variable; treatment, baseline SBP value, baseline eGFR level (≥30 versus <30 mL/min/1.73 m^2), and background antihypertensive medications (3 or more versus fewer than 3) will be included as covariates.

For second key efficacy endpoint of change in seated trough cuff SBP from Week 48 to Week 52, Week 48 visit will be considered as baseline and the randomization assignment at Week 48 will be used as the treatment in the above model.

4.10.1.5 Mixed Model with Repeated Measures (MMRM)

A mixed model with repeated measures (MMRM) will be used as the analysis model to support the primary efficacy endpoint (Section 4.10.2.4), the main analysis model for secondary (Section 4.10.4 and Section 4.10.5) and exploratory endpoints (Section 4.10.6) to evaluate change from baseline in outcome variable with 2 or more follow-up visits. The change from baseline will be outcome variable; treatment, visit, treatment × visit interaction, baseline SBP value, baseline eGFR level (≥30 versus <30 mL/min/1.73 m2), background antihypertensive medications (3 or more versus fewer than 3) will be included as covariates, all nested within visit. In order to allow for model misspecification and heterogeneity of treatment effects in the repeated measures model, a Huber-White sandwich estimator will be used (Huber, 1967). An unstructured covariance matrix may be used; if the unstructured covariance matrix does not converge, a compound symmetry covariance matrix will be used instead.

4.10.1.6 Generalized Linear Mixed Model (GLMM)

A generalized Linear Mixed Model (GLMM) will be used as the analysis model for categorical exploratory endpoints with 2 or more follow-up visit (Section 4.10.6). The model will include treatment, visit, treatment × visit interaction, baseline SBP value, baseline eGFR level (≥30 versus <30 mL/min/1.73 m^2), and background antihypertensive medications (3 or more versus fewer than 3) as covariates. An unstructured covariance matrix may be used; if the unstructured covariance matrix does not converge, a compound symmetry covariance matrix will be used instead.

4.10.1.7 Logistic Regression Model

A logistic regression model will be used as the analysis model for categorical exploratory endpoints with only one follow-up visit (Section 4.10.6). The model will include treatment, baseline SBP value, baseline eGFR level (≥30 versus <30 mL/min/1.73 m^2), and background antihypertensive medications (3 or more versus fewer than 3) as covariates.

4.10.1.8 Handling of Dropouts and Missing Data

Every reasonable effort will be made to collect all data. However, despite best efforts, some data may be missing or incomplete. All missing or partial data will be presented in the relevant data listings as reported on the eCRF.

The main analysis of the primary efficacy endpoint, Retrieved Dropout-Based Multiple Imputation (MI), will include all subjects from the ITT Population. Imputation of missing values will be based on the data retrieved from the subjects who prematurely discontinue study treatment but have the measurement collected for the endpoint.

To explore plausible assumptions about missing data, the following sensitivity analyses will be performed: MI assuming Missing at Random (MAR), Control Based MI assuming Missing Not at Random (MNAR) and tipping point analysis.

Multiple Imputation (MI)

For each analysis where MI is performed, 1000 imputed datasets will be created and missing values for baseline covariates that will be used in the imputation model for Retrieved Dropout-Based MI (Section 4.10.1.8.1), MI assuming MAR (4.10.1.8.2) and Control-Based MI assuming MNAR (Section 4.10.1.8.3) will be imputed first for all subjects in the ITT Population through MI assuming MAR using a Markov Chain Monte Carlo (MCMC) approach. The covariates will be listed in the following order: baseline eGFR level (log-transformed), baseline age (continuous), gender, region (North America, Asian including China, Hong Kong and Taiwan, and other Asian Countries, Europe/Other), BMI (continuous), history of diabetes (yes/no), alcohol use (current/former/never), tobacco use (current/former/never), history of hypertension (yes/no), baseline heart rate (continuous), and background antihypertensive medication (3 or more versus fewer than 3), baseline SBP (continuous).

4.10.1.8.1 Retrieved Dropout-Based MI – (Main Analysis of the Primary Efficacy Endpoint)

Imputation steps:

Imputation of missing Week 12 data will be done within 4 groups of participants defined by treatment arm and treatment status at Week 12, i.e., whether participants at Week 12 (i) are still on study treatment or (ii) have discontinued study treatment. The approach is similar to the method described by McEvoy (2015):

For each treatment arm and treatment status, an analysis of covariance model (ANCOVA) with baseline seated trough SBP, last observation on treatment and time since last observation on treatment (in weeks) as covariates will be used to impute 1000 values for each participant with missing Week 12 data. As such only participants who have discontinued study treatment and completed Week 12 will be used to inform the imputation of missing data for participants who have discontinued study treatment.

If the observed data for participants who have discontinued study treatment is too sparse to fit the above defined imputation model by treatment group, then the imputation of subjects off treatment will be done based on available placebo subjects. This corresponds to assuming that the treatment effect is reduced to the placebo effect by the time of originally planned end of treatment.

Analysis Step: Once all missing values have been imputed, analysis of covariance model (ANCOVA) as described in Section 4.10.1.4**.** will be performed for each imputed dataset. The analysis result for all imputed datasets will be combined with Rubin's rules via PROC MIANALYZE (SAS Version 9.4 or newer) to provide the adjusted least square (LS) mean, standard error (SE), and the two-sided 95% CI for each treatment group, and the LS mean of the difference, the 95% CI of the difference, and p-value for comparing the KBP-5074 and placebo group.

