Document Type: Final Protocol

Document Date: 16 September 2021

Study Title: A First-in-Human, Phase I, Double-blind, Placebo-controlled, Single and Multiple Ascending Oral Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of KRP-A218 in Healthy Subjects, including Food-Effect and Drug-drug Interaction with Itraconazole

Protocol Reference Number: KRPA218-T101

NCT Number: NCT04908800

Protocol

A First-in-Human, Phase I, Double-blind, Placebo-controlled, Single and Multiple Ascending Oral Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of KRP-A218 in Healthy Subjects, including Food-Effect and Drug-drug Interaction with Itraconazole

Investigational Product: KRP-A218

Protocol Reference Number: KRPA218-T101
Labcorp Drug Development Study: 8411601
EudraCT Number: 2020-004687-26

Protocol Version Number: 5.0
Protocol Status: Final
Protocol Date: 16 September 2021

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SPONSOR APPROVAL

I have read the protocol and approve it:

PPD

INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

PPD

Rationale for Protocol Amendments

Version 4.0 to Version 5.0

This substantial amendment has been issued to make the following changes:

Primary Changes:

1. **Section 1.2:** Additional information has been added regarding the in vivo pharmacodynamics of CCI and the no observed adverse effect level (NOAEL) of CCI in mice.
2. **Section 1.3:** A summary of the safety and pharmacokinetic (PK) data of this ongoing Phase 1 study have been included in the Summary of Clinical Experience section.
3. **Table 3:** A new table has been added to present PK parameter data from the current ongoing Phase 1 study.
4. **Figure 5:** Dose levels specified in Part A, Groups A4 and A5, have been updated based on review of the safety and PK data from the preceding cohorts.
5. **Section 3.5:** The maximum dose level of Part A has been increased to 24 mg. The efficacy of CCI was determined in a CV-B3 infected mouse model and was observed to be dose dependent. CCI showed antiviral efficacy and improvement of survival rate. Significant efficacy was observed at 1, 3, and 10 mg/kg; however, the predicted therapeutic range (area under the concentration-time curve from time 0 to 24 hours [$AUC_{0\text{-}24h}$]) initially selected was 276 to 988 ng•h/mL, as 988 ng•h/mL (the $AUC_{0\text{-}24h}$ at 3 mg/kg) was lower than the exposure at the NOAEL in male rats whereas the mouse exposure at 10 mg/kg was higher than the exposure at the NOAEL in male rats. Therefore, the therapeutic range initially proposed was a conservative estimate and the optimal clinical therapeutic range may exceed the $AUC_{0\text{-}24h}$ of 988 ng•h/mL. Considering that the indication of KRP-A218 is human rhinovirus infection with a high risk of progressing to lower respiratory infection or other severe complications, it is necessary to achieve the expected exposure on the first day of administration. Based on the mean $AUC_{0\text{-}24h}$ observed in Groups A1 to A3 (Part A of this study), the expected clinical therapeutic dose that covers the $AUC_{0\text{-}24h}$ of 276 to 988 ng•h/mL on Day 1 is 2 to 8 mg (Table 4). To cover the estimated steady-state exposure of 8 mg with a single dose in this study, the mean exposure would need to be above 1730 ng•h/mL (mean $AUC_{0\text{-}24h}$*R) based on current human PK data. Moreover, considering the individual $AUC_{0\text{-}24h}$ values observed in Groups A1 to A3, it has been assumed that the maximum $AUC_{0\text{-}24h}$ may be in the range of approximately 2-fold the mean $AUC_{0\text{-}24h}$. Therefore, it is considered reasonable to set the dose escalation criteria at the NOAEL equivalent exposure (maximum $AUC_{0\text{-}24h}$ of 3930 ng•h/mL), which is approximately 2-fold of the estimated steady-state exposure at 8 mg (mean $AUC_{0\text{-}24h}$*R of 1730 ng•h/mL). In addition, based on safety data from this ongoing study at doses of 1 to 6 mg (Groups A1 to A3), no gastrointestinal findings of any concern have been observed. Therefore, in this Phase 1 study, it is planned to investigate higher doses within the range up to the NOAEL (5 mg/kg in male rats: maximum observed concentration [C_{max}] 1220 ng/mL, $AUC_{0\text{-}24h}$ 3930 ng•h/mL) as the maximum exposure for individuals. Exploring these higher doses in a Phase 1 study will allow adverse events to be more closely monitored than in Phase 2 or 3 studies. It will also allow the exploratory objective to collect data for concentration-QTc analysis to be more

relevant as according to regulatory guidance, the QTc response should be characterised at a sufficiently high multiple of the clinically relevant exposure. In addition, considering the predicted maximum systemic exposure and the observed maximum individual AUC_{0-24h} at 6 mg in Part A, the highest dose is estimated to be 17 mg (Table 6). Regardless of this estimate, the highest dose will be determined based on the review of the maximum AUC_{0-24h} value at the previous dose level; however, the maximum dose that will be administered in Part A will not exceed 24 mg, which is 2-fold the previous dose level.

