

# CLINICAL STUDY PROTOCOL

## **A Phase 1, Open-Label Study in Hemodialysis and Non-Hemodialysis Patients with Severe Chronic Kidney Disease to Evaluate the Safety, Tolerability, and Pharmacokinetics of KBP-5074 Following Oral Administration**

**Protocol: KBP5074-1-003**

**IND: 117743**

**Sponsor:** KBP Biosciences Co., Ltd.  
116 Village Blvd, Suite 210  
Princeton, New Jersey 08540

**Sponsor Contact:** Peter Pelka  
Director, Clinical Operations  
KBP Biosciences Co., Ltd.  
116 Village Blvd, Suite 210  
Princeton, New Jersey 08540  
Telephone: (732) 668-4280

**Medical Monitor:** Bin Zhang, MD  
Senior Vice President, Clinical Development  
KBP Biosciences Co., Ltd.  
116 Village Boulevard, Suite 210  
Princeton, New Jersey 08540  
Telephone: 609-216-2032

**Version of Protocol:** Final

**Date of Protocol:** 17 May 2016

### **CONFIDENTIAL**

All financial and nonfinancial support for this study will be provided by KBP Biosciences Co., Ltd. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of KBP Biosciences Co., Ltd.

The study will be conducted according to the International Conference on Harmonisation (ICH) harmonised tripartite guideline E6 (R1): Good Clinical Practice (GCP).

### Protocol Approval - Sponsor Signatory

**Study Title** A Phase 1, Open-Label Study in Hemodialysis and Non-Hemodialysis Patients with Severe Chronic Kidney Disease to Evaluate the Safety, Tolerability, and Pharmacokinetics of KBP-5074 Following Oral Administration

**Protocol Number** KBP5074-1-003

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**Protocol Date** 17 May 2016

Protocol accepted and approved by:

Bin Zhang, MD  
Senior Vice President, Clinical Development  
KBP Biosciences Co., Ltd.  
116 Village Boulevard, Suite 210  
Princeton, New Jersey 08540



May 18, 2016

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Signature

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Date

### **Protocol Approval - Investigator**

**Study Title** A Phase 1, Open-Label Study in Hemodialysis and Non-Hemodialysis Patients with Severe Chronic Kidney Disease to Evaluate the Safety, Tolerability, and Pharmacokinetics of KBP-5074 Following Oral Administration

**Protocol Number** KBP5074-1-003

**Protocol Version** Final

**Protocol Date** 17 May 2016

Protocol accepted and approved by:

**Investigator**

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Signature

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Date

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Printed Name

### **Declaration of Investigator**

I have read and understood all sections of the protocol titled “A Phase 1, Open-Label Study in Hemodialysis and Non-Hemodialysis Patients with Severe Chronic Kidney Disease to Evaluate the Safety, Tolerability, and Pharmacokinetics of KBP-5074 Following Oral Administration” and the accompanying Investigator’s Brochure, version 2, dated 21 July 2015.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the protocol, the ICH harmonised tripartite guideline E6 (R1): GCP, and all applicable government regulations. I will not make changes to the protocol before consulting with KBP Biosciences Co., Ltd or implement protocol changes without Institutional Review Board approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a Sub-Investigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from KBP Biosciences Co., Ltd.

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Signature of Investigator

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Date

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Printed Name of Investigator

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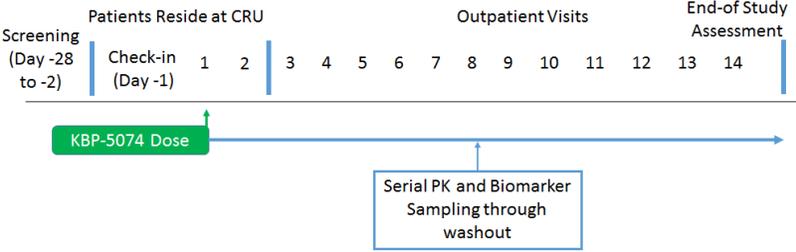
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## Protocol Synopsis

<b>Protocol Number:</b>	KBP5074-1-003
<b>Title:</b>	A Phase 1, Open-Label Study in Hemodialysis and Non- Hemodialysis Patients with Severe Chronic Kidney Disease to Evaluate the Safety, Tolerability, and Pharmacokinetics of KBP-5074 Following Oral Administration
<b>Sponsor:</b>	KBP Biosciences Co., Ltd. 116 Village Blvd, Suite 210 Princeton, New Jersey 08540
<b>Study Phase:</b>	Phase 1
<b>Study Sites:</b>	Up to 4 centers in the United States (US)
<b>Indication:</b>	Hypertension and nephropathy
<b>Rationale:</b>	To further explore potential use of KBP-5074 in patients with advanced stages of Chronic Kidney Disease (CKD) (including patients with severe renal impairment and those on hemodialysis [HD]) and to assess the safety, tolerability, and pharmacokinetics (PK) of single doses of KBP-5074 in male and female patients with severe CKD (defined as estimated glomerular filtration rate [eGFR] $\geq 15$ mL/min/1.73 m <sup>2</sup> and $\leq 29$ mL/min/1.73 m <sup>2</sup> , based on the Modification of Diet in Renal Disease [MDRD] equation) and a subset of patients requiring HD.
<b>Objectives:</b>	<p>The primary objectives of this study are:</p> <ul style="list-style-type: none"> <li>• To evaluate the safety and tolerability of a single dose of KBP-5074 in HD and non-HD patients with severe CKD.</li> <li>• To evaluate the PK of KBP-5074 following a single oral dose administration of 0.5 mg KBP-5074 in non-HD patients with severe CKD (defined as eGFR <math>\geq 15</math> mL/min/1.73 m<sup>2</sup> and <math>\leq 29</math> mL/min/1.73 m<sup>2</sup> based on the MDRD equation) in Part 1 of the study.</li> <li>• To evaluate the PK of KBP-5074 following a single oral dose of 0.5 mg KBP-5074 administered to HD patients in Part 2 of the study. Pharmacokinetics will be evaluated during the following periods in Part 2:             <ul style="list-style-type: none"> <li>○ During a single interdialytic interval (from approximately 0 to 44 hours postdose).</li> <li>○ During a single dialysis session (from approximately 44 to 48 hours postdose).</li> <li>○ Overall through washout (from the time of dose administration through 312 hours postdose, as data permit).</li> </ul> </li> </ul> <p>The secondary objective of this study is:</p> <ul style="list-style-type: none"> <li>• To evaluate the changes in plasma aldosterone and serum potassium from baseline levels following KBP-5074 dosing in patients with severe CKD and HD patients in Part 1 and Part 2, respectively.</li> </ul>

<p><b>Patient Population:</b></p>	<p>Patients will be male or female, between 18 and 75 years of age, inclusive; with body mass index between 19 and 42 kg/m<sup>2</sup>, inclusive; with severe CKD defined as eGFR <math>\geq 15</math> mL/min/1.73 m<sup>2</sup> and <math>\leq 29</math> mL/min/1.73 m<sup>2</sup> based on the isotope dilution mass spectrometry (IDMS) traceable MDRD equation according to laboratory results at Screening (non-HD patients only [Part 1]); with serum potassium between 3.3 and 4.8 mmol/L, inclusive, at both Screening and Check-in (Day -1) (non-HD patients only [Part 1]); who are on a hemodialysis schedule for at least 45 days with KT/V <math>\geq 1.2</math> for end-stage renal disease (ESRD) regardless of the etiology including diabetes, with an average 3 hemodialysis sessions per week (HD patients only [Part 2]); and who are nonsmokers or light smokers (smokes fewer than 10 cigarettes per day).</p>
<p><b>Study Design:</b></p>	<p>This will be a Phase 1, multicenter, open-label, 2-part study designed to assess the PK, safety, and tolerability of KBP-5074 in patients undergoing HD and non-HD patients with severe CKD (defined using the eGFR <math>\geq 15</math> mL/min/1.73 m<sup>2</sup> and <math>\leq 29</math> mL/min/1.73 m<sup>2</sup> based on the MDRD equation). The study will be conducted at up to 4 clinical research units (CRUs) in the US. Approximately 12 patients will be enrolled in the study (a single cohort of 6 patients in each of Part 1 and Part 2). Parts 1 and 2 of the study will be conducted in parallel. If Part 1 is completed prior to the completion of Part 2, or vice versa, the PK, safety, and tolerability analyses for the completed study part may proceed as planned and will not be delayed based on the timing of the other respective study part.</p> <p><b>Part 1</b></p> <p>In Part 1, a single cohort (Cohort 1) of 6 non-HD patients with severe CKD will receive a single oral dose of 0.5 mg KBP-5074 on Day 1 in the fasted state (following a fast between 2 and 4 hours). Following dosing, patients will be followed for 13 days for PK and safety assessments. A study design schematic for Part 1 is presented in the following figure.</p> <p><b>Study Design Schematic for Part 1</b></p>  <p>The diagram shows a horizontal timeline from Day -28 to Day 14. Key events are marked with vertical bars: Screening (Day -28 to -2), Check-in (Day -1), a KBP-5074 Dose (green box) on Day 1, and End-of Study Assessment (Day 14). A box labeled 'Serial PK and Biomarker Sampling through washout' spans from Day 1 to Day 14. Above the timeline, 'Patients Reside at CRU' is indicated for Days 1-2, and 'Outpatient Visits' are indicated for Days 3-14.</p> <p>Abbreviations: CRU = clinical research unit; PK = pharmacokinetic.</p>

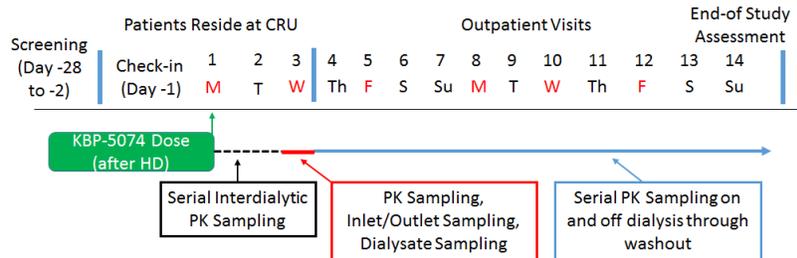
**Part 2**

In Part 2, a single cohort (Cohort 2) of 6 HD patients will receive a single dose of 0.5 mg KBP-5074 on the same day of HD (immediately after the HD). Following dosing, patients will be followed for 13 days for PK and safety assessments. The PK samples will be obtained relative to dose administration as follows (All PK samples will be collected within ±5 minutes of the nominal time unless otherwise specified):

- During the interdialytic interval (using a venous stick or cannula) immediately predose (at time 0 [-5 min]); collected immediately prior to dosing, but following the termination of a previous dialysis session), 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose;
- During the second HD session at 44 (immediately prior to HD [using a venous stick or cannula; -5 min] and 5 minutes after the start of HD [inlet {arterial; ±1 min} and outlet {venous; ±1 min} samples]), 44.25, 44.5, 46, and 47 hours postdose, and at the end of the second HD session;
- Following dialysis at 48.5, 49, 50, 52, 72, 96, 120, 168, 216, 264, and 312 hours postdose.

A study design schematic for a Monday, Wednesday, Friday (MWF) and Tuesday, Thursday, Saturday (TTS) HD schedule for Part 2 is presented in the following figures.

**Study Design Schematic for Part 2 (Monday, Wednesday, Friday HD Schedule)**



Abbreviations: CRU = clinical research unit; HD = hemodialysis; PK = pharmacokinetic.

Note: hemodialysis days are represented in red text.