4.10.1.8.2 Multiple Imputation Assuming MAR – Sensitivity Analysis #1

This approach will be used as sensitivity analysis 1; however, in case the main analysis, retrieved dropout-based MI may not work out due to limited number of dropout subjects available for imputation, this approach will be used as the main analysis of the primary efficacy endpoint.

Imputation Step:

Missing outcome variables at post-baseline visit are assumed to follow the efficacy from the subjects within the same treatment group in the following 2 steps:

[1]. Non-monotone missing values at post-baseline visits will be imputed to produce imputed datasets with a monotone missing pattern:

Non-monotone missing values at post-baseline visits will be imputed within the same treatment group assuming MAR using an MCMC approach; the imputation model will include the covariates in the following order: the same baseline covariates as listed in Imputation Step [1], SBP at Week 2 (Visit 3), SBP at Week 4 (Visit 4), …, SBP at Week 12 (Visit 7).

[2]. Monotone missing values are imputed sequentially for each visit:

The remaining missing values in the imputed datasets from Imputation Step [2] are assumed to have the same efficacy as those who prematurely discontinue the study treatment or experienced change in background antihypertensive medication but have data collected afterwards.

A regression model will be used to sequentially impute monotone missing values at each visit from the imputed datasets as produced from Imputation Step [2]:

the outcome variable at Visit [X] = the same covariates from [1] + outcome variable at Visit [X-1] + outcome variable at Visit [X-2] + … + Outcome variable at baseline **Model 1**

The outcome variable at a particular visit will be included as the response variable in the regression model; the same baseline covariates from Imputation Step [1] + the outcome variables from all previous visit(s) prior to the specific visit will be included as the explanatory variable in the imputation model.

The missing outcome variable at the first post-baseline visit will be imputed first, followed by the second post-baseline visit, until missing values from all post-baseline visits are imputed.

Analysis Step: Once all missing values have been imputed, analysis of covariance model (ANCOVA) as described in Section 4.10.1.4 will be performed for each imputed dataset. The analysis results for all imputed datasets will be combined with Rubin's rules via PROC MIANALYZE. The adjusted LS mean, SE, and the two-sided 95% CI for each treatment group, and the LS mean of the difference, the 95% CI of the difference, and p-value will be presented.

4.10.1.8.3 Control Based MI Model Assuming MNAR – Sensitivity Analysis #2

A control-based MI (Ratitch and O'Kelly, 2013) will be used as the second sensitivity analysis.

Imputation Step:

Missing outcome variables at post-baseline visit are assumed to have similar efficacy from subjects in the control group.

Missing values at each post-baseline visit from the imputed datasets as produced previously will be imputed sequentially within all subjects from the control group using Model 1 from Section 4.10.1.8.2.

The outcome variable at a particular visit will be included as the response variable in the regression model; the same baseline covariates from imputation step from Section 4.10.1.8.1 and the outcome variables prior to the response visit will be included as the explanatory variable in the imputation model.

The missing outcome variable at the first post-baseline visit will be imputed first within subjects from the control group, followed by the second post-baseline visit, until missing values from all post-baseline visits are imputed.

Analysis Step: Once all missing values have been imputed, analysis of covariance model (ANCOVA) as described in Section 4.10.1.4 will be performed for each imputed dataset. The analysis results for all imputed datasets will be combined with Rubin's rules via PROC MIANALYZE. The adjusted LS mean, SE, and the two-sided 95% CI for each treatment group, and the LS mean of the difference, the 95% CI of the difference, and p-value will be presented.

4.10.1.9 Multiple Comparisons/Multiplicity

The IDMC will meet to review data when approximately 10% of subjects are enrolled, when 25%, 50%, 75%, and 100% of subjects complete their Week 12 Visit, when 50% of subjects complete their Week 24 Visit, and when 100% of subjects complete or discontinue the study. The details of the adjustment of Type I error will be described in the related Type 1 Error Control section (Section 4.10.1.2) and the Interim Analyses section (Section 4.10.1.10).

4.10.1.10 Interim Analyses

IDMC safety monitoring

This study will conduct at least seven interim analyses to support IDMC meetings. The IDMC will independently review the safety data and determine if it is safe to continue the study according to the protocol.

For the formal Interim analysis for assessment of lack of efficacy (Futility) after the last subject has completed the Week 12 visit, all subjects will have their primary efficacy endpoint assessed. The data collected at this time will be cleaned, locked, unblinded, and analyzed for the primary and some key secondary efficacy endpoints. The analysis of these interim data which is used to assess lack of efficacy will be carried out by designated unblinded Biostatistics and Programming teams at Parexel (a CRO), the same teams already contracted to support the IDMC meetings for this study. 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 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. After the interim analysis, the review and conduct of the study will continue in a blinded manner by study team members who are blinded to all study data until all subjects have completed the study. The process of the analysis will be documented in the study IDMC charter.

4.10.1.11 Examination of Subgroups

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

- Age (18 to 45 years, >45 to ≤65 years, >65 to ≤75 years, and >75 years)
- Region (North America, Asia (Overall, China/Hong Kong/Taiwan), Europe/Other
- Sex (Male, Female)
- Race (White, Black, Asian, Other)

- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Baseline BMI (≤30 mg/kg^2, >30 mg/kg^2)
- Baseline Serum Potassium Value (≤4.5 mmol/L and >4.5 mmol/L)
- Baseline eGFR Value (≥30 and ≤44 mL/min/1.73 m^2, ≥15 and <30 mL/min/1.73 m^2)
- Diabetic (Yes/No)
- Baseline Proteinuria (UACR >300 mg/g, UACR ≥30 and ≤300 mg/g, UACR <30 mg/g)
- Baseline systolic blood pressure (≥160 mm Hg or < 160 mm Hg)
- Background Antihypertensive Medication Change (Yes/No)
- Number of Background Antihypertensive Medications (3 or more versus fewer than 3)

If, however, the total number of subjects in a subgroup category is <15, the analysis for that level of the subgroup will not be performed.