6. **Table 5:** Doses for Part A, Groups A4 and A5, have been changed based on the same rationale as described for the changes in Section 3.5.
7. **Tables 4 and 6:** These tables have been added to present the observed and estimated human exposures at Day 1 and steady state.
8. **Section 3.7:** The PK dose escalation stopping criterion that capped mean systemic exposure levels at a C_{max} of 179 ng/mL and/or AUC_{0-24h} of 988 ng•h/mL has been removed based on the same rationale as described for the changes in Section 3.5. The PK dose escalation stopping criterion for individual systemic exposure levels has not been removed.
9. **Section 5.1:** The United Kingdom is no longer part of the European Union, so the Qualified Person in the European Union is now described as a Qualified Person in the United Kingdom.
10. **Table 7:** Doses for Part A, Groups A4 and A5, have been changed and therefore, the number of 1 and 10 mg KRP-A218 and placebo tablets have been updated to reflect the change in dose levels.
11. **Section 9:** The reference list has been updated with new references due to the new information added into Section 3.5.

Minor Changes:

1. **Throughout document:** Numbers have replaced Roman numerals when describing the phase of a study within the protocol body and synopsis. No change has been made to the study title.
2. **Synopsis:** Updated to reflect changes in the protocol body, as applicable.
3. Due to rebranding of Covance to Labcorp Drug Development, updates throughout the protocol have been made, as appropriate.
4. The amendment/version number and date were updated throughout the protocol.
5. Minor editorial changes.

Version 3.0 to Version 4.0

This nonsubstantial amendment has been issued to make the following changes:

1. **Synopsis:** clarified that the washout period for Group A2a will comprise an interval 7 to 10 days between doses of KRP-A218 (up to and including Day -1 of Treatment Period 2). The maximum study duration in Part A was updated from 51 to 50 days.
2. **Figure 2:** the washout period was updated to an interval of 7 to 10 days between doses (up to and including Day -1 of Treatment Period 2).
3. **Section 3.1.1:** clarified that the washout period for Group A2a will comprise an interval of 7 to 10 days between doses of KRP-A218 (up to and including Day -1 of

Treatment Period 2). Additionally, the maximum study duration for subjects in Group A2a has been updated from 47 to 50 days.

4. **Section 3.4:** the interval between doses of KRP-A218 updated to 7 to 10 days.
5. **Section 7.2.3:** Clarified that only a single pharmacogenetic sample will be required from each subject during the course of the study.
6. **Appendix 6 (Table 7: Schedule of Assessments-Part A [Group A2a; Single-Dose] [Washout to Follow-up visit]):** the duration of the washout period was updated to an interval of 7 to 10 days between dosing and footnote r updated to clarify that the interval is up to and including Day -1 of Treatment Period 2.

Version 2.0 to Version 3.0

This nonsubstantial amendment has been issued to make the following changes:

1. **Study Identification:** CCI has been added as an additional Clinical Laboratory for the measurement of faecal calprotectin, conduct of the faecal occult blood test, and as a DNA banking facility. CCI has been added as an electrocardiogram (ECG) vendor.
2. **Section 4.2:** addition of an exclusion criterion (#32) to exclude subjects that have received or plan to receive a Coronavirus Disease 2019 (COVID 19) vaccine within 28 days prior to dosing until after the follow-up visit.
3. **Appendix 1:** the serious adverse event reporting section has been updated for consistency with the Study Management Plan.
4. **Appendix 6 (Table 6: Schedule of Assessments-Part A [Groups A1, A2b, and A3 to A5; Single-Dose] and Table 7: Schedule of Assessments-Part A [Group A2a; Single-Dose]):** clarified that a continuous 12-lead ECG will be obtained from 2 hours predose and the timepoints for continuous ECG monitoring have been added to footnote g for Table 6 and footnote d for Table 7. Additionally, it has been clarified in these footnotes that subjects should be resting in a supine or semi-recumbent position during these monitoring periods.

Version 1.0 to Version 2.0

In the CV-B3-infected mouse model, CCI has shown significant antiviral efficacy in a dose dependent manner from 1 to 10 mg/kg and significantly improved the survival rate over 3 mg/kg. In the toxicological study, the NOAEL in male rat was < 5mg/kg. Therefore, the clinical therapeutic range has been set as 4.9 to 14.6 mg/subject based on the HED calculated from effective dose range in mouse from 1 to 3 mg/kg, considering the current NOAEL in the rat.