<b>Study Design Schematic for Part 2 (Tuesday, Thursday, Saturday HD Schedule)</b>																															
<p>Screening (Day -28 to -2)</p> <p>Patients Reside at CRU</p> <p>Outpatient Visits</p> <p>End-of Study Assessment</p>	<table border="1" style="width: 100%; border-collapse: collapse; text-align: center;"> <tr> <td style="width: 10%;">Check-in (Day -1)</td> <td style="width: 5%;">1</td> <td style="width: 5%;">2</td> <td style="width: 5%;">3</td> <td style="width: 5%;">4</td> <td style="width: 5%;">5</td> <td style="width: 5%;">6</td> <td style="width: 5%;">7</td> <td style="width: 5%;">8</td> <td style="width: 5%;">9</td> <td style="width: 5%;">10</td> <td style="width: 5%;">11</td> <td style="width: 5%;">12</td> <td style="width: 5%;">13</td> <td style="width: 5%;">14</td> </tr> <tr> <td></td> <td style="color: red;">T</td> <td style="color: red;">W</td> <td style="color: red;">Th</td> <td style="color: red;">F</td> <td style="color: red;">S</td> <td style="color: red;">Su</td> <td style="color: red;">M</td> <td style="color: red;">T</td> <td style="color: red;">W</td> <td style="color: red;">Th</td> <td style="color: red;">F</td> <td style="color: red;">S</td> <td style="color: red;">Su</td> <td style="color: red;">M</td> </tr> </table> 	Check-in (Day -1)	1	2	3	4	5	6	7	8	9	10	11	12	13	14		T	W	Th	F	S	Su	M	T	W	Th	F	S	Su	M
Check-in (Day -1)	1	2	3	4	5	6	7	8	9	10	11	12	13	14																	
	T	W	Th	F	S	Su	M	T	W	Th	F	S	Su	M																	
<p>Abbreviations: CRU = clinical research unit; HD = hemodialysis; PK = pharmacokinetic.</p> <p>Note: hemodialysis days are represented in red text.</p> <p>Patients in Part 1 and Part 2 will be screened to enter the study within 28 days (Day -28 to Day -2) prior to administration of KBP-5074 on Day 1. Eligible patients in Part 1 and Part 2 will be admitted to the CRU at Check-in (Day -1) and will undergo baseline assessments. Patients will remain confined from Check-in (Day -1) until 24 hours postdose for Part 1 and 52 hours postdose for Part 2 and PK and safety assessments will be performed during outpatient visits through the end of study assessment on Day 14.</p> <p>Patients who withdraw prematurely from the study may be replaced at the discretion of the Investigator and KBP Biosciences Co., Ltd. to ensure that 12 patients complete the study (6 patients in each of Cohorts 1 and 2, in Parts 1 and 2, respectively).</p> <p>Study assessments including physical examination findings, vital signs (blood pressure, pulse rate, respiratory rate and oral temperature), 12-lead ECGs, clinical laboratory findings, monitoring of AEs, and PK blood sampling will be performed at either screening, Check-in (Day -1), or after KBP-5074 dosing through the end of study assessment. Adverse events (AEs) and serious adverse events (SAEs) will be assessed from the time the patient signs the informed consent form until exit from the study.</p>																															
<b>Estimated Study Duration:</b>	<p><u>Screening Duration:</u> 28 days</p> <p><u>Confinement Period:</u> Patients will remain confined from Check in (Day -1) until 24 hours postdose for Part 1 and 52 hours postdose for Part 2 and PK and safety assessments will be performed during outpatient visits through the end of study assessment on Day 14.</p> <p><u>Total Study Duration:</u> 42 days for Part 1 and Part 2</p>																														

<p><b>Study Drug, Dosage, and Route of Administration:</b></p>	<p>The Sponsor (KBP Biosciences Co., Ltd.) will provide adequate supplies of KBP-5074 capsules, 0.5 mg for use during the study.</p> <p>In Part 1 of the study, non-HD patients with severe CKD in Cohort 1 will receive a single oral capsule dose of 0.5 mg KBP-5074 with up to 240 mL of room temperature water on Day 1 following a fast between 2 and 4 hours.</p> <p>In Part 2 of the study, HD patients with severe CKD will receive a single 0.5 mg oral capsule dose of KBP-5074 with up to 240 mL of room temperature water following a fast between 2 and 4 hours. The dose of KBP-5074 will be administered on Day 1 immediately following a dialysis session.</p> <p>All doses of KBP-5074 will be administered orally to patients at the CRU. Administration of each dose of study drug will be supervised, verified, and documented according to the CRU's standard operating procedures.</p>
<p><b>Study Assessments:</b></p>	<p><b>Pharmacokinetic:</b> For Part 1, the following PK parameters will be calculated using noncompartmental methods, whenever possible, based on plasma KBP-5074 concentrations: maximum concentration (<math>C_{max}</math>), time to maximum concentration (<math>t_{max}</math>), area under the concentration-time curve (AUC) from time 0 until the last quantifiable concentration (<math>AUC_{0-t}</math>), AUC from time 0 until 24 hours postdose (<math>AUC_{0-24h}</math>), AUC extrapolated to infinity (<math>AUC_{0-\infty}</math>), apparent terminal elimination rate constant (<math>\lambda_z</math>), terminal elimination phase half-life (<math>t_{1/2}</math>), total body clearance (CL/F), and volume of distribution (Vz/F).</p> <p>For Part 2, the following PK parameters will be calculated using noncompartmental methods, whenever possible, based on plasma KBP-5074 concentrations during the initial interdialytic interval: <math>C_{max}</math>, <math>t_{max}</math>, <math>AUC_{0-24h}</math>, AUC from time 0 until 44 hours postdose (<math>AUC_{0-44h}</math>), AUC from time 0 until the last timepoint during the first interdialytic interval (<math>AUC_{0-t_i}</math>), <math>\lambda_z</math>, and <math>t_{1/2}</math>.</p> <p>The following PK parameters will be calculated using noncompartmental methods, whenever possible, based on plasma KBP-5074 concentrations during dialysis: AUC from start of dialysis (<math>t_0</math>) to the end of dialysis (<math>t_1</math>) based on inflow concentrations (Inlet <math>AUC_{t_0-t_1}</math>), AUC from start of dialysis (<math>t_0</math>) to the end of dialysis (<math>t_1</math>) based on outflow concentrations (Outlet <math>AUC_{t_0-t_1}</math>), ratio of outflow to inflow concentrations based on time-matched inflow and outflow samples (Outlet:Inlet Concentration Ratio), ratio of Outlet <math>AUC_{t_0-t_1}</math> to Inlet <math>AUC_{t_0-t_1}</math> (Outlet:Inlet AUC Ratio), estimated hemodialysis recovery clearance (<math>CL_D</math>, Recovery), estimated hemodialysis clearance (<math>CL_D</math>), hemodialysis extraction ratio (<math>ER_D</math>), <math>\lambda_z</math>, and <math>t_{1/2}</math>.</p> <p>The following PK parameters will be calculated using noncompartmental methods, whenever possible, based on plasma KBP-5074 concentrations overall: <math>C_{max}</math>, <math>t_{max}</math>, <math>AUC_{0-t}</math>, <math>AUC_{0-\infty}</math>, <math>\lambda_z</math>, <math>t_{1/2}</math>, CL/F, and Vz/F.</p> <p><b>Pharmacodynamic:</b> The pharmacodynamic (PD) analysis will include assessments of the change from baseline in concentrations of plasma aldosterone and serum potassium after single doses of KBP-5074.</p> <p><b>Safety:</b> The safety analysis will include physical examination findings, vital signs (blood pressure, pulse rate, respiratory rate and oral temperature), 12-lead ECGs, clinical laboratory findings (hematology, clinical chemistry, and urinalysis), and assessments of AEs.</p>

<b>Sample Size:</b>	No formal sample size calculations were performed. The sample size is based on what will provide sufficient data to obtain a PK profile. A total of 12 patients, both male and female patients with CKD, are planned for enrollment in the study.
<b>Statistical Methods:</b>	<p><b>Pharmacokinetic:</b> Pharmacokinetic parameter endpoints for KBP-5074 will be calculated, listed, and summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum, and maximum). Pharmacokinetic parameter listings and statistical summaries will be generated separately for each study part. Part 2 PK parameters also will be listed and summarized for the following periods: during the interdialytic interval, during dialysis, and overall. KBP-5074 concentration data will be listed and summarized by study part and collection time point. Part 2 concentration data will be listed and summarized for the following periods: during the interdialytic interval, during dialysis, and overall.</p> <p><b>Pharmacodynamic:</b> The change from baseline in concentrations of plasma aldosterone and serum potassium after single doses of KBP-5074 will be summarized by study part and cohort, and at each scheduled time point using descriptive statistics. The baseline value is the last value observed prior to first administration of study drug and any values after first administration of study drug are regarded as post-baseline values. The change-from-baseline variables will be calculated as the post-baseline value minus the value at baseline.</p> <p><b>Safety:</b> Safety assessments, including physical examination findings, vital signs, 12-lead ECGs, clinical laboratory findings, and AE assessments will be analyzed descriptively. No formal statistical analyses are planned.</p>
<b>Date of Protocol:</b>	17 May 2016

## List of Abbreviations

<b>Abbreviation</b>	<b>Definition</b>
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC <sub>0-∞</sub>	area under the concentration-time curve extrapolated to infinity
AUC <sub>0-t</sub>	area under the concentration-time curve from time 0 until the last quantifiable concentration
AUC <sub>0-ti</sub>	area under the concentration-time curve from time 0 until the last timepoint during the first interdialytic interval
AUC <sub>0-24h</sub>	area under the concentration-time curve from time 0 until 24 hours postdose
AUC <sub>0-44h</sub>	area under the concentration-time curve from time 0 until 44 hours postdose
BMI	body mass index
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CKD	Chronic Kidney Disease
CL <sub>D</sub>	estimated hemodialysis clearance
CL <sub>D, Recovery</sub>	estimated hemodialysis recovery clearance, where: CL <sub>D, Recovery</sub> = Amount Recovered in Dialysate/Inlet AUC <sub>t0-t1</sub>
CL/F	total body clearance
C <sub>max</sub>	maximum concentration
CRU	Clinical Research Unit
CS	clinically significant
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
ER <sub>D</sub>	hemodialysis extraction ratio
ESRD	end-stage renal disease
ET	Early Termination
FDA	Food and Drug Administration
FSH	follicle stimulating hormone

<b>Abbreviation</b>	<b>Definition</b>
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HD	hemodialysis
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
Inlet AUC <sub>t0-t1</sub>	area under the concentration-time curve from start of dialysis (t0) to the end of dialysis (t1) based on inflow concentrations
IRB	Institutional Review Board
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MR	mineralocorticoid receptor
MRA	mineralocorticoid receptor antagonist
MTD	maximum tolerated dose
MWF	Monday, Wednesday, Friday
n	number of non-missing observations
NCS	not clinically significant
Outlet AUC <sub>t0-t1</sub>	area under the concentration-time curve from start of dialysis (t0) to the end of dialysis (t1) based on outflow concentrations
Outlet:Inlet Concentration Ratio	ratio of outflow to inflow concentrations based on time-matched inflow and outflow sample
Outlet:Inlet AUC Ratio	ratio of Outlet AUC <sub>t0-t1</sub> to Inlet AUC <sub>t0-t1</sub>
PD	pharmacodynamic
PK	pharmacokinetic
PT	preferred term
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAAS	renin-angiotensin-aldosterone system

<b>Abbreviation</b>	<b>Definition</b>
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
$t_{\max}$	time to maximum concentration
TTS	Tuesday, Thursday, Saturday
$t_{1/2}$	terminal elimination phase half-life
ULN	upper limit of normal
US	United States
$V_z/F$	volume of distribution
$\lambda_z$	apparent terminal elimination rate constant

## 1 Introduction

### 1.1 Background

Hypertension and hypertensive kidney damage pose a significant health risk in the US and in 2013 were ranked as one of the top 15 leading causes of morbidity and mortality.<sup>1</sup> Hypertension is also a major risk factor for other causes of death such as heart failure<sup>2</sup> stroke, and coronary vascular disease.<sup>3</sup> Although considerable progress has been made in the treatment of hypertension and renal failure, the development of new therapy remains critical.

Therapies for the treatment of hypertension and hypertensive kidney damage have targeted the mineralocorticoid receptor (MR), which is a member of the steroid receptor family. Mineralocorticoid receptors are found on epithelial cells located in the kidney, colon, salivary, and sweat glands, and promote sodium retention and a loss of potassium and magnesium. Disturbances in these electrolytes may impair cardiac function and increase or enhance the risk of morbid cardiac and vascular events.<sup>4</sup> Treatments such as aldosterone receptor antagonists have been shown to inhibit the effects of aldosterone signaling at MR, thus preventing sodium retention and loss of potassium.<sup>4</sup> Mineralocorticoid receptors have also been shown to have a major pathophysiological role in the progression of kidney diseases.<sup>5,6,7</sup> It has been shown that the inhibition of mineralocorticoid receptor signaling considerably reduces proteinuria in subjects with chronic kidney disease (CKD).<sup>5,8,9</sup>

Compounds that have been tested for MR activity include, but are not limited to, eplerenone and spironolactone. Spironolactone is a first-generation aldosterone antagonist with anti-androgen properties. While used primarily as a diuretic and antihypertensive agent, spironolactone has demonstrated efficacy in the treatment of advanced heart failure.<sup>10</sup> However, the anti-androgen properties and tendency to cause hyperkalemia<sup>11</sup> are patient tolerance and safety concerns in the clinical setting. Eplerenone is a highly selective aldosterone blocker developed for the treatment of hypertension and heart failure.<sup>12</sup> It has a lesser affinity for the androgen receptor, however some anti-androgen activity is present. Although eplerenone has been shown to be active against MR, there are risks associated with its use in patients. Mineralocorticoid receptor antagonism with eplerenone causes a dose-dependent increase in serum potassium concentrations.<sup>13</sup> Therefore eplerenone should generally be avoided in patients receiving potassium supplementation or other potassium-sparing diuretics, such as amiloride and triamterene, particularly in patients with renal insufficiency, diabetes, and microalbuminuria.<sup>14</sup> In addition, eplerenone also causes mild dose-dependent increase in cholesterol, triglycerides, and serum creatinine and decrease in serum sodium.<sup>13</sup> For these reasons, a new MR antagonist with an improved efficacy and a low potential for adverse effects is needed in order to address this public health issue.