4.10.2 Primary Efficacy Variable – seated trough cuff SBP

A descriptive summary of the primary efficacy endpoints will be provided following the same strategy as described in section 4.2.2: observed data from all subjects in the ITT Population will be included; missing values will not be explicitly imputed for descriptive summaries.

- A summary of SBP values and change from baseline values at Week 12 by treatment group for the ITT Population will be presented.
- A line plot of the observed change in SBP values from baseline to Week 12 will be provided for the ITT Population. Mean values with SE bars will be presented.
- A line plot of change in SBP values from baseline to Week 12 using ANCOVA model will be provided for the ITT Population. LS mean values with SE bars will be presented.

A by-subject listing of SBP data will be provided.

4.10.2.1 Main Analysis of Primary Efficacy Endpoint at Week 12

Primary Efficacy Endpoint and Estimand

The primary estimand is the mean difference between KBP-5074 QD 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. 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, or background antihypertensive medication changes after randomization and up to Week 12. The intercurrent events will be handled using a treatment policy strategy where the value for the variable of interest is used regardless of the occurrence of the intercurrent events. The absence of a seated trough cuff SBP measurement on or before Week 12 following these subjects' treatment discontinuation, or background antihypertensive medication change will be imputed by multiple imputation and using the information from retrieved dropouts (Section 4.10.1.8.1).

Intercurrent Event	**Strategy for Primary Estimand**
Discontinuation of study treatment up to Week 12	Treatment policy

Change in background antihypertensive medications prior to Week 12	Treatment policy

Treatment policy: data will be used regardless of occurrence of the intercurrent events.

The retrieved dropout-based MI will be carried out following the steps as described in Section 4.10.1.8.1. The adjusted LS mean, SE, and the two-sided 95% CI for each treatment group and the LS mean difference, the corresponding 95% CI of the difference, and p-value from analysis step as described in Section 4.10.1.8.1 will be presented.

Other sensitivity analyses for the primary efficacy endpoint at Week 12 may be explored to evaluate plausible missing data assumptions, i.e., MI assuming MAR (Section 4.10.2.2), Control-based MI assuming MNAR (Section 4.10.2.3).

4.10.2.2 MI Assuming MAR — Sensitivity Analysis 1

If the retrieved dropout-based MI cannot be performed because of limited number of dropout subjects available for imputation, MI assuming MAR will be considered as the main analysis of the primary efficacy endpoint. Otherwise, MI assuming MAR will be considered as a sensitivity analysis.

Missing values of seated trough cuff SBP on or before Week 12 will be imputed within each treatment group assuming MAR as described in Section 4.10.1.8.2.

The adjusted LS mean, SE, and the two-sided 95% CI for each treatment group and the LS mean difference, the corresponding 95% CI, and p-value for comparing the KBP-5074 and placebo group produced from PROC MIANALYZE (Section 4.10.1.8.1) will be presented.

4.10.2.3 Control-Based MI Assuming MNAR — Sensitivity Analysis 2

The permanent monotone missing values of seated trough cuff SBP measurement on or before Week 12 are assumed MNAR; i.e., the missing values are imputed together with the data from subjects in the control group as described in Section 4.10.1.8.3.

The adjusted LS mean, SE, and the two-sided 95% CI for each treatment group and the LS mean difference, the corresponding 95% CI of the difference, and p-value for comparing the KBP-5074 and placebo group produced from PROC MIANALYZE (Section 4.10.1.8.1) will be presented.

4.10.2.4 Tipping Point Analysis – Sensitivity Analysis 3

In line with International Conference on Harmonization (ICH) E9 (R1), a tipping point multiple imputation sensitivity analysis will be performed investigating the robustness of the conclusions made on the basis of the primary analyses towards the impact of missing data. A two-dimensional tipping point sensitivity analysis will be used to address the assumption of MAR within imputation groups. Subjects with missing data will be assumed to have a worse outcome in the KBP-5074 treatment arm and a better outcome in the placebo arm compared to the imputations in the primary analysis.

Missing data will first be imputed as in the primary analysis. Secondly, penalties will be added to or subtracted from the imputed week-12 values. The approach is to gradually increase these penalties independently in the treatment arms until the confirmed seated trough SBP conclusion from the primary analysis is changed. For each hypothesis tested, the values of the penalties that changes the conclusion will be used to evaluate the robustness of the primary analysis results.

4.10.2.5 MMRM for Additional Estimand – Supplemental Analysis

The additional estimand of this analysis is the mean difference between KBP-5074 QD and the placebo group of the 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 if all subjects had remained on trial treatment without use of rescue medication. The set of intercurrent events for this estimand consists of discontinuation of study treatment up to Week 12, or background antihypertensive medications increase after randomization and up to Week 12. The intercurrent events will be handled using a hypothetical policy strategy where the value for the variable of interest is only included in the analysis if collected before the occurrence of the intercurrent events. The endpoint will be analyzed in a MMRM model as described in Section 4.10.1.5.

Intercurrent Event	Strategy for Primary Estimand
Discontinuation of study treatment up to Week 12	Hypothetical strategy
Increase in background antihypertensive medications prior to Week 12	Hypothetical strategy

Increase in background antihypertensive medications prior to Week 12 is defined as adding or increase in dose for any antihypertensive medication.