At the request of the Medicines and Healthcare products Regulatory Agency (MHRA), the primary changes in this amendment are:

1. **Section 3.1.1:** it has been clarified that the washout period in Group A2a may be extended based on the observed $t_{1/2}$ of CCI In addition, it has been clarified

that the follow-up period in Part A may also be extended based on the observed $t_{1/2}$ of CCI

2. **Section 3.1.2:** it has been clarified that the follow-up period in Part B may be extended based on the observed $t_{1/2}$ of CCI
3. **Section 3.1.3:** it has been clarified that the interval between the first dose of KRP-A218 and first dose of itraconazole may be extended depending on the observed $t_{1/2}$ of CCI In addition, it has been clarified that the follow-up period in Part C may also be extended based on the observed $t_{1/2}$ of CCI
4. **Section 3.4:** it has been clarified that the washout period in Group A2 may be extended based on the observed $t_{1/2}$ of CCI
5. **Section 3.5**: the maximum absolute clinical dose to be used in Part A has been updated to 15 mg, and rationale has been provided appropriately.
6. **Section 3.7:** dose escalation stopping criteria were updated to include the upper limit of the predicted therapeutic range.
7. **Appendix 4:** updated to exclude double-barrier methods as acceptable contraceptive methods.
8. **Figures 1, 2, 3, and 4, and Appendix 6**: footnotes have been added to reflect the changes to the study design about the timings of the washout period in Part A, interval between the first dose of KRP-A218 and first dose of itraconazole in Part C, and follow-up visits for all study parts that will now depend on the observed $t_{1/2}$ of CCI CCI as appropriate.
9. **Throughout:** Group A6 has been removed from Part A of the study, due to the change in the maximum absolute clinical dose to be used in Part A. Any reference to Group A6 has therefore now been replaced by Group A5, as this will now be the final dosing group in Part A of the study.

Minor changes:

10. The synopsis was updated according to the protocol body, as applicable.
11. The amendment/version number and date were updated throughout the protocol.

STUDY IDENTIFICATION

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Project Physician	PPD
Clinical Laboratory	CCI
Clinical Laboratory (Calprotectin Measurement, Faecal Occult Blood Test, and DNA Banking)	CCI

ECG Vendor	CCI
Bioanalytical Laboratory	CCI CCI
Statistician	PPD

SYNOPSIS

Title of Study:
A First-in-Human, Phase I, Double-blind, Placebo-controlled, Single and Multiple Ascending Oral Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of KRP-A218 in Healthy Subjects, including Food-Effect and Drug-drug Interaction with Itraconazole.

Objectives:

Single and Multiple Ascending Dose Study (Parts A and B):

The primary objective is:

- to evaluate the safety and tolerability of single and multiple oral doses of KRP-A218 in healthy subjects.

The secondary objectives are:

- to assess the pharmacokinetics (PK) of CCI (the active ingredient of KRP-A218) following single and multiple oral doses of KRP-A218 in healthy subjects.
- to assess the effect of food on the PK of CCI following a single oral dose of KRP-A218 in healthy male subjects.
- to assess the effect of sex on the PK of CCI following a single oral dose of KRP-A218.

The exploratory objectives are:

- to explore blood and urine samples for the metabolite profiles of CCI following single and multiple oral doses of KRP-A218 in healthy male subjects.
- to explore faecal samples for the metabolite profiles following a single oral dose of KRP-A218 in healthy male subjects.
- to explore blood and urine samples for pharmacodynamic biomarkers.
- to explore a potential effect of KRP-A218 on phospholipid-C in serum and faecal calprotectin.
- to collect blood samples for potential pharmacogenetic analyses.
- to collect continuous ECG waveforms for concentration-QTc analysis, following single oral doses of KRP-A218 in healthy subjects (Part A only).

Drug-drug Interaction Study (Part C):

The primary objective is:

- to assess the effect of multiple doses of itraconazole (cytochrome P450 3A4 inhibitor) on the single-dose PK of CCI in healthy male subjects.

The secondary objectives are:

- to assess the safety and tolerability of single oral doses of KRP-A218 when co-administered with multiple oral doses of itraconazole in healthy male subjects.
- to assess the PK of itraconazole and its metabolite hydroxy-itraconazole when co-administered with KRP-A218 in healthy male subjects.