KBP Biosciences Co., Ltd. Is developing KBP-5074, a new investigational non-steroidal mineralocorticoid receptor antagonist (MRA) for the treatment of hypertension and nephropathy including diabetic and hypertensive nephropathy.

KBP-5074 binds to the MR and blocks the binding of aldosterone, a component of the renin-angiotensin-aldosterone system (RAAS). Aldosterone binds to MR in both epithelial (e.g., kidney) and non-epithelial (e.g., heart, blood vessels, and brain) tissues and increases blood pressure through induction of sodium reabsorption and possibly other mechanisms. KBP-5074 selectively binds to recombinant human mineralocorticoid receptors relative to its binding to recombinant human glucocorticoid, progesterone, and androgen receptors.

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

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

## 1.2 Summary of Preclinical Studies

A battery of pharmacology and toxicology studies have been conducted to support the Investigational New Drug (IND) opening for clinical studies including rat and dog acute toxicity studies, rat and dog 4-week repeated dose toxicity studies, genotoxicity, and safety pharmacology studies, and in summary, the collective pre-clinical data support KBP-5074 for the proposed early clinical investigational plan.

No apparent toxicity was observed in Sprague-Dawley rats or in beagle dogs after oral administration of KBP-5074 solid dispersion at a single dose of 60, 200, or 600 mg/kg and the maximum tolerated dose (MTD) was determined to be equal to or greater than 600 mg/kg, the maximum dose level that could be formulated. KBP-5074 demonstrated dose dependent anti-hypertension and renal protection characteristics in several animal models with placebo and eplerenone treatments. Genotoxicity studies of mutagenicity, chromosomal aberration, and micronucleus test of KBP-5074 were conducted. The results of these studies indicate that KBP-5074 has no genotoxicity effect.

Additional information regarding the preclinical evaluation of KBP-5074 can be found in the Investigator's Brochure (IB).

### 1.3 Summary of Clinical Studies

As of 31-March-2016, one clinical study (Protocol #: KBP5074-1-001, NCT02228733) has been completed and evaluated the safety, tolerability, and pharmacokinetics (PK) of KBP-5074 single dose administration in healthy male and female subjects. This was an open-label, parallel-group, single ascending dose study with a food effect panel. A total of 46 subjects received KBP-5074 at dose levels of 0.5, 1.0, 5, 10, and 30 mg in the fasting state and 10 mg in the fed state.

KBP-5074 was safe and well tolerated in healthy male and female subjects. There were no drug related adverse events (AE) reported during the study. There were no clinically meaningful trends noted based on safety laboratory assessments including the complete blood count and potassium levels, physical examinations, vital sign measurements or electrocardiograms (ECGs) during this study. No evidence of bone marrow suppression was observed with increasing drug exposure. Specifically, no clinically meaningful trends of the complete blood counts, (white blood cell, neutrophils, red blood cell, or platelets) with increasing drug exposure were observed. No gender difference of drug exposure was observed.

At the dose levels tested, the mean maximum concentration ( $C_{max}$ ) ranged from 9.37 ng/mL (0.5 mg) to 259.4 ng/mL (30 mg), area under the concentration-time curve from time 0 until 24 hours postdose ( $AUC_{0-24h}$ ) ranged from 162.5 ng\*hr/mL (0.5 mg) to 5016 ng\*hr/mL (30 mg), and area under the concentration-time curve extrapolated to infinity ( $AUC_{0-\infty}$ ) increased from 678.4 ng\*hr/mL (0.5 mg) to 28195 ng\*hr/mL (30 mg). The time to maximum concentration ( $t_{max}$ ) under fasted conditions varied from 4 to 7 hours suggesting relatively fast absorption of KBP-5074 following oral administration under fasted conditions. The average half-life is greater than 50 hours.

There is an ongoing clinical study (Protocol #: KBP5074-1-002, NCT02653014) that will assess the safety, tolerability, and PK of KBP-5074 multiple dose administration in healthy adults and subjects with mild to moderate CKD (defined as estimated glomerular filtration rate [eGFR]  $\geq 30$  and  $\leq 89$  mL/min/1.73 m<sup>2</sup>).

Additional information regarding the clinical evaluation of KBP-5074 can be found in the IB.

### 1.4 Study Rationale

As described above, KBP-5074 might have potential to improve health outcomes of patients with CKD. To further explore potential use of KBP-5074 in patients with advanced stages of CKD (including patients with severe renal impairment and those on hemodialysis [HD]), KBP Biosciences Co., Ltd has designed this new clinical study to assess the safety, tolerability, and PK of single doses of KBP-5074 in male and female patients with severe

CKD (eGFR  $\geq 15$  mL/min/1.73 m<sup>2</sup> and  $\leq 29$  mL/min/1.73 m<sup>2</sup>, based on the Modification of Diet in Renal Disease [MDRD] equation)<sup>15</sup> and a subset of patients requiring HD.

## 1.5 Dose Rationale

The human equivalent exposure range of KBP-5074 proposed by this study has been shown to be safe and tolerated in preclinical animal studies and a previous clinical study conducted in healthy subjects. The 0.5 mg dose level proposed represents the lowest exposure to KBP-5074 tested in human subjects and has been shown to be safe and well tolerated based on all data currently available. The anticipated dosing regimen for KBP-5074 is once daily for oral administration.

## 2 Study Objectives

### 2.1 Primary Objectives

The primary objectives of this study are:

- To evaluate the safety and tolerability of a single dose of KBP-5074 in HD and non-HD patients with severe CKD.
- To evaluate the PK of KBP-5074 following a single oral dose administration of 0.5 mg KBP-5074 in non-HD patients with severe CKD (defined as eGFR  $\geq 15$  mL/min/1.73 m<sup>2</sup> and  $\leq 29$  mL/min/1.73 m<sup>2</sup> based on the MDRD equation) in Part 1 of the study.
- To evaluate the PK of KBP-5074 following a single oral dose of 0.5 mg KBP-5074 administered to HD patients in Part 2 of the study. Pharmacokinetics will be evaluated during the following periods in Part 2:
  - During a single interdialytic interval (from approximately 0 to 44 hours postdose).
  - During a single dialysis session (from approximately 44 to 48 hours postdose).
  - Overall through washout (from the time of dose administration through 312 hours postdose, as data permit).

### 2.2 Secondary Objectives

The secondary objective of this study is:

- To evaluate the changes in plasma aldosterone and serum potassium from baseline levels following KBP-5074 dosing in patients with severe CKD and HD patients in Part 1 and Part 2, respectively.

### 3 Investigational Plan

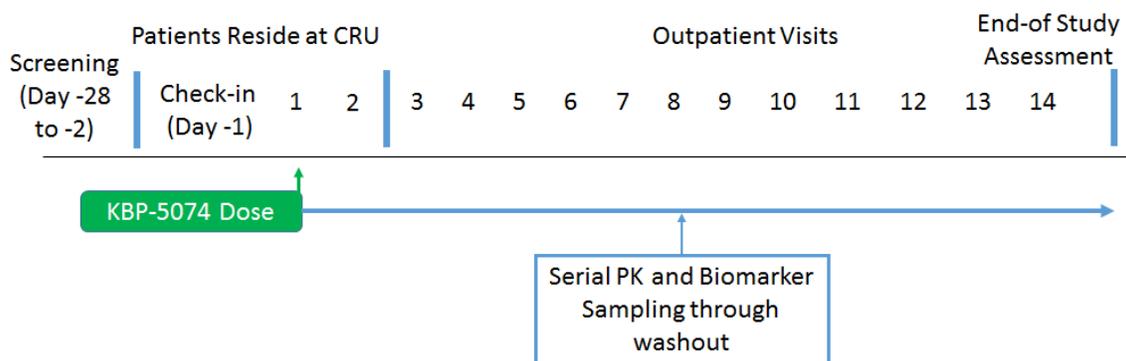
#### 3.1 Study Design

This will be a Phase 1, multicenter, open-label, 2-part study designed to assess the PK, safety, and tolerability of KBP-5074 in patients undergoing HD and non-HD patients with severe CKD (defined using the eGFR  $\geq 15$  mL/min/1.73 m<sup>2</sup> and  $\leq 29$  mL/min/1.73 m<sup>2</sup> based on the MDRD equation). The study will be conducted at up to 4 clinical research units (CRUs) in the US. Approximately 12 patients will be enrolled in the study (a single cohort of 6 patients in each of Part 1 and Part 2). Parts 1 and 2 of the study will be conducted in parallel. If Part 1 is completed prior to the completion of Part 2, or vice versa, the PK, safety, and tolerability analyses for the completed study part may proceed as planned and will not be delayed based on the timing of the other respective study part.

##### Part 1

In Part 1, a single cohort (Cohort 1) of 6 non-HD patients with severe CKD will receive a single oral dose of 0.5 mg KBP-5074 on Day 1 in the fasted state (following a fast between 2 and 4 hours). Following dosing, patients will be followed for 13 days for PK and safety assessments (see Table 12-1). A study design schematic for Part 1 is presented in Figure 3-1.

**Figure 3-1 Study Design Schematic for Part 1**



Abbreviations: CRU = clinical research unit; PK = pharmacokinetic.

##### Part 2

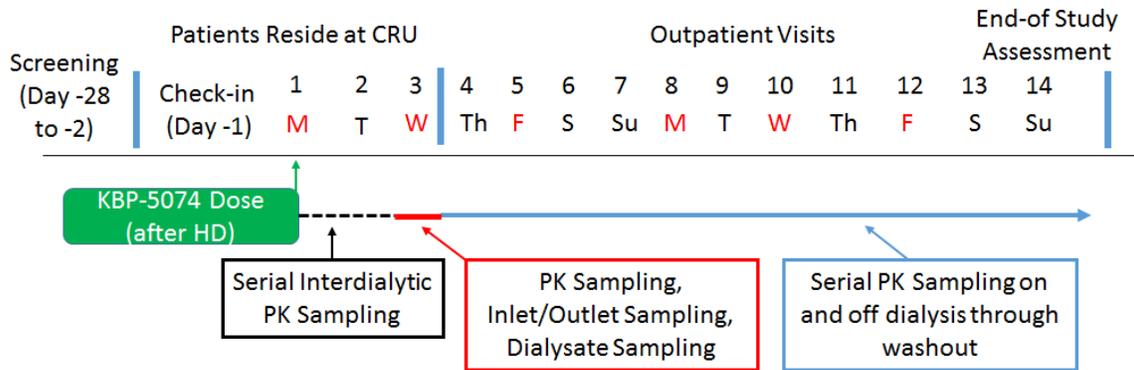
In Part 2, a single cohort (Cohort 2) of 6 HD patients will receive a single dose of 0.5 mg KBP-5074 on the same day of HD (immediately after the HD). Following dosing, patients will be followed for 13 days for PK and safety assessments (see Table 12-2). The PK

samples will be obtained relative to dose administration as follows (All PK samples will be collected within  $\pm 5$  minutes of the nominal time unless otherwise specified):

- During the interdialytic interval (using a venous stick or cannula) immediately predose (at time 0 [-5 min]; collected immediately prior to dosing, but following the termination of a previous dialysis session), 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose;
- During the second HD session at 44 (immediately prior to HD [using a venous stick or cannula; -5 min] and 5 minutes after the start of HD [inlet {arterial;  $\pm 1$  min} and outlet {venous;  $\pm 1$  min} samples]), 44.25, 44.5, 46, and 47 hours postdose, and at the end of the second HD session;
- Following dialysis at 48.5, 49, 50, 52, 72, 96, 120, 168, 216, 264, and 312 hours postdose.