4.10.3 Key Endpoint for Durability at the End of Randomized Withdrawal Period

Key Endpoint for Durability and Estimand

The key estimand for durability is the mean difference between KBP-5074 QD and the placebo group in change in seated trough cuff SBP from Week 48 to Week 52 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 key estimand for durability will be used for the analysis of the key endpoint for durability. The treatment condition and population of the estimand for this key endpoint for durability is the same as for the primary endpoint. The set of intercurrent events for this estimand only consists of discontinuation of study treatment from Week 48 to Week 52. Since this analysis is performed on the Randomized Withdrawal Population, by definition the subject must have been randomized at Week 48 (i.e. had a qualifying SBP for the visit) and have at least one SBP after the Week 48 visit. The intercurrent events will similarly be handled using the treatment policy strategy. The absence of any key endpoint for durability measurement at Week 52 following these subjects' withdrawal will be imputed by using the ET SBP as the value at Week 52.

Missing data will be imputed using retrieved dropout-based MI approach, following the similar procedure described in Section 4.10.1.8.1, except that ANCOVA model as described in Section 4.10.1.4 will be used as the imputation and analysis model, where Week 48 will be considered as baseline for this analysis.

The adjusted LS mean, SE, and the two-tailed 95% CI for each treatment group and the LS mean difference, the corresponding 95% CI, and p-value for comparing the KBP-5074 and placebo groups will be presented.

Supportive Analyses of Key Endpoint for Durability

If the retrieved drop-out based multiple imputation cannot be performed because of availability of only a limited number of dropout subjects, MI assuming MAR following the imputation procedure described in Section 4.10.1.8.2, will be considered the main analysis.

To further evaluate the impact of different assumptions concerning missingness, control-based multiple imputation assuming MNAR will be performed following Section 4.10.1.8.3.

4.10.4 Key Secondary Efficacy Endpoints

Descriptive summary of the key secondary efficacy endpoints following Section 4.2.2 will be provided.

The key secondary efficacy endpoints for the study are:

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

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 primary efficacy analysis as described in 4.10.1.8.1.

4.10.5 Other Secondary Efficacy Endpoints

The following summaries and listings related to SBP/DBP will be provided based on the ITT Population; UACR-related endpoints will be based on the UACR Population:

- A summary of change in trough cuff SBP from baseline to Week 48.
- A summary of change in trough cuff 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.
- Based on the following UACR baseline levels, a summary of mean changes and percentage changes in UACR from baseline to Week 12, Week 24, and Week 48 will be provided for the UACR Population in the following groups:
  - Subjects with microalbuminuria (defined as UACR ≥30 and <300 mg/g) at baseline
  - Subjects with macroalbuminuria (defined as UACR ≥300 mg/g) at baseline

The following endpoints will be analyzed for the Randomized Withdrawal Population:

- A summary of change in trough cuff DBP from Week 48 to 52.
- Based on the following UACR baseline level, a summary of mean changes and percentage changes in UACR from Week 48 to Week 52 will be provided in the Randomized Withdrawal Population by following group:
  - Subjects with UACR ≥30 mg/g at baseline
  - Subjects with microalbuminuria (defined as UACR ≥30 and <300 mg/g) at baseline

- Subjects with macroalbuminuria (defined as UACR ≥300 mg/g) at baseline

4.10.6 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints will be provided based on the ITT Population.

exploratory data with 2 categories will be summarized and analyzed by using a logistic regression model with factors such as baseline eGFR group and baseline SBP groups. Categorical exploratory data with 3 or more categories will be summarized and analyzed by either a multinomial regression model or an ordinal regression model, as appropriate. Changes in SBP, DBP, UACR, and eGFR at each visit will be summarized in box plots.

- For the variables based on ambulatory blood pressure monitoring (ABPM), descriptive statistics summarizing change in the following variables from baseline to Week 12 by treatment group will be provided:
  - 24-hour mean SBP and DBP
  - daytime mean SBP and DBP
  - nighttime mean SBP and DBP
  - mean arterial pressure (MAP)
  - heart rate

  Only observed data will be used for the summary and analyses of ABPM parameters. No imputation will be performed for missing data. A by-subject listing of ABPM variables will be provided.

  The following will also be provided:

- Line plots of change in seated trough cuff SPB and DBP, UACR, Serum Potassium, eGFR and ABPM for all visits through Week 48, displayed by treatment group for the ITT Population.
- A line plot of change in DBP values from baseline to Week 12 using MMRM estimates will be provided for the ITT Population. LS mean values with standard error bars will be presented.
- A summary of the number and percentage 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, by treatment group.
- A summary of the number and percentage of subjects who achieve the target goal of seated trough cuff SBP ≤130 mm Hg at Week 12, Week 24, and Week 48, by treatment group.
- A summary of the number and percentage of subjects who have a decrease from baseline in seated trough cuff SBP ≥10 mm Hg at Week 12, Week 24, and Week 48, by treatment group.
- For subjects with DBP ≥90 mm Hg at baseline, a summary of individual DBP values and change from baseline values will be provided at Week 12, Week 24, and Week 48, by treatment group.
- For subjects with DBP ≥90 mm Hg at baseline, a summary of individual SBP values and change from baseline values will be provided at Week 12, Week 24, and Week 48, by treatment group.

- A summary of the number and percentage of subjects who have an increase in seated trough cuff SBP ≥5 mm Hg from Week 48 to Week 52, by treatment group based on Randomized Withdrawal Population.
- A summary of the number and percentage of subjects who have an increase in seated trough cuff SBP ≥10 mm Hg from Week 48 to Week 52, by treatment group based on Randomized Withdrawal Population.
- A summary of the number and percentage of subjects who achieve the target goal of seated trough cuff SBP ≤130 mm by Week 48, by treatment group. This endpoint will also be analyzed using the following subgroups:
  - Without study drug titration or change in background antihypertensive medications;
  - Without study drug titration but with change in background antihypertensive medications;
  - With study drug titration but no change in background antihypertensive medications;
  - With study drug titration and change in background antihypertensive medications.
- Summaries of the mean change and mean percentage change in UACR from Baseline to Weeks 12, 24, and 48 will be analyzed using the following subgroups:
  - Region (North America, Asia (Overall, China/Hong Kong/Taiwan), Europe/Other)
  - Race (White, Black, Asian, Other)
  - Diabetic (Yes/No)
  - Baseline Proteinuria (UACR >300 mg/g, UACR 30-300 mg/g, UACR <30 mg/g)
- For the evaluation of the long-term hypertensive effect of KBP-5074, 2 summaries will be provided:
  - Time to up-titration of study drug will be evaluated over 12 and 24 weeks.
  - Time to change in background antihypertensive medications will be evaluated over 12 and 24 weeks.

These exploratory endpoints are described in Sections 3.6.

- Summaries to evaluate changes in biomarkers of hypertension, CKD, and inflammation.
- Summaries to evaluate effect of KBP-5074 on subject quality of life.
- Summaries to evaluate the PK, PD, and PK/PD relationships of KBP-5074.

4.11 Safety Evaluation

All safety summaries and analyses will be based on the Safety Population.

4.11.1 Extent of Exposure

Exposure data will be summarized and listed for the Safety Population. Exposure data will be summarized by study treatment period (Double-Blind Treatment Period, Open-Label Treatment Period, Randomized Double-Blind Withdrawal Period).

In general, treatment duration for each treatment group and overall will be calculated as follows:

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

- A summary of treatment duration will be provided by treatment group and overall for each study period.
- The titration status (yes/no, up- or down-titration), regardless of actual or sham titration, will be summarized by treatment group, visit, and overall for each study period.
- Exploratory Endpoint: A summary of the number and percentage of subjects experiencing up-titration and down-titration will be summarized at specific periods (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), by treatment group and overall.
- A by-subject listing of drug administration and drug accountability will be provided.

4.11.2 Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by Preferred Term (PT) and System Organ Class (SOC).

AEs will be classified as pre-treatment AEs (PTAEs) and TEAEs, according to the period of occurrence, as follows:

- PTAEs: all AEs onset before the first dose of study drug.
- TEAEs:

  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.

  Drug related TEAEs, defined as any TEAE with Possibly Related, Probably Related, Related or missing relationship to study drug as assessed by the investigator.

  If needed, TEAEs will be summarized by period, including Double-Blind Treatment Period, Open-Label Treatment Period, Randomized Double-Blind Withdrawal Period, Follow-Up. Where AE dates are missing or partially missing, the dates will be imputed for further judgment about whether it is or is not a TEAE. The TEAE by each period of interest will be based on imputed dates.

  To evaluate dose related safety events, TEAE and SAE will also be summarized by dose group when the event occurs.

  The imputation rule is described in Appendix 6.2.3.

Any TEAE with missing relationship to study drug will be imputed to be drug-related. TEAEs related to COVID-19 will be identified by both standard MeDDRA queries and a review by the Parexel Safety team.

The number and the percentage of subjects reporting TEAEs, treatment-emergent SAEs, severe TEAEs, TEAEs leading to discontinuation and TEAEs leading to death will be presented within each study period by treatment group, along with the number of events occurring. Only TEAEs will be included in the summary tables. Individual data listings will include all AEs recorded; a separate listing will be provided for treatment-emergent SAEs.

For all TEAE tables, a subject will be counted for the most severe event only once for each SOC and each PT, even if the subject reported more than one event under each subcategory. All TEAEs will be summarized by treatment group and overall within each study period. Unless specified otherwise, TEAE tables will be ordered in terms of decreasing number of subjects for SOC and then PT within the SOC in the Treatment group then by Placebo group, and then alphabetically for SOC and PT within the SOC if the frequency is tied.

For each subject and each adverse event, the severity recorded will be attributed and used in the by-severity summaries. Similarly, the relationship (related to treatment) will be attributed and used in the by- relationship summaries.

An overview table will summarize the number and percentage on subject level for each study period of the following categories:

- Any TEAE
- Any TEAE related to study drug
- Any severe TEAE
- Any severe TEAE related to study drug
- Any TEAE with outcome of death
- Any fatal TEAE related to study drug
- Any serious TEAE
- Any non-serious TEAE
- Any serious TEAE related to study drug
- Any TEAE leading to discontinuation of treatment
- Any TEAE leading to discontinuation of study
- Any TEAE leading to study drug reduced
- Selected TEAEs (including hyperkalemia, hypertension, hypotension, renal toxicity, major adverse cardiac event, hepatotoxicity and decreases in eGFR)

TEAE summaries will present the number and percentage of subjects reporting at least one TEAE for each study period. The following summaries will be provided by study period:

- TEAEs by SOC and PT
- TEAEs by SOC and PT, by severity
- TEAEs by relationship to study drug, by SOC and PT
- TESAEs by SOC and PT