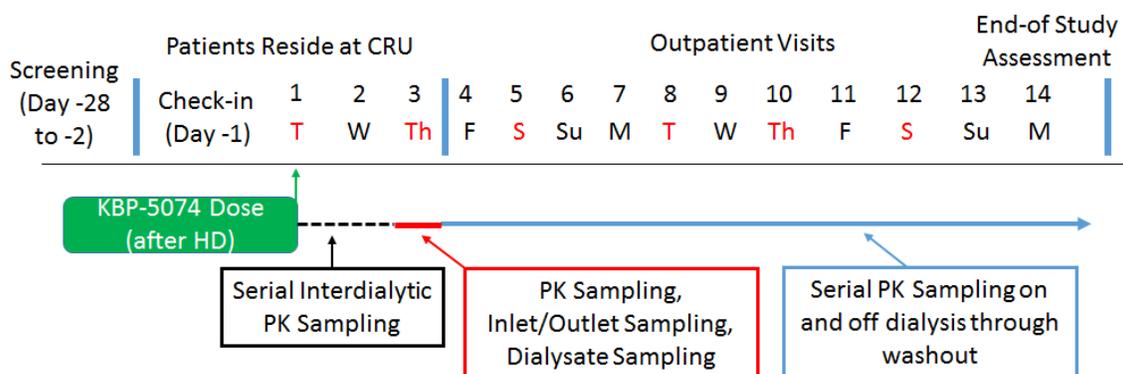
A study design schematic for a Monday, Wednesday, Friday (MWF) and Tuesday, Thursday, Saturday (TTS) HD schedule for Part 2 is presented in [Figure 3-2](#) and [Figure 3-3](#), respectively.

**Figure 3-2 Study Design Schematic for Part 2 (Monday, Wednesday, Friday HD Schedule)**



Abbreviations: CRU = clinical research unit; HD = hemodialysis; PK = pharmacokinetic.  
 Note: hemodialysis days are represented in red text.

**Figure 3-3 Study Design Schematic for Part 2 (Tuesday, Thursday, Saturday HD Schedule)**



Abbreviations: CRU = clinical research unit; HD = hemodialysis; PK = pharmacokinetic.  
 Note: hemodialysis days are represented in red text.

Patients in Part 1 and Part 2 will be screened to enter the study within 28 days (Day -28 to Day -2) prior to administration of KBP-5074 on Day 1. Eligible patients in Part 1 and Part 2 will be admitted to the CRU at Check-in (Day -1) and will undergo baseline assessments. Patients will remain confined from Check-in (Day -1) until 24 hours postdose for Part 1 and 52 hours postdose for Part 2 and PK and safety assessments will be performed during outpatient visits through the end of study assessment on Day 14.

Patients who withdraw prematurely from the study may be replaced at the discretion of the Investigator and KBP Biosciences Co., Ltd. to ensure that 12 patients complete the study (6 patients in each of Cohorts 1 and 2, in Parts 1 and 2, respectively).

Study assessments including physical examination findings, vital signs (blood pressure, pulse rate, respiratory rate and oral temperature), 12-lead ECGs, clinical laboratory findings, monitoring of AEs, and PK blood sampling will be performed at either screening, Check-in (Day -1), or after KBP-5074 dosing through the end of study assessment. Adverse events and serious adverse events (SAEs) will be assessed from the time the patient signs the informed consent form until exit from the study. A schedule of events for Part 1 and Part 2 is presented in [Table 12-1](#) and [Table 12-2](#), respectively.

### 3.1.1 Rationale of Study Design

The PK, safety, and tolerability of a single dose of KBP-5074 (up to 30 mg) have been evaluated previously in healthy male and female subjects. The PK, safety, and tolerability of multiple doses of KBP-5074 are also currently being evaluated in patients with mild and moderate CKD. In Part 1 of this study, patients with severe CKD will be enrolled in order to evaluate safety, tolerability, and PK in this patient population. Hemodialysis patients are included in Part 2 of this study because they represent the target population and PK and

safety data are needed in this population to support further clinical development of KBP-5074.

Females are included because both males and females are well-represented in the target clinical populations. Inclusion of both genders allows assessment of the possibility of a gender difference in the PK profile requiring gender-specific dose adjustment(s) in future clinical trials. Pregnancy precautions are specified to minimize the risk of unintentional fetal exposure.

The single dose study design is typically used for patient studies. Patients will be closely monitored throughout the study. A cohort size of 6 patients receiving KBP-5074 for Part 1 (Cohort 1) and Part 2 (Cohort 2) was empirically selected based on feasibility.

The safety assessments for this study are accepted measures for ensuring safety of patients during a clinical trial. The timepoints allowed for collection of PK samples for determination of KBP-5074 concentration are considered appropriate given the currently available information.

In contrast to many small molecule drugs, KBP-5074 has a relatively long terminal elimination phase half-life ( $t_{1/2}$ ; average >50 hours). For a drug with a long  $t_{1/2}$ , limited PK information can be obtained during a single interdialytic interval. Elimination of KBP-5074 will occur over several days and multiple dialysis sessions. As such, a single interdialytic interval will represent a small portion of the overall concentration-time profile for KBP-5074.

To address the long elimination half-life of KBP-5074, the current study will evaluate the PK following a single oral dose of KBP-5074. This dose will be administered following a dialysis session in Part 2. This single-dose approach has been used in the PK assessment for compound with relative long  $t_{1/2}$  in patients requiring HD.<sup>16</sup> Pharmacokinetic assessments will be performed during the subsequent interdialytic interval (approximately 44 hours), during the following dialysis session (approximately 4 hours), and through 312 hours postdose.

This approach will allow for a limited estimation of KBP-5074 PK parameters during the interdialytic period. In addition it will allow for estimation of parameters related to hemodialysis clearance of KBP-5074 (e.g., hemodialysis extraction ratio and hemodialysis clearance, hemodialysis recovery clearance). Finally, this approach will provide a full single-dose PK profile of KBP-5074 collected over multiple dialysis sessions and interdialytic intervals. This full PK profile can be compared to previous single-dose profiles in healthy patients and renally-impaired patients not undergoing hemodialysis.

Safety and tolerability will be assessed through physical examination findings, vital signs, 12-lead ECGs, clinical laboratory findings, and monitoring of AEs. The PK of KBP-5074 in

Part 2 will be assessed during the interdialytic period, during dialysis, and overall by obtaining blood samples, dialysate samples, and by calculating appropriate PK parameters.

## **4 Patient Selection and Withdrawal Criteria**

### **4.1 Selection of Study Population**

Approximately 12 patients will be enrolled at up to 4 sites in the US. Patients will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential.

#### **4.1.1 Inclusion Criteria**

Each patient must meet all of the following criteria to be enrolled in this study:

1. Male or female, between 18 and 75 years of age, inclusive.
2. Body mass index (BMI) between 19 and 42 kg/m<sup>2</sup>, inclusive.
3. Has severe CKD, defined as eGFR  $\geq 15$  mL/min/1.73 m<sup>2</sup> and  $\leq 29$  mL/min/1.73 m<sup>2</sup> based on the IDMS traceable<sup>15</sup> MDRD equation, according to laboratory results at Screening (non-HD patients only [Part 1]). Patients with a prior history of greater than 2 weeks of dialysis in the past and who have dialyzed in the 6 months prior to dosing on Day 1 will be excluded. Patients who have had temporary dialysis for acute kidney injury will be allowed at the discretion of the Investigator.
4. Serum potassium between 3.3 and 4.8 mmol/L, inclusive, at both Screening and Check-in (Day -1) (non-HD patients only [Part 1]). One repeat test will be allowed to exclude lab error or hemolyzed samples.
5. Is on a hemodialysis schedule for at least 45 days with KT/V  $\geq 1.2$  for end-stage renal disease (ESRD) regardless of the etiology including diabetes, with an average 3 hemodialysis sessions per week (HD patients only [Part 2]).
6. Is a nonsmoker or light smoker (smokes fewer than 10 cigarettes per day). Alcohol addressed in exclusion.

7. Female patients cannot be pregnant or lactating/breast-feeding and will either be postmenopausal (female patients who state they are postmenopausal should have had cessation of menses for >1 year and have serum follicle stimulating hormone [FSH] levels >40 mIU/mL and estradiol <20 pg/mL, surgically sterile (including bilateral tubal ligation, salpingectomy [with or without oophorectomy], surgical hysterectomy, or bilateral oophorectomy [with or without hysterectomy]) for at least 3 months prior to Screening, or will agree to use, from the time of Check-in (Day -1) until 90 days following the last dose of study drug, the following forms of contraception: double-barrier method, hormonal contraceptives, barrier with spermicide, diaphragm or cervical cap with spermicide, intrauterine device, oral, implantable, or injectable contraceptives, or a sterile sexual partner. All female patients will have a negative urine or serum pregnancy test result prior to enrollment in the study.
8. Male patients will either be surgically sterile or agree to use, from the time of Check-in (Day -1) until 90 days following the last dose of study drug, the following forms of contraception: male or female condom with spermicide and a female partner who is sterile or agrees to use the following contraceptives:
  - Diaphragm or cervical cap with spermicide.
  - Intrauterine device, oral, implantable, or injectable contraceptives.Male patients will refrain from sperm donation from the time of Check-in (Day -1) until 90 days following the last dose of study drug.
9. Is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.

#### 4.1.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. History of any prior or concomitant clinical condition or acute and/or unstable systemic disease compromising patient inclusion, at the discretion of the Investigator.
2. Has a history or presence of clinically significant (CS) cardiovascular, pulmonary, hepatic, gallbladder or biliary tract, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or psychiatric disease, which in the Investigator's opinion would not be suitable for the study from patient safety consideration and could interfere the results of the trial.
3. History of CS hypotension during the 6 months prior to the dose of study drug on Day 1 as determined by the Investigator.

4. History of symptomatic intradialytic hypotension as determined by the Investigator (mild to moderate decrease in blood pressure during dialysis is allowed; HD patients only [Part 2]).
5. History of CS hyperkalemia while on an angiotensin converting enzyme inhibitor, angiotensin receptor blocker, direct renin inhibitor, and/or MRA.
6. Hospitalization for hyperkalemia during the last 6 months prior to the dose of study drug on Day 1 or hyperkalemia  $>5.5$  mmol/L during the 2 weeks prior to the Screening visit.
7. History of stroke within 3 months prior to the dose of study drug on Day 1.
8. History of cardiac transplant.
9. History of severe uncontrolled arrhythmia, acute myocardial infarction, or acute coronary syndrome within 3 months prior to the dose of study drug on Day 1.
10. Clinical diagnosis of heart failure and persistent symptoms (New York Heart Association Class II to IV) at either the Screening visit or at Check-in (Day -1).
11. History of stomach or intestinal surgery (except that cholecystectomy, appendectomy, and/or hernia repair will be allowed).
12. History of prescription drug abuse, illicit drug use, or alcohol abuse according to medical history within 6 months prior to the Screening visit or any alcohol use or for at least 48 hours prior to dosing on Day 1.
13. History of clinically significant acute or chronic hepatitis (including infectious, metabolic, autoimmune, genetic, ischemic, or other forms), hepatocirrhosis, or hepatic tumors.
14. Positive blood screen for human immunodeficiency virus (HIV), hepatitis B surface antigen (HbsAg), or hepatitis C (HCV) antibody. If a patient with Severe renal impairment or on HD has positive test results for HCV antibody but liver function tests are otherwise not CS, the patient may be included at the Investigator's discretion.
15. Clinically significant abnormal liver function test at screening or Check-in (Day -1), defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT)  $>1.5$  times upper limit of normal (ULN) or total bilirubin  $>ULN$ .
16. Recent (within 3 month prior to the dose of study drug on Day 1) or planned coronary revascularization by angioplasty or cardiovascular surgery (excluding HD vascular access).