- TESAEs by SOC and PT, by severity
- TESAEs by relationship to study drug by SOC and PT
- TEAEs leading to discontinuation of treatment, by SOC and PT
- TEAEs leading to discontinuation of study, by SOC and PT
- TESAEs leading to discontinuation of treatment, by SOC and PT
- TESAEs leading to discontinuation of study, by SOC and PT
- TEAEs leading to death, by SOC and PT
- TEAEs related to study drug and leading to death, by SOC and PT
- TEAE related to covid-19 by SOC and PT
- Selected TEAEs by SOC and PT
- TEAEs by SOC, PT, and eGFR status at baseline (<30 mL/min/1.73 m^2 and ⩾30 mL/min/1.73 m^2)
- TESAEs by SOC, PT, and eGFR status at baseline
- Selected TEAEs by SOC, PT and Age Group (<75 years, ≥75 years)
- Selected TEAEs by SOC, PT and eGFR status at baseline

The following by-subject AE listings will be provided:

- AEs
- TESAEs
- TEAEs leading to discontinuation of treatment
- TEAEs leading to discontinuation of study
- TEAEs leading to death
- Selected TEAEs

The listings will include subject identifier, age, sex, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, severity, seriousness, action taken, outcome and relationship.

4.11.3 Deaths, Serious Adverse Events, and Other Significant Adverse Events

For deaths, the summaries provided may include the following:

A summary of the number and percentage of deaths during the study, by treatment group by study period (overall and related to study drug)A by-subject listing of all deaths that occurred during the study will be provided.

A summary of deaths and treatment discontinuations related to COVID-19 will be provided.

For serious adverse events, and other significant adverse events, please refer to Section 4.11.2.

4.11.4 Clinical Laboratory Evaluation

For clinical laboratory parameters (hematology, serum chemistry, coagulation, viral serology, urinalysis, and other evaluations), raw values at each scheduled visit, change from baseline at each post-baseline visit, shift from baseline and shift from reference range will be summarized by study period using descriptive statistics or frequency tabulations. No statistical hypothesis testing will be performed.

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.

All values outside the clinical reference ranges will be flagged in the data listings. Abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings. Quantitative laboratory assessment reported as '<X', or '>X', i.e. above the upper limit of quantification, will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as '<X' or '>X' in the listings.

The following analysis will be provided:

- For continuous laboratory variables, a summary of individual values and change from baseline values will be provided at each scheduled visit using standard unit.
  - A summary of Week 52 values and change from Week 48 values will be provided using standard unit based on Randomized Withdrawal Population as well.
- Shift tables will be presented by category of 'Normal', 'Abnormal - Low', 'Abnormal - High' at each scheduled visit for select laboratory parameters (chemistry and hematology), by treatment group and study period.
- A summary of the number and percentage of subjects with level of serum potassium '>5.0 and <5.6 mmol/L', '≥5.6 and <6.0 mmol/L', and '≥6.0 mmol/L' at each scheduled visit, by treatment group and overall, study period and eGFR status at baseline.
  - Additional summary tables for serum potassium frequencies will be presented for diabetes status (Yes/No) at baseline and UACR status (<30 mg/g and ≥30 mg/g) at baseline.
- A summary of the number and percentage of subjects experiencing sustained eGFR decreases from baseline ≥30% (an eGFR decrease of ≥30% from baseline will be considered sustained if the eGFR reduction is still ≥30% from baseline at least 4 weeks after the initial measurement), by treatment group, study period and eGFR status at baseline.
- A summary of the number and percentage of subjects experiencing eGFR decreases from baseline <30%, ≥30%, <40%, % ≥40%, <50%, and ≥50% by treatment group, study period and eGFR status at baseline.
  - Additional summary tables for eGFR decreases will be presented for diabetes status (Yes/No) at baseline and UACR status (<30 mg/g and ≥30 mg/g) at baseline.
- A shift table between Week 48 and Week 52 will be presented by level of serum potassium '>5.0 and <5.6 mmol/L', '≥5.6 and <6.0 mmol/L', and '≥6.0 mmol/L' by treatment group based on Randomized Withdrawal Population.

- A summary of individual eGFR values at Week 52 and change from Week 48 values will be provided by treatment group and overall based on the Randomized Withdrawal Population.
- A summary of serum creatinine increases from baseline by more than 30% by treatment group, study period, and eGFR status at baseline.
- By-subject listings of laboratory data will be provided.
- A by-subject listing of pregnancy test will be provided.

4.11.5 Vital Signs, Physical Findings and 12-lead electrocardiograms (ECGs)

The following summaries and listings will be provided for vital signs:

- A summary of vital signs (temperature, respiratory rate, heart rate, systolic blood pressure, diastolic blood pressure, weight, BMI, waist circumference) by treatment group, study period and overall.
- By-subject listings of vital signs data will be provided.

The following summaries will be provided for physical examination:

- A summary of the number and percentage of subjects with category of PE 'Normal', 'Abnormal Not Clinically Significant (NCS)', and 'Abnormal Clinically Significant (CS)' at each scheduled visit, by treatment group, study period and overall.
- By-subject listings of physical examination data will be provided.

The following summaries will be provided for 12-lead electrocardiograms (ECGs):

- A summary of ECG variables (heart rate, PR interval, QRS complex, RR interval and QT interval) by treatment group, study period and overall.
- A shift table will be presented by category or overall interpretation of ECG 'Normal', 'Abnormal NCS', and 'Abnormal CS' at each scheduled visit by treatment group and study period.
- By-subject listings of ECG data will be provided.

4.12 Other Analyses

4.12.1 Pharmacokinetics

4.12.1.1 Concentration Summaries and Listings

Pharmacokinetic concentration data for KBP-5074 in plasma will be summarized using descriptive statistics by treatment group, study period, and visit. Plasma concentration data will also be summarized by eGFR status at baseline and UACR status at baseline.

Listings will include actual sampling times relative to dose administration. Plasma concentrations below the lower limit of quantification (LLOQ) will be presented as BLQ in the listings.

4.12.1.2 Population PK and PK-PD analysis

A separate population PK and PK-PD analysis is planned. The data analysis plan (DAP) for the population PK and PK-PD analyses will be described in a separate document from the SAP, and the results will be reported separately from the clinical study report.

4.12.2 Biomarkers

For continuous biomarker variables, a summary of individual values and change from baseline values will be provided at each scheduled visit based on biomarker population using standard unit, by treatment group and study period for the PD/Biomarker Population. Line plots and box plots of change in each biomarker parameter value for all visits through Week 48 will be displayed by treatment group.

By-subject listing of biomarker data will be provided.

4.12.3 Patient Reported Outcome (PRO) Measures

4.12.3.1 EQ-5D-5L

The EQ-5D-5L will be used to explore the impact of study drug and disease state on health state utility. The questionnaire comprises six questions that cover five dimensions of health:

- Mobility
- Self-care
- Usual activities
- Pain/discomfort
- Anxiety/depression

For each dimension, subjects select which statement describes their health on that day from a possible five options.

Subjects will also assess their health using the EQ-VAS which ranges from 0 (worst imaginable health) to 100 (best imaginable health).

The EQ-5D profile will be converted into a weighted health state utility value, termed the EQ-5D index, by applying the United Kingdom specific equation to the EQ-5D-5L profile that represents the comparative value of health states. Other country specific weights may be used when needed.

If one or more of the 5 dimensions are missing, the index value cannot be derived and is missing as well.

A summary of change from baseline will be provided at Week 12, Week 24, Week 48, and Week 52 by treatment group.

A by-subject listing of all EQ-5D-5L results will be provided.

4.12.3.2 KDQOL-36

The KDQOL-36 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 (Hays and Kallich, 1994).

For KDQOL-36 scores, a summary of change from baseline will be provided at Week 24, Week 48, and Week 52 by treatment group.

A by-subject listing of KDQOL-36 scores will be provided.

4.13 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 1.

Table 1 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 protocol 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 increases 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 were 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.

4.14 Changes in the Conduct of the Study or Planned Analysis

There are no changes to the conduct of the study or planned analyses from the protocol.

5 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics).

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics).

Bradley W. McEvoy (2016) Missing data in clinical trials for weight management, Journal of Biopharmaceutical Statistics, 26:1, 30-36, DOI: 10.1080/10543406.2015.1094814

Hays RD, Kallich JD, Mapes DL, Coons SJ, Carter WB. Development of the kidney disease quality of life (KDQOL) instrument. Qual Life Res. 1994 Oct; 3(5):329338.

Huber, P. J. (1967). "The Behavior of Maximum Likelihood Estimates under Nonstandard Conditions," Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability, vol. I, pp. 221–33.

Ratitch B, O'Kelly M, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharm Stat. 2013;12(6):337 - 347. (doi:10.1002/pst.1549 - DOI - PubMed).

6 APPENDICES

6.1 Appendix 1: SAS Code for Primary Efficacy Analysis

The following SAS example code will be utilized to perform retrieved dropout-based MI and analyses (ANCOVA) for primary efficacy analysis:

```
/* Step 1: Separate the input dataset into four groups: treatment arms
and on-treatment versus discontinued treatment at Week 12 */

data primary_dataset;
  set input_dataset;

  /* Check if participants are still on study treatment or have
discontinued treatment at Week 12 */

  if trt01p='KBP-5074' then do;
     if EOTSTT in ('COMPLETED','ONGOING') then analysis_group=1;
     else if EOTSTT in ('DISCONTINUED') then analysis_group=2;
  end;

  else if trt01p='Placebo' then do;
     if EOTSTT in ('COMPLETED','ONGOING') then analysis_group=3;
     else if EOTSTT in ('DISCONTINUED') then analysis_group=4;
  end;

  /* Keep only the relevant variables for imputation and primary model
(ANCOVA) */
  keep usubjid trt01p trt01pn base pblegfr anthpgrp last_obs_sbp
time_since_last week12 analysis_group;
run;

proc sort data=primary_dataset;
   by analysis_group;
run;

%let seedval=XXXXXXX;

/* Step 2: Run PROC MI based on ANCOVA for each group using by statement
   Imputation for active subjects who are on study treatment at Week 12,
where week12 is the SBP value at Week 12, base is the baseline SBP value,
last_obs_sbp is the last observation on treatment and time_since_last is
the time since last observation on treatment in weeks.
   Seed used in Proc MI will be documented and retained for
reproducibility */

proc mi data=primary_dataset nimpute=1000 seed=&seedval
out=imputed_dataset;
  FCS REG(week12 = base last_obs_sbp time_since_last / details);
  by analysis_group;
  var week12 base last_obs_sbp time_since_last;
run;
```

```
/* Step 4: re-compute the change from baseline to Week 12 SBP based on
imputed values */

data imputed_dataset;
   set imputed_dataset;
   chg = week12 - base;
run;

proc sort data=imputed_dataset;
   by _imputation_ chg;
run;

/* Step 5: Run an ANCOVA model for each imputation to evaluate the
primary efficacy endpoint of change from baseline at Week 12 in seated
trough cuff SBP using the imputed data, where base is baseline SBP
value (continuous), pblegfr is baseline egfr strata (via IRT), anthpgrp
is background antihypertensive medication strata (via IRT) */

ODS OUTPUT LSMEANS=LS_MEANS ESTIMATES=LS_MEANS_DIFF_EST;
proc glm data = imputed_dataset;
class trt01pn pblegfr anthpgrp;
by _imputation_;
model chg = trt01pn base pblegfr anthpgrp;
lsmeans TRT01PN / stderr;
estimate 'Difference in LS Means for Change in seated trough cuff SBP
from Baseline to Week 12' TRT01PN 1 -1;
run;
quit;

proc sort data=ls_means;
by trt01pn;
run;

/* Step 6: Use Rubin's Rule to obtain the adjusted LS mean, standard
error, and the two-sided 95% CI for each treatment group, and the LS mean
of the difference, the 95% CI of the difference, and p-value for
comparing the KBP-5074 and placebo groups */

PROC MIANALYZE DATA=LS_MEANS alpha=0.05;
ODS OUTPUT PARAMETERESTIMATES=ANCOVA_TEST_LSMEANS_COMBINED;
by TRT01PN;
MODELEFFECTS LSMEAN;
STDERR STDERR;
RUN;

PROC MIANALYZE DATA=LS_MEANS_DIFF_EST alpha=0.05;
ODS OUTPUT PARAMETERESTIMATES=ANCOVA_TEST_DIFFERENCES_COMBINED;
MODELEFFECTS ESTIMATE;
STDERR STDERR;
RUN;
```