17. Kidney transplant scheduled within the year.
18. Systolic blood pressure <90 or >200 mmHg and/or diastolic blood pressure <60 or >110 mmHg during the Screening visit and before the dose of study drug on Day 1; may be repeated at the discretion of the Investigator.
19. Positive screen for alcohol or drugs of abuse (except for patients with a positive drug screen test if it is a result of a prescribed medication from their physician) at Screening and Check-in (Day -1). Hemodialysis patients will be tested with serum drug screen at Screening and using salivary testing at Check-in (Day -1).
20. Female is pregnant or breastfeeding within 2 years prior to the dose of study drug on Day 1 or positive pregnancy test (serum/urine) result during the Screening visit and before the dose of study drug on Day 1. Patients who have a false positive test attributable to their post-menopausal state or kidney disease, as determined by the Investigator, will be allowed to participate.
21. Has a known hypersensitivity to KBP-5074, aldosterone antagonists, or related compounds.
22. Receipt of any other investigational product within 30 days or 5 half-lives (whichever is longer) prior to the dose of study drug on Day 1.
23. Currently on a MRA (eg, spironolactone, eplerenone) or potassium sparing diuretics (eg, amiloride, triamterene).
24. Concomitant use of or treatment with any prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications within 14 days prior to Check-in (Day -1) and during the study. Exceptions may be made on a case by case basis following discussion and agreement between the Investigator and the Sponsor. Patients requiring HD (Part 2) may continue to receive routine medications (including vitamins, antidepressants, antihypertensive, and low dose aspirin) to maintain their stable medication regimen.
25. Use of any nutrients known to modulate cytochrome P450 (CYP)3A activity (based on the KBP-5074 metabolic pathway) or any strong or moderate inhibitors or inducers of CYP3A4, starting from 14 days prior to dose administration on Day 1 until the final end of study assessments, including but not limited to the following: inhibitors such as ketoconazole, miconazole, itraconazole, fluconazole, atazanavir, erythromycin, clarithromycin, ranitidine, cimetidine, verapamil, and diltiazem and inducers such as rifampicin, rifabutin, glucocorticoids, carbamazepine, phenytoin, phenobarbital, and St. John's wort.

26. Participated in strenuous exercise from 48 hours prior to Check-in (Day -1) or during the study through the final end of study assessment.
27. Has donated or lost a significant volume (>500 mL) of blood or plasma within 30 days prior to Check-in (Day -1).
28. Is an employee or family member of the Investigator or study site personnel.
29. Has problems understanding the protocol requirements, instructions, study related restrictions, and/or problems understanding the nature, scope, and potential consequences of participating in this clinical study.
30. Is unlikely to comply with the protocol requirements, instructions, and/or study related restrictions (eg, uncooperative attitude, unavailable for follow up call, and/or improbability of completing the clinical study).

## **4.2 Withdrawal of Patients from the Study**

The duration of the study is defined for each patient as the date signed written informed consent is provided through the end of study assessment, which will be on Day 14 for Part 1 and Part 2 or the date of Early Termination (ET) for patients who are withdrawn prior to the end of study assessment.

### **4.2.1 Reasons for Withdrawal/Discontinuation**

Patients may withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the study site. Every effort should be made to keep patients in the study. The reasons for patients not completing the study will be recorded. A patient may be withdrawn from the study for any of the following reasons:

1. Does not meet the protocol inclusion or exclusion criteria.
2. Noncompliance with the protocol.
3. A serious or intolerable AE that in the Investigator's opinion requires withdrawal from the study, including but not limited to laboratory safety assessments that reveal CS hematological or biochemical changes from the baseline values and symptoms or an intercurrent illness that justifies withdrawal.
4. Lost to follow-up.
5. Other (eg, pregnancy, development of contraindications of use of study drug).

6. The patient withdraws consent, or the Investigator or Sponsor decide to discontinue the patient's participation in the study.
7. The Investigator will also withdraw a patient if KBP Biosciences Co., Ltd. terminates the study.

Upon occurrence of a serious or intolerable AE, the Investigator will confer with the Sponsor. If a patient is discontinued because of an AE, the event will be followed until it is resolved. Any patient may withdraw his or her consent at any time.

Patient safety will be closely monitored throughout the study and the study will be conducted following GCP. All safety data and any available PK data will be reviewed after each cohort for Part 1 and Part 2 of the study to ensure patient safety. The entire study may be stopped at any time at the discretion of the Investigator in consultation with KBP Biosciences Co., Ltd.

#### **4.2.2 Handling of Withdrawals**

Patients are free to withdraw from the study or study treatment at any time upon request. Patient participation in the study may be stopped at any time at the discretion of the Investigator or at the request of the Sponsor.

Patients who discontinue study treatment or active participation in the study will no longer receive study drug. When a patient withdraws from the study, the reason(s) for withdrawal shall be recorded by the Investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, all patients who discontinue study treatment or withdraw from the study prematurely will undergo all end-of-study assessments at the time of ET. Patients who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. Methods for follow up will consist of 2 documented phone calls followed by 1 registered letter.

It is vital to obtain follow-up data on any patient withdrawn because of an AE or serious adverse event (SAE). In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures.

#### **4.2.3 Replacements**

If the Investigator withdraws a patient for a reason related to the study drug (in the opinion of the Investigator), then the patient is considered discontinued from the study. Discontinued patients will be replaced if deemed necessary by the Sponsor.

If a patient does not complete the study for a reason that is unrelated to the study drug, the patient may be replaced if the Sponsor instructs the site to do so. The decision regarding the replacement of patients will be documented.

## 5 Study Treatments

### 5.1 Method of Assigning Patients to Treatment Groups

Severe CKD patients (Cohort 1) and HD patients (Cohort 2) will receive a single dose of 0.5 mg KBP-5074. A total of 6 patients will be assigned to each of Cohorts 1 and 2.

Each patient will be assigned a screening number. Once enrolled into the study, patients will be assigned a unique patient number starting with a 2 digit site number, followed by a unique 3 digit patient number.

Patients who replace discontinuing patients after the first study drug administration has taken place will be assigned the number of the discontinued patient +500 (eg, Patient 01101 will be replaced by Patient 01601, Patient 02202 will be replaced by Patient 02702).

### 5.2 Treatments Administered

All doses of KBP-5074 will be administered orally to patients at the CRU. Administration of each dose of study drug will be supervised, verified (see [Section 5.7](#)), and documented according to the CRU's standard operating procedures. The actual date and time of each dose administration will be entered in the eCRF.

In Part 1 of the study, non-HD patients with severe CKD in Cohort 1 will receive a single oral capsule dose of 0.5 mg KBP-5074 with up to 240 mL of room temperature water on Day 1 following a fast between 2 and 4 hours. The exact amount of water consumed will be recorded in the eCRF.

In Part 2 of the study, HD patients with severe CKD will receive a single 0.5 mg oral capsule dose of KBP-5074 with up to 240 mL of room temperature water following a fast between 2 and 4 hours. The exact amount of water consumed with the dose of KBP-5074 will be recorded in the eCRF. The dose of KBP-5074 will be administered on Day 1 immediately following a dialysis session.

### 5.3 Identity of Investigational Product

The Sponsor (KBP Biosciences Co., Ltd.) will provide adequate supplies of KBP-5074 for use during the study as shown in [Table 5-1](#).

**Table 5-1 Investigational Product**

	<b>KBP-5074</b>	
<b>Strength</b>	0.5 mg	
<b>Formulation</b>	Capsules	
<b>Supplier/ manufacturer</b>	KBP Biosciences Co., Ltd. 116 Village Blvd, Suite 210 Princeton, New Jersey 08540	Frontage Laboratories, Inc. 75 East Uwchlan Ave, Suite 126 Exton, Pennsylvania 19341

## **5.4 Management of Clinical Supplies**

### **5.4.1 Study Drug Packaging and Storage**

KBP-5074 capsules, 0.5 mg are packaged in high-density polyethylene (HDPE) bottles and sealed with aluminum foil.

KBP-5074 capsules, 0.5 mg must be stored at room temperature in tightly closed containers and protected from light. Doses of KBP-5074 will be prepared and dispensed by qualified CRU staff.

### **5.4.2 Test Article Accountability**

The Investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much test article is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations.

## **5.5 Overdose Management**

An overdose is any dose of study treatment given to a patient or taken by a patient that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the Investigator. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported on relevant AE/SAE sections in the eCRF.

### **5.5.1 Treatment of Overdose**

In the event of suspected overdose, the appropriate supportive clinical care should be instituted at the discretion of the Investigator or as dictated by the patient's clinical status.

## **5.6 Blinding**

This is an open-label study and no blinding procedures will be used.

## **5.7 Treatment Compliance**

Each dose of study drug will be administered by delegated study staff under direct medical supervision of the Investigator. A hand and mouth check will be performed immediately after each study drug administration to verify that the study drug was swallowed. The determination of plasma concentrations of KBP-5074 during the analytical phase will provide further confirmation of treatment compliance.

## **5.8 Prior and Concomitant Therapy**

Prior medications will be collected within 30 days prior to KBP-5074 dosing on Day 1. Use of all concomitant medications will be recorded in the patient's eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications also will be recorded in the patient's eCRF.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the Investigator. However, it is the responsibility of the Investigator to ensure that details regarding the medication are recorded in full in the eCRF.

### **5.8.1 Permitted Therapy**

Concomitant therapy includes all medications and non-medication interventions used by a patient starting from 4 weeks prior to the first dosing through the end of study assessment. Medications include prescription drugs, over-the-counter drugs, approved dietary and herbal supplements, and nutritional supplements; examples of non-medication interventions include individual psychotherapy, cognitive behavioral therapy, smoking cessation therapy, and rehabilitative therapy. All concomitant medications and non-medication interventions should be reported to the Investigator and recorded in the concomitant medications eCRF.

As a general rule, no concomitant medication will be permitted unless the rationale for use is discussed between the Investigator and the Sponsor, and is clearly documented. The following medications are exceptions:

- Medications used to treat AEs may only be prescribed after consultation with the Medical Monitor (with the exception of acetaminophen and paracetamol), unless there is an immediate medical need to ensure the well-being of the patient that should

not be delayed. All therapy and/or medication administered to manage AEs should be recorded in the AE eCRF.

- Hormone replacement therapy: continue using if initiated at least 2 months prior to the first dose of study drug.
- Acetaminophen and paracetamol is allowed at a maximum dose of 2 g per day up to 48 hours prior to dosing. During the confinement period at the CRU, patients will be restricted from the use of acetaminophen and paracetamol and other non-prescription medications beginning 4 hours prior to study drug administration through 4 hours after study drug dosing, unless deemed necessary to treat an AE by the Investigator.
- Patients requiring HD may continue to receive routine medications to maintain their stable medication regimen.

### **5.8.2 Prohibited Therapy**

Prohibited medications include but are not limited to:

- Any other investigational drug taken within 30 days or 5 half-lives (whichever is longer) prior to the dose of study drug on Day 1.
- Patients will refrain from taking MRAs (eg, spironolactone, eplerenone) or potassium sparing diuretics (eg, amiloride, triamterene).
- Use of or treatment with any prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications within 14 days prior to Check-in (Day -1) and during the study. Exceptions may be made on a case by case basis following discussion and agreement between the Investigator and the Sponsor. Patients requiring HD (Part 2) may continue to receive routine medications (including vitamins, antidepressants, antihypertensive, and low dose aspirin) to maintain their stable medication regimen.
- Use of any nutrients known to modulate CYP3A activity (based on the KBP-5074 metabolic pathway) or any strong or moderate inhibitors or inducers of CYP3A4, starting from 14 days prior to dose administration on Day 1 until the final end of study assessments, including but not limited to the following: inhibitors such as ketoconazole, miconazole, itraconazole, fluconazole, atazanavir, erythromycin, clarithromycin, ranitidine, cimetidine, verapamil, and diltiazem and inducers such as rifampicin, rifabutin, glucocorticoids, carbamazepine, phenytoin, phenobarbital, and St. John's wort.

- Unless part of an established, stable medication regimen for patients requiring HD, any prescribed or over-the-counter medications, are prohibited within 2 weeks prior to the first dosing until the final end of study assessment.

## **5.9 Diet, Fluid, and Activity Control**

Patients will refrain from strenuous exercise from 48 hours prior to Check-in (Day -1) or during the study through the final end of study assessment.

Doses of KBP-5074 will be administered with up to 240 mL of room temperature water. Patients will be required to abstain from consuming water from 1 hour prior to dosing of KBP-5074 and for 1 hour postdose. At all other timepoints, patients may consume water on an ad libitum basis.

Light smoking (fewer than 10 cigarettes per day) is permitted during the study.

During confinement at the CRU, patients will receive standardized meals. Meals or snacks may be provided to patients requiring HD as needed per the Investigator's discretion.

Patients will be advised to maintain their normal diet and not consume alcohol or potassium-rich foods or drinks during the study period.

## **6 Study Assessments and Procedures**

Before performing any study procedures, all potential patients will sign an informed consent form (ICF). Patients will have the opportunity to have any questions answered before signing the ICF. The Investigator must address all questions raised by the patient.