6.2 Appendix 2: Partial Date and Interested Period Conventions

6.2.1 Algorithm for Partial Date Imputation

Imputed dates will NOT be presented in the listings. The algorithm for partial date imputation is described in Table 2. For partially missing stop date of medication, please include last known assessment date (LKAD) as a reference timepoint to impute missing date. This date is subject's last date in study, ideally is equal to end of study date, or the maximum AE end date. However, LKAD should be determined on the basis of the real data.

Table 2 Algorithm for Partial Date Imputation

Type of the Date	Missing Status	Action
Start Date	Partially Missing	**For the imputation of CM:** If the start day/month is missing, the first day of the month and January will be used. **For the imputation of AE:** If the start day/month is missing, the day/month of informed consent form (ICF) date will be used.
	Completely Missing	**For the imputation of CM:** The earlier known assessment date will be used. **For the imputation of AE:** The ICF date will be used.
Stop Date	Partially Missing	**If the day and month of stop date is missing:** • If year of partial date < year of the LKAD, assign the last day and month of the year (i.e. December 31st). • If year of partial date = year of the LKAD, assign the LKAD date to the missing fields. **If only the day of stop date is missing:** • If month of partial date < month of the LKAD, assign the last day of the month. If month of partial date = month of the LKAD, assign the LKAD date to the missing fields.
	Completely Missing	The LKAD date will be used.

6.2.2 Algorithm for the Period Interest for background antihypertensive medications

The period of background antihypertensive medications of interest includes Run-In Period, 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. The start/stop date for each period of interest is defined in Table 3.

Table 3 algorithm for the start/stop date for each interested period

Period of interest	Start Date	Stop Date*
Run-In Period	The first known scheduled assessment date in Run-In Period	One day before first dosing date of study drug at Day 1
From Day 1 to Week 12	First dosing date of study drug at Day 1	One day before the first known scheduled assessment date at Week 12
From Week 12 to Week 24	The first known scheduled assessment date at Week 12	One day before the first dosing date of Open-Label study drug
From Week 24 to Week 48	The first dosing date of Open-Label study drug	One day before the first dosing date of Randomized Double-Blind Withdrawal Study Drug
From Week 48 to Week 52	The first dosing date of Randomized Double-Blind Withdrawal study drug	One day before the first known scheduled assessment date at Week 52
* For subject early withdrawal before specified week: One day before the first known scheduled assessment date at Follow-Up.		

After the partial date is imputed based on the imputation rule (refer to Appendix 6.2.1), please classify the interested period for background antihypertensive medications as following:

- If start date and stop date of a medication fall within one period, assign this medication to the period.
- If start date and stop date of a medication are in the different periods, assign this medication to all periods involved. For example, if a medication starts at 'From Day 1 to Week 12' and stops at 'From Week 48 to Week 52', then this medication needs to be included in 4 periods, including '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'.

6.2.3 Algorithm for the Period Interest for AEs

The AE period of interest includes Double-Blind Treatment Period, Open-Label Treatment Period, Randomized Double-Blind Withdrawal Period, Follow-Up. The start/stop date for each period of interest is defined in Table 4.

Table 4 algorithm for the start/stop date for each period of interest

Period of interest	Start Date	Stop Date	
Double-Blind Treatment Period	First dosing date of study drug at Day 1	One day before the first dosing date of Open-Label study drug	For subject early withdrawal before specified period: One day before the first known scheduled assessment date at Follow-Up
Open-Label Treatment Period	The first dosing date of Open-Label study drug	One day before the first dosing date of Randomized Double-Blind Withdrawal Study Drug	
Randomized Double-Blind Withdrawal Period	The first dosing date of Randomized Double-Blind Withdrawal study drug	One day before the first known scheduled assessment date at Week 52	
Follow-Up	The first known scheduled assessment date at Follow-Up	The last known assessment date in study	

After the partial date is imputed based on the imputation rule (refer to Appendix 6.2.1), please classify the period of interested in AE as following:

- If start date and stop date of an AE fall within one period, this AE will be counted only in the period.
- If start date and stop date of an AE are in different periods, assign this AE to all periods involved. For example, if an AE starts during 'Double-Blind Treatment Period' and stops at 'Follow-Up', then this AE will be counted in 4 periods, including 'Double-Blind Treatment Period', 'Open-Label Treatment Period', 'Randomized Double-Blind Withdrawal Period' and 'Follow-Up'.

Approval Signatures

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