The study assessments to be performed at each visit and timepoint are specified in separate schedules for each part of the study. The schedule of events for Part 1 and Part 2 are presented in [Table 12-1](#) and [Table 12-2](#), respectively.

### **6.1 Safety and Tolerability Assessments**

The safety and tolerability of KBP-5074 will be assessed by evaluation of AEs, physical examinations, vital sign measurements, ECGs, and clinical laboratory parameters (hematology, clinical chemistry, and urinalysis). Additional safety assessments may be performed as needed at the discretion of the Investigator. Safety assessments will be performed at scheduled intervals from Day 1 through the end of study assessment.

### **6.1.1 Body Height, Weight, and BMI**

At Screening, body height (centimeters) and weight (kilograms) will be measured, and BMI will be calculated ( $\text{BMI} [\text{kg}/\text{m}^2] = \text{body weight} [\text{kg}] / \text{height}^2 [\text{m}^2]$ ).

### **6.1.2 Physical Examinations**

Full physical examinations include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose, and throat, respiratory system, cardiovascular system, gastrointestinal system, neurologic condition, blood and lymphatic systems, and the musculoskeletal system. A licensed physician or qualified designee will conduct the examinations.

Brief physical examinations include, at a minimum, assessment of the following systems: skin, head, eyes, and throat, chest and heart auscultation, abdominal examination, neurologic condition (ie, alert and oriented x3; not including cranial nerves), and edema assessment. A licensed physician or qualified designee will conduct the examinations.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator. Symptom-directed physical examinations will be performed as appropriate for patients experiencing AEs.

Medical history and demographic data, including name, sex, age, race, and use of alcohol and tobacco, will be recorded at Screening.

### **6.1.3 Vital Sign Measurements**

Vital sign measurements will include systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate, and body temperature and will be performed at the timepoints specified in [Table 12-1](#) and [Table 12-2](#) for Part 1 and Part 2, respectively. The allowable window for vital signs to be measured with respect to their nominal timepoint is -60 minutes for predose vital sign measurements and  $\pm 30$  minutes for postdose vital sign measurements.

Patients will remain at rest in a semi-recumbent position for a minimum of 5 minutes before vital sign measurements are obtained. For all patients, blood pressure and pulse rate will be measured using an automated sphygmomanometer. A confirmatory repeat vital sign measurement may be performed at the discretion of the Investigator. If other procedures are scheduled at the same timepoint, vital signs will be obtained first, before an ECG and/or blood draw.

### 6.1.4 12-Lead Electrocardiograms

Electrocardiogram parameters of ventricular rate, PQ or PR interval, QRS duration, QT interval (uncorrected), and QT interval corrected for heart rate according to Fridericia's formula (QTcF) will be performed at the timepoints specified in [Table 12-1](#) and [Table 12-2](#) for Part 1 and Part 2, respectively.

Electrocardiograms will be obtained with the patient remaining in a semi-recumbent position following 5 minutes of rest. If other procedures are scheduled at the same timepoint, the ECG should be obtained after vital sign measurements and/or before the scheduled blood draw. The allowable window for ECGs to be obtained with respect to their nominal timepoint is -60 minutes for predose ECGs and  $\pm 30$  minutes for postdose ECGs.

For all patients, ECGs will be reviewed, signed, and dated by the Investigator or a qualified designee. The ECGs will be classified as being one of three categories: normal, abnormal but not clinically significant (NCS), or abnormal and CS. All CS findings will be reported as AEs.

### 6.1.5 Clinical Laboratory Tests

Laboratory measurements (including hematology, clinical chemistry, and urinalysis) will be performed at the timepoints specified in [Table 12-1](#) and [Table 12-2](#) for Part 1 and Part 2, respectively. Clinical laboratory parameters for analysis are presented in [Table 6-1](#).

Serum potassium levels of study patients will be closely monitored throughout this study. To ensure quick access to laboratory results, serum potassium levels will be tested in local laboratories in this study. If serum potassium is  $>5.6$  mmol/L during a scheduled/unscheduled visit, serum potassium levels should be repeated as early as feasible (no more than 48 hours). For patients who currently take potassium supplementation, it is recommended that the repeat test of serum potassium be taken 24 hours after the stopping of potassium supplementation if the Investigator considers it clinically safe and feasible.

A single repeat of laboratory testing at Screening and Day -1 are allowed to rule out lab error (i.e. hemolysis in potassium specimens).

Urine or serum pregnancy tests (all female patients) and FSH tests (postmenopausal female patients) will be performed at the timepoints specified in [Table 12-1](#) and [Table 12-2](#) for Part 1 and Part 2, respectively.

An alcohol breath test and drug screen will be administered to all patients at the timepoints specified in [Table 12-1](#) and [Table 12-2](#) for Part 1 and Part 2, respectively.

**Table 6-1 Clinical Laboratory Parameters**

<b>Chemistry Panel</b>	<b>Hematology</b>	<b>Urinalysis</b>
Alanine aminotransferase	Hematocrit	pH
Albumin	Hemoglobin	Specific gravity
Alkaline phosphatase	Red blood cell count	Protein
Aspartate aminotransferase	Quantitative platelet count	Glucose
Bilirubin	White blood cell count	Ketones
Blood urea nitrogen	with differential (total and %):	Bilirubin
Calcium	Neutrophils	Blood
Chloride	Lymphocytes	Nitrite
Cholesterol	Monocytes	Urobilinogen
CO <sub>2</sub>	Eosinophils	Leukocyte esterase
Creatinine	Basophils	
Gamma-glutamyltransferase		
Glucose	<b>Other Tests</b>	<b>Drug Screen</b>
Iron	HIV	Alcohol test –Breathalyzer
Lactate dehydrogenase	HbsAg	Drug screen: <sup>a</sup>
Phosphorous	HCV	Cocaine
Potassium	Pregnancy test (female patients)	Amphetamines
Protein	FSH (postmenopausal female	Barbiturates
Sodium	patients)	Benzodiazepines
Triglycerides		Opiates
Uric acid		Methadone

Abbreviations: FSH = follicle stimulating hormone; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus.

<sup>a</sup> For patients in Part 1, a urine or salivary drug test will be performed at Screening and Check-in (Day -1). Hemodialysis patients in Part 2 will be tested with a serum drug screen at Screening and using salivary testing at Check in (Day -1).

### 6.1.5.1 Sample Collections

Instructions regarding the collection, processing, and shipment of laboratory samples is detailed in a separate laboratory manual. All samples will be given a unique identifier. The exact clock time of dosing, as well as actual sample collection date and time will be entered on the eCRF.

After all of the PK samples from a single patient have been collected and frozen at  $-70^{\circ}\text{C}$  or colder, the primary samples from each time point can be batched together with corresponding primary samples from other patients and carefully packaged and shipped frozen at  $-70^{\circ}\text{C}$  or colder to the bioanalytical laboratory designated by the Sponsor. Samples are to be shipped with sufficient dry ice to remain frozen during overnight transit. For each patient and time point, the remaining stored aliquots will be retained on site at  $-70^{\circ}\text{C}$  or colder until released or requested by the Sponsor.

### **Pharmacokinetic Blood Collection and Processing**

Blood samples for the PK analysis of KBP-5074 will be collected at the timepoints specified in [Table 12-1](#) and [Table 12-2](#) for Part 1 and Part 2, respectively. In Part 1, all blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. In Part 2, blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein during the interdialytic interval and following HD. While HD patients are undergoing dialysis treatment, blood samples must be drawn from the predialyzer (inlet [arterial line]) and postdialyzer (outlet [venous line]) at the timepoints specified in [Table 12-2](#). Blood samples will be collected into labeled tubes containing sodium heparin.

In Part 2, serial PK samples will initially be collected during the postdose interdialytic interval (through approximately 44 hours postdose). Approximately 44 hours following dose administration, the next dialysis session will occur. Serial blood samples (inlet and outlet) as well as dialysate samples will be collected for the duration of this dialysis session (from approximately 44 hours postdose through approximately 48 hours postdose). Additional serial PK samples will be collected following this dialysis session through 312 hours postdose (see [Table 12-2](#)).

Immediately after the sample is collected, the tube should be gently inverted 5 to 8 times to thoroughly mix the anticoagulant and then placed upright in a cryoblock or test tube rack surrounded by ice until centrifugation. Samples will be centrifuged at  $1500 \times g$  for 10 minutes at approximately  $4^{\circ}\text{C}$  within 30 minutes of collection. The resultant plasma will be divided into 2 equal aliquots, placed in individual cryovials, and immediately frozen at  $-70^{\circ}\text{C}$  or colder within 1 hour of collection. The samples will be kept frozen at  $-70^{\circ}\text{C}$  or colder pending shipment to the bioanalytical laboratory. Additional details, including the acceptance of shipments by the bioanalytical laboratory, will be provided in a separate laboratory manual.

### **Dialysate Collection and Processing**

Dialysate will be collected for HD patients in Part 2 only. Pooled dialysate samples will be collected during specific intervals as specified in [Table 12-2](#). Sample aliquots of the dialysate will be collected and frozen at  $-70^{\circ}\text{C}$  or colder and the total volume of the collected dialysate will be recorded. The samples will be kept frozen at  $-70^{\circ}\text{C}$  or colder pending

shipment to the bioanalytical laboratory. Additional details, including the acceptance of shipments by the bioanalytical laboratory, will be provided in a separate laboratory manual. DaVita Clinical Research will document the make and model of the dialyzer, blood flow, and dialysate flow for this study.

## **6.1.6 Adverse Events**

### **6.1.6.1 Definitions of Adverse Events**

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug. Patients will be instructed to contact the Investigator at any time after signing the ICF until the final end of study assessment if any symptoms develop.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

An SAE is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### **6.1.6.2 Eliciting and Documenting Adverse Events and Serious Adverse Events**

Adverse events and SAEs will be assessed from the time the patient signs the informed consent form until exit from the study.

At every study visit, patients will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to patient observations, AEs will be documented from any data collected on the AE page of the eCRF (eg, laboratory values, physical examination findings, ECG changes) or identified from review of other documents (eg, patient diaries) that are relevant to patient safety.

### **6.1.6.3 Reporting Adverse Events**

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, dose, event term, time of onset, Investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital sign measurements), including those that worsen from baseline, deemed to be CS in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

However, any CS safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition, are not to be reported as AEs or SAEs.

Any AE that meets SAE criteria ([Section 6.1.6.1](#)) must be reported to the Sponsor and Medical Monitor immediately (ie, within 24 hours) after the time site personnel first learn about the event.

The Medical Monitor will be notified immediately (ie, within 24 hours) upon receipt of an SAE from the CRU using the following contact information:

Bin Zhang, MD  
Senior Vice President, Clinical Development  
KBP Biosciences Co., Ltd.  
116 Village Boulevard, Suite 210  
Princeton, New Jersey 08540  
Telephone: 609-216-2032

In addition the SAE will be reported to DaVita Clinical Research within 24 hours as outlined in the site training materials and SAE reporting instructions. The immediately reportable SAE reports will be submitted to DaVita Clinical Research for documentation and handling and 24 hour monitoring of SAEs will be provided by the Investigator at the CRU as listed on the FDA 1572.

#### **6.1.6.4 Assessment of Severity**

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild: These events require minimal or no treatment and do not interfere with the patient's daily activities.

Moderate: These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning.

Severe: These events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

#### **6.1.6.5 Assessment of Causality**

The Investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the test article in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the Investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

### **6.1.6.6 Follow-Up of Patients Reporting Adverse Events**

All AEs must be reported in detail on the appropriate page of the eCRF and followed to satisfactory resolution, until the Investigator deems the event to be chronic or not CS, or until the patient is considered to be stable.

## **6.2 Laboratory Analyses**

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital sign measurements), including those that worsen from baseline, felt to be CS in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

However, any CS safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition, are not to be reported as AEs or SAEs.

### **6.3 Pregnancy**

Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using a clinical study pregnancy reporting form. To ensure patient safety, each pregnancy must be reported to KBP Biosciences Co., Ltd. Within 2 weeks of learning of its occurrence. The pregnancy must be followed-up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient was discontinued from the study. Pregnancy complications and elective terminations for medical reasons will be reported as an SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the patient has completed the study, and considered by the Investigator as possibly related to the study treatment, must be promptly reported to KBP Biosciences Co., Ltd.

## **7 Statistical and Analytical Plan**

### **7.1 Pharmacokinetic Variables**

#### **Part 1:**

The following PK parameters will be calculated using noncompartmental methods, whenever possible, based on plasma KBP-5074 concentrations:

<b>PK Parameter</b>	<b>Definition</b>
$C_{\max}$	maximum concentration
$t_{\max}$	time to maximum concentration
$AUC_{0-t}$	area under the concentration-time curve from time 0 until the last quantifiable concentration, calculated using the linear trapezoidal rule for increasing values, and the log trapezoidal rule for decreasing values
$AUC_{0-24h}$	area under the concentration-time curve from time 0 until 24 hours postdose, calculated using the linear trapezoidal rule for increasing values, and the log trapezoidal rule for decreasing values
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity, calculated as: $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda z$
$\lambda z$	apparent terminal elimination rate constant
$t_{1/2}$	terminal elimination phase half-life, calculated as $\ln(2)/\lambda z$
$CL/F$	total body clearance, calculated as $Dose/AUC_{0-\infty}$
$V_z/F$	volume of distribution

## Part 2:

The following PK parameters will be calculated using noncompartmental methods, whenever possible, based on plasma KBP-5074 concentrations during the initial interdialytic interval:

<b>During Interdialytic Interval</b>	
<b>PK Parameter</b>	<b>Definition</b>
$C_{max}$	maximum concentration
$t_{max}$	time to maximum concentration
$AUC_{0-24h}$	area under the concentration-time curve from time 0 until 24 hours postdose, calculated using the linear trapezoidal rule for increasing values, and the log trapezoidal rule for decreasing values
$AUC_{0-44h}$	area under the concentration-time curve from time 0 until 44 hours postdose, calculated using the linear trapezoidal rule for increasing values, and the log trapezoidal rule for decreasing values
$AUC_{0-ti}$	area under the concentration-time curve from time 0 until the last timepoint during the first interdialytic interval, calculated using the linear trapezoidal rule for increasing values, and the log trapezoidal rule for decreasing values
$\lambda_z$	apparent terminal elimination rate constant
$t_{1/2}$	terminal elimination phase half-life, calculated as $\ln(2)/\lambda_z$

The following PK parameters will be calculated using noncompartmental methods, whenever possible, based on plasma KBP-5074 concentrations during dialysis and overall:

<b>During Dialysis</b>	
<b>PK Parameter</b>	<b>Definition</b>
Inlet $AUC_{t0-t1}$	area under the concentration-time curve from start of dialysis ( $t_0$ ) to the end of dialysis ( $t_1$ ) based on inflow concentrations. AUC will be calculated using the linear trapezoidal rule for increasing values, and the log trapezoidal rule for decreasing values
Outlet $AUC_{t0-t1}$	area under the concentration-time curve from start of dialysis ( $t_0$ ) to the end of dialysis ( $t_1$ ) based on outflow concentrations. AUC will be calculated using the linear trapezoidal rule for increasing values, and the log trapezoidal rule for decreasing values.
Outlet:Inlet Concentration Ratio	ratio of outflow to inflow concentrations based on time-matched inflow and outflow samples
Outlet:Inlet AUC Ratio	ratio of Outlet $AUC_{t0-t1}$ to Inlet $AUC_{t0-t1}$
$CL_{D, Recovery}$	estimated hemodialysis recovery clearance, where: $CL_{D, Recovery} = \text{Amount Recovered in Dialysate} / \text{Inlet } AUC_{t0-t1}$

$CL_D$	estimated hemodialysis clearance, where: $CL_D = Q * (C_i - C_o) / C_i$ $Q$ – Inlet blood flow, $C_i$ – Inlet concentration (arterial), and $C_o$ – Outlet concentration (venous)
$ER_D$	hemodialysis extraction ratio, where: $ER_D = (C_i - C_o) / C_i$ $C_i$ – Inlet concentration (arterial) and $C_o$ – Outlet concentration (venous)
$\lambda_z$	apparent terminal elimination rate constant, as data permit
$t_{1/2}$	terminal elimination phase half-life, calculated as $\ln(2) / \lambda_z$ , as data permit

<b>Overall</b>	
<b>PK Parameter</b>	<b>Definition</b>
$C_{max}$	maximum concentration
$t_{max}$	time to maximum concentration
$AUC_{0-t}$	area under the concentration-time curve from time 0 until the last quantifiable concentration, calculated using the linear trapezoidal rule for increasing values, and the log trapezoidal rule for decreasing values
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity, calculated as: $AUC_{0-inf} = AUC_{0-t} + C_t / \lambda_z$
$\lambda_z$	apparent terminal elimination rate constant
$t_{1/2}$	terminal elimination phase half-life, calculated as $\ln(2) / \lambda_z$
$CL/F$	total body clearance, calculated as $Dose / AUC_{0-\infty}$
$V_z/F$	volume of distribution

Pharmacokinetic parameters will be calculated using a validated software program such as WinNonlin version 6.4 or higher. Additional PK parameters may be calculated or compartmental analysis may be performed, as appropriate, to fully characterize available data.

Additional details regarding the PK parameter calculations are presented in the Statistical Analysis Plan (SAP).

## 7.2 Safety Variables

The safety analysis will include physical examination findings, vital signs (blood pressure, pulse rate, respiratory rate and oral temperature), 12-lead ECGs, clinical laboratory findings (hematology, clinical chemistry, and urinalysis), and assessments of AEs. Safety data will be listed and summarized as detailed in the SAP.

## 7.3 Pharmacodynamic Variables

The pharmacodynamic (PD) analysis will include assessments of the change from baseline in concentrations of plasma aldosterone and serum potassium after single doses of KBP-5074. Pharmacodynamic data will be listed and summarized as detailed in the SAP.

## 7.4 Sample Size Calculations

No formal sample size calculations were performed. The sample size is based on what will provide sufficient data to obtain a PK profile. A total of 12 patients, both male and female patients with CKD, are planned for enrollment in the study.

## 7.5 Analysis Populations

The following analysis populations will be used in the statistical analyses.

Safety Population: The Safety Population will consist of all patients who receive any study drug. All analyses using the safety set will group patients according to treatment actually received.

Pharmacokinetic Population: The PK Population will consist of all patients who receive study drug and have adequate concentration-time data for the determination of PK parameters. All PK analyses will be performed using the PK Population.

Pharmacodynamic Population: The PD Population will consist of all patients who receive study drug and have at least 1 postdose PD concentration of aldosterone and potassium. All PD analyses will be performed using the PD Population.

## 7.6 Description of Subgroups to be Analyzed

No subgroup analyses are planned.

## 7.7 Statistical Analysis Methodology

Statistical analysis will be performed using SAS<sup>®</sup> software Version 9.3 or higher. All continuous variables will be summarized using the following descriptive statistics: n, mean,

standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using the following descriptive statistics: frequency counts and percentages. All data will be listed in data listings.

Further details of the statistical analyses, methods, and data conventions are described in the SAP. The SAP will be prepared by DaVita Clinical Research and approved by the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate in the plan.

The general principles listed below will be applied throughout the study:

- Unless otherwise stated, continuous data will be summarized with the following descriptive statistics: number of non-missing observations (n), mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, frequencies and percentages of patients will be presented.
- All study data will be included in the individual patient data listings. All summary tables will present descriptive statistics for the parameters to be analyzed, wherever applicable.
- Missing data will not be imputed but will be analyzed as missing.

### **7.7.1 Pharmacokinetic Analysis**

Pharmacokinetic parameter endpoints for KBP-5074 will be calculated, listed, and summarized using descriptive statistics as detailed in the SAP. Pharmacokinetic parameter listings and statistical summaries will be generated separately for each study part. Part 2 PK parameters also will be listed and summarized for the following periods: during the interdialytic interval, during dialysis, and overall.

KBP-5074 concentration data will be listed and summarized by study part and collection time point as detailed in the SAP. Part 2 concentration data will be listed and summarized for the following periods: during the interdialytic interval, during dialysis, and overall.

### **7.7.2 Safety Analyses**

#### Adverse Events

An overall summary of the number and percentage of patients in each category will be presented, as will an overall summary of the number of events in each category. The number and percentage of patients reporting AEs in each category above will be summarized by

cohort and part of the study according to the system organ class (SOC) and preferred term (PT) assigned to the event using MedDRA.

All AE data will be listed for all patients. Both the Investigator's verbatim terms and the MedDRA preferred terms will be listed for each patient. Listings will also include the SAEs, start and end time and date of AEs, relationship to study drug, severity, and action taken for the AEs. A summary of deaths (for all deaths, AE outcome, not AE term, is death) will be provided by number and percentage of patients by cohort.

### Vital Signs

Changes from baseline in vital signs at each scheduled timepoint will be summarized by study part and cohort for the safety population using descriptive statistics (number [n], mean, SD, median, minimum, and maximum). The baseline value is defined as the last value observed prior to first administration of study drug on Day 1. The change from baseline is defined as the post-baseline value minus the baseline value. There will not be any imputation for missing values. All vital sign data will be listed individually by each patient based on the safety population.

### ECGs

A listing will be provided for Investigator-identified ECG abnormalities from safety ECGs. Overall evaluation of safety ECGs will be summarized by study part and cohort using frequency counts and percentage of patients as normal or abnormal, and the relevance of the abnormality will be summarized by "CS" or "NCS".

Continuous ECG parameters including heart rate, ventricular rate, PQ or PR interval, QRS duration, QT interval (uncorrected), and QTcF interval will be summarized for each study part and over each scheduled timepoint in terms of absolute values using descriptive statistics (n, mean, SD, median, minimum, and maximum).

### Physical Examination

Changes in baseline in physical examination findings (Normal, Abnormal-NCS, Abnormal-CS) will be summarized using counts and percentages for each study part and each cohort, and will also be listed individually for each scheduled timepoint.

### Clinical Laboratory Tests

All laboratory data will be summarized by study part and cohort, and at each scheduled timepoint using descriptive statistics (n, mean, SD, median, minimum, and maximum).

The baseline value is the last value observed prior to first administration of study drug and any information taken after first administration of study drug is regarded as post baseline

information. The change-from-baseline variables will be calculated as the post-baseline value minus the value at baseline. Change from baseline on continuous data will be summarized using descriptive statistics at each scheduled time point by cohort. For categorical data, change-from-baseline will be summarized using frequency and proportion at each scheduled timepoint by cohort.

Individual data listings of laboratory results will be presented for each patient. Values outside of the laboratory's reference range (i.e, those with low or high values) will be flagged in the laboratory listings.

### **7.7.3 Pharmacodynamic Analyses**

The change from baseline in concentrations of plasma aldosterone and serum potassium after single doses of KBP-5074 will be summarized by study part and cohort, and at each scheduled time point using descriptive statistics (n, mean, SD, median, minimum, and maximum).

The baseline value is the last value observed prior to first administration of study drug and any values after first administration of study drug are regarded as post-baseline values. The change-from-baseline variables will be calculated as the post-baseline value minus the value at baseline.

### **7.7.4 Other Analyses**

Summary statistical analyses will be provided for patient disposition, demographics, medical history, physical examination, and concomitant medications.

## **7.8 Data Quality Assurance**

Standard operating procedures are available for all activities performed at the study sites relevant to the quality of this study. Designated study site personnel will be responsible for maintaining quality assurance and quality control to ensure that the study conduct as well as data collection and documentation are performed in compliance with the study protocol, GCP, and Good Laboratory Practice requirements, and applicable regulatory requirements.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS<sup>®</sup> to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to statistical database lock.

Electronic CRFs can be printed directly from the database. Each eCRF will be reviewed and signed by the Investigator.

## **7.8.1 Data Management**

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECGs, etc.

Investigative site personnel will enter patient data into eCRFs using the Oracle Clinical Remote Data Capture program. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data) and follow Clinical Data Interchange Standards Consortium (CDISC) standard.

Clinical data management will be performed in accordance with applicable KBP Biosciences Co., Ltd. standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse events and concomitant medication terms will be coded using the MedDRA and World Health Organization Drug Dictionaries, respectively.

After database lock, each study site will receive a CD-ROM containing all site-specific eCRF data as entered into Oracle Clinical Remote Data Capture for the study, including full discrepancy and audit history. Additionally, a CD-ROM copy of all of the study site's data from the study will be created and sent to the Sponsor for storage. DaVita Clinical Research will maintain a duplicate CD-ROM copy for their records. In all cases, patient initials will not be collected or transmitted to the Sponsor.

## **8 Ethics**

### **8.1 Institutional Review Board**

Federal regulations and the ICH guidelines require that approval be obtained from an Institutional Review Board (IRB) before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with ICH harmonised tripartite guideline E6 (R1): GCP will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The Investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB. The Investigator must promptly supply the Sponsor or its designee, the IRB, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

## **8.2 Ethical Conduct of the Study**

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

## **8.3 Patient Information and Consent**

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each patient before entering the study or performing any unusual or non-routine procedure that involves risk to the patient. An informed consent template may be provided by the Sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor or its designee or both before IRB submission. Once reviewed, the consent will be submitted by the Investigator to his or her IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF.

The Investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

## **9 Investigator's Obligations**

The following administrative items are meant to guide the Investigator in the conduct of the study but may be patient to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

## **9.1 Confidentiality**

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the Food and Drug Administration (FDA), or the IRB.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

## **9.2 Financial Disclosure and Obligations**

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the Investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the Sponsor nor DaVita Clinical Research is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor DaVita Clinical Research is financially responsible for further treatment of the patient's disease.

## **9.3 Investigator Documentation**

Before beginning the study, the Investigator will be asked to comply with ICH E6 (R1) Section 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB approval
- Original signed Investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the Investigator and each Sub-Investigator listed on Form FDA 1572

- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493

#### **9.4 Study Conduct**

The Investigator agrees that the study will be conducted according to the principles of ICH E6 (R1). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins.

#### **9.5 Adherence to Protocol**

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6 (R1) and all applicable guidelines and regulations.

#### **9.6 Adverse Events and Study Report Requirements**

By participating in this study the Investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the Investigator agrees to submit annual reports to the study site IRB as appropriate.

#### **9.7 Investigator's Final Report**

Upon completion of the study, the Investigator, where applicable, should inform the institution; the Investigator/institution should provide the IRB with a summary of the study's outcome and the Sponsor and regulatory authority with any reports required.

#### **9.8 Records Retention**

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal

discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

## **9.9 Publications**

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor, but data and publication thereof will not be unduly withheld.

## **10 Study Management**

### **10.1 Monitoring**

#### **10.1.1 Monitoring of the Study**

The clinical monitor and/or designee, as a representative of the Sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the Investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and personnel.

All aspects of the study will be carefully monitored, by the Sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

#### **10.1.2 Inspection of Records**

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or a regulatory agency (eg, FDA or other regulatory agency) access to all study records.

The Investigator should promptly notify the Sponsor and DaVita Clinical Research of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

## **10.2 Management of Protocol Amendments and Deviations**

### **10.2.1 Modification of the Protocol**

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Sponsor or its designee. Amendments to the protocol must be submitted in writing to the Investigator's IRB for approval before patients can be enrolled into an amended protocol, and before the changes can be implemented.

### **10.2.2 Protocol Deviations**

The Investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

A protocol deviation is defined as an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB and agreed to by the Investigator. A major deviation occurs when there is not adherence to the protocol by the patient or Investigator that results in a significant, additional risk to the patient. Major deviations can include not adhering to inclusion or exclusion criteria, enrollment of the patient without prior Sponsor approval, or not adhering to FDA regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study ([Section 4.2](#)).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Investigators will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations in a timely manner.

## **10.3 Study Termination**

Although KBP Biosciences Co., Ltd. has every intention of completing the study, KBP Biosciences Co., Ltd. reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last patient completes the final end of study assessment.

## **10.4 Final Report**

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency as required by the applicable regulatory requirement(s). The Sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the Sponsor will provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study patients, as appropriate. The study results will be posted on publicly available clinical trial registers.

## 11 Reference List

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12. Pitt, B. et al. Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction. *N Engl JMed.* 348:1309–1321 (2003).
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## **12 Appendices**

### **12.1 Appendix: Schedule of Events**

**Table 12-1 Schedule of Events for Part 1**

Day	Screening	Patients Resident at CRU											Outpatient Visits						EOS <sup>11</sup>	
	-28 to -2	-1	Day 1 to Day 2											3	4	5	6	8	10	12
Hours		-24	0	2	4	6	8	10	12	18	24	48	72	96	120	168	216	264	312	
Admission to CRU		X																		
Discharge from CRU											X									
Informed Consent	X																			
Eligibility Assessment	X	X																		
Medical History	X																			
Demographics	X																			
Height (cm), Weight (kg), BMI	X																			
Previous Medications	X	X																		
Concomitant Medications			X																	
Physical Examination	X	X <sup>1</sup>																		X
Single 12-lead ECG <sup>2</sup>	X		X			X														X
Vital Signs (BP, PR, RR, T) <sup>3</sup>	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X
AE Assessment	X	X	X																	
Clinical Laboratory Samples <sup>4</sup>	X	X				X					X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X <sup>5</sup>	X
Dose Administration			X																	
PK Blood Samples <sup>6</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomarker Samples <sup>7</sup> (Aldosterone and Potassium)			X	X		X			X		X	X	X	X	X	X	X	X	X	X
HIV, Hepatitis B and C Screen	X																			
Drug/Alcohol Screen <sup>8</sup>	X	X <sup>9</sup>																		
Serum/Urine Pregnancy Test <sup>10</sup>	X	X																		X

AE= adverse event; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; EOS = end of study; HIV = human immunodeficiency virus; PR = pulse rate; PK = pharmacokinetics; RR = respiratory rate; T = temperature.  
 Note: baseline is the Day 1 predose (time 0) sample.

<sup>1</sup>Brief physical examination will be conducted at Check-in (Day -1).

<sup>2</sup>Patient should be resting in a semi-recumbent position for at least 5 minutes prior to ECG.

<sup>3</sup>Blood pressure, heart rate, respiratory rate and oral temperature will be measured in patients in a semi-recumbent position for at least 5 minutes.

<sup>4</sup>Clinical laboratory samples include: hematology, clinical chemistry, liver function, and urinalysis.

<sup>5</sup>Laboratory samples for only creatinine will be collected at 24, 48, 72, 96, 120, 168, 216, and 264 hours postdose.

<sup>6</sup>Blood samples for the determination of KBP-5074 concentrations and corresponding PK analysis will be collected at the following time points (All PK samples will be collected within  $\pm 5$  minutes of the nominal time unless otherwise specified): predose (at time 0 [-5 min], collected immediately prior to dosing) and 2, 4, 6, 8, 10, 12, 18, 24, 48, 72, 96, 120, 168, 216, 264, and 312 hours post dose.

<sup>7</sup>Serum and plasma samples for biomarkers (aldosterone and serum potassium) will be collected at the following time points (All biomarker samples will be collected within  $\pm 5$  minutes of the nominal time unless otherwise specified): predose (at time 0 [-5 min], collected immediately prior to dosing) and 2, 6, 12, 24, 48, 72, 96, 120, 168, 216, 264, and 312 hours post dose.

<sup>8</sup>Urine or salivary drug test performed at Screening and Check-in (Day -1).

<sup>9</sup>Alcohol test (via Breathalyzer) is performed at Check-in (Day -1).

<sup>10</sup>For female patients, urine or serum pregnancy test must be negative to enroll in the study. Patients who have a false positive test attributable to their post-menopausal state or kidney disease, as determined by the Investigator, will be allowed to participate.

<sup>11</sup>End-of-study assessment will be performed after PK blood draw on Day 14 or upon withdrawal/dismissal of a patient from the study.

**Table 12-2 Schedule of Events for Part 2**

Day	Screening	Patients Resident at CRU																				Outpatient Visits						EOS <sup>13</sup>				
	-28 to -2	-1	1						2						3						4	5	6	8	10	12	14					
Hours		-24	0	2	4	6	8	10	12	18	24	44	44.25	44.5	45	46	47	48	48.5	49	50	52	72	96	120	168	216	264	312			
Admission to CRU		X																														
Discharge from CRU																							X <sup>1</sup>									
Informed Consent	X																															
Eligibility Assessment	X	X																														
Medical History	X																															
Demographics	X																															
Height (cm), Weight (kg), BMI	X																															
Previous Medications	X	X																														
Concomitant Medications			X																													
Physical Examination	X	X <sup>2</sup>																												X		
Single 12-lead ECG <sup>3</sup>	X		X			X																								X		
Vital Signs (BP, PR, RR, T) <sup>4</sup>	X	X	X	X	X	X	X		X		X							X							X	X	X	X	X	X	X	X
AE Assessment	X	X	X																													
Clinical Laboratory Samples <sup>5</sup>	X	X				X																								X		
Dose Administration <sup>6</sup>			X																													

Day	Screening	Patients Resident at CRU																				Outpatient Visits						EOS <sup>13</sup>		
	-28 to -2	-1	1						2						3						4	5	6	8	10	12	14			
Hours		-24	0	2	4	6	8	10	12	18	24	44	44.25	44.5	45	46	47	48	48.5	49	50	52	72	96	120	168	216	264	312	
PK Blood Samples <sup>7</sup>			X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dialysate Sampling <sup>8</sup>													X	X	X	X	X													
Biomarker Samples (Aldosterone and Potassium) <sup>9</sup>			X	X		X			X		X												X	X	X	X	X	X	X	X
HIV, Hepatitis B and C Screen	X																													
Drug/Alcohol Screen <sup>10</sup>	X	X <sup>11</sup>																												
Serum/Urine Pregnancy Test <sup>12</sup>	X	X																												X

AE= adverse event; BP = blood pressure; CRU = clinical research unit; ECG = electrocardiogram; HIV = human immunodeficiency virus; PR = pulse rate; PK = pharmacokinetics; RR = respiratory rate; T = temperature.

Note: baseline is the Day 1 predose (time 0) sample.

<sup>1</sup>Patients in Part 2 will be discharged from the CRU after the dialysate collection on Day 3.

<sup>2</sup>Brief physical examination will be conducted at Check-in (Day -1).

<sup>3</sup>Patient should be resting in a semi-recumbent position for at least 5 minutes prior to ECG.

<sup>4</sup>Blood pressure, heart rate, respiratory rate and oral temperature will be measured in patients in a semi-recumbent position for at least 5 minutes.

<sup>5</sup>Clinical laboratory samples include: hematology, clinical chemistry, liver function, and urinalysis.

<sup>6</sup>Dosing will be based on the post dialysis weight from the last dialysis session prior to dosing.

<sup>7</sup>Blood samples for the determination of KBP-5074 concentrations and PK analysis will be collected relative to dose administration as follows (All PK samples will be collected within ±5 minutes of the nominal time unless otherwise specified):

- During the interdialytic interval (using a venous stick or cannula) immediately predose (at time 0 [-5 min]; collected immediately prior to dosing, but following the termination of a previous dialysis session), 2, 4, 6, 8, 10, 12, 18, and 24 hours postdose;
- During the second HD session at 44 (immediately prior to HD [using a venous stick or cannula; -5 min] and 5 minutes after the start of HD [inlet {arterial; ±1 min} and outlet {venous; ±1 min} samples]), 44.25, 44.5, 46, and 47 hours postdose, and at the end of the second HD session;
- Following dialysis (using a venous stick or cannula) at 48.5, 49, 50, 52, 72, 96, 120, 168, 216, 264, and 312 hours postdose.

<sup>8</sup>Cumulative dialysate will be collected and weight/volume determined for the following intervals: 44 to 44.5 hours, 44.5 to 45 hours, 45 to 46 hours, 46 to 47 hours, and 47 to 48 hours postdose. The dialysate collection will end at the end of dialysis (rather than at 48 hours) if a patient has dialysis for <4 hours. An additional sample may be collected until the end of dialysis for sessions lasting longer than 4 hours. The cumulative volume of dialysate collected during each interval will be documented. A 25 mL aliquot will be collected at the end of each interval for determination of KBP-5074 concentration.

<sup>9</sup>Serum and plasma samples for biomarkers (aldosterone and serum potassium) will be collected at the following time points (All biomarker samples will be collected within  $\pm 5$  minutes of the nominal time unless otherwise specified): predose (at time 0 [-5 min], collected immediately prior to dosing) and 2, 6, 12, 24, 48, 72, 96, 120, 168, 216, 264, and 312 hours post dose.

<sup>10</sup>Hemodialysis patients will be tested with a serum drug screen at Screening and using salivary testing at Check-in (Day -1).

<sup>11</sup>Alcohol test (via Breathalyzer) is performed at Check-in (Day -1).

<sup>12</sup>For female patients, urine or serum pregnancy test must be negative (to accommodate dialysis patients) to enroll in the study. Patients who have a false positive test attributable to their post-menopausal state or kidney disease, as determined by the Investigator, will be allowed to participate.

<sup>13</sup>End-of-study assessment will be performed after PK blood draw on Day 14 or upon withdrawal/dismissal of a patient from the study.