The exploratory objectives are:

- to explore blood samples for the metabolite profiles of CCI administered KRP-A218 alone and when co-administered with itraconazole in healthy male subjects.
- to explore a potential effect of KRP-A218 on phospholipid-C in serum and faecal calprotectin.
- to collect blood samples for potential pharmacogenetic analyses.

Study Design:

This Phase 1 study will consist of 3 parts, Parts A, B, and C.

Part A will comprise a double-blind, randomised, placebo-controlled, single-dose, sequential-group, escalating-dose design, enrolling healthy male and female subjects (female subjects in Group A2b only). Part A will include a sex-effect (Groups A2a and A2b) which will investigate the effect of sex on PK of CCI by comparing PK parameters following dosing in females versus dosing in males. Part A will also include a food-effect Group A2a which will be a 2-period arm to investigate the effect of food on PK of CCI by comparing PK parameters following dosing in fed conditions versus dosing in fasted conditions.

Part B will comprise a double-blind, randomised, placebo-controlled, multiple-dose, sequential-group, escalating-dose design, enrolling healthy male subjects.

Part C will comprise an open-label, fixed-sequence, enrolling healthy male subjects to investigate the effect of multiple oral doses of itraconazole on the single oral dose PK of CCI in healthy subjects.

Part A:

There will be 5 groups, of which 4 will comprise male subjects, 1 will comprise male and female subjects.

Overall, 48 subjects will be studied in 5 groups (Groups A1 to A5); Groups A1, and A3 to A5 will consist of 8 male subjects, and Group A2 will consist of 16 subjects split into 2 subgroups (Group A2a [male subjects only] and Group A2b [female subjects only]) that will consist of 8 subjects each.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only, except for Group A2a, where each subject will participate in 2 treatment periods where doses of KRP-A218 will be separated by an interval of 7 to 10 days (up to and including Day -1 of Treatment Period 2). The washout period may be extended depending on the observed apparent terminal elimination half-life ($t_{1/2}$) of CCI. Subjects will reside at the study site from Day -1 (the day before dosing) to Day 4 of each treatment period.

All subjects will return for a follow-up visit 7 to 10 days after their final dose. The follow-up period may be extended depending on the observed $t_{1/2}$ of CCI In each of Groups A1, A2a, A2b, and A3 to A5, 6 subjects will receive KRP-A218 and 2 subjects will receive placebo. In Groups A1, A2b, and A3 to A5, all doses will be administered in the fasted state on the morning of Day 1. For Group A2a, Period 1, Day 1 doses will be administered in the fasted state and Period 2, Day 1 doses be will be given 30 minutes after starting a standard high-fat breakfast. Each subject in Groups A1, A2b, and A3 to A5 will receive only a single dose of KRP-A218 or placebo during the study. In Group A2a, subjects will have the same treatment in both periods, such that each subject will receive 2 single doses of KRP-A218 or placebo during the study.

All groups in Part A (with the exception of Group A2a in Treatment Period 2) will receive the investigational medicinal product (IMP) using a sentinel approach. For each group, 2 subjects (1 KRP-A218 and 1 placebo) will receive the IMP at least 24 hours before the remaining subjects.

Part B:

There will be 4 groups, consisting of male subjects. Part B may overlap with Part A.

Overall, 40 subjects will be studied in 4 groups (Groups B1 to B4), with each group consisting of 10 male subjects. Part B may start after completion of Group A3, at dose equal to or less than given in Groups A1 to A3.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only and reside at the clinical research unit (CRU) from Day -1 (the day before dosing) until the morning of Day 17 (following assessments at 72 hours after final dosing).

All subjects will return for a follow-up visit 7 to 10 days after their final dose. The follow-up period may be extended depending on the observed $t_{1/2}$ of CCI In each of Groups B1 to B4, 8 subjects will receive KRP-A218 and 2 subjects will receive placebo in accordance with a randomisation schedule. The dietary state for dosing in Part B will be subject to review of the PK data from the fed/fasted comparison in Part A. For all subjects, dosing will occur on Days 1 to 14. The planned dosing frequency is once per day, however the dosing frequency in Part B may be changed following review of data from groups in Part A. On Day 14, the last dose will be the morning dose regardless of the dosing frequency (QD, BID, TID).

The total daily dose administered will not exceed an exposure shown to be safe and well tolerated in Part A. All groups in Part B will receive the IMP using a sentinel approach. For each group, 2 subjects (1 KRP-A218 and 1 placebo) will receive the IMP at least 7 days before the remaining subjects.

Part C:

There will be 1 group, with Group C1 consisting of 12 male subjects. Part C will start after completion of blinded safety, tolerability, and PK data review in Part A. All subjects will receive each of the following treatments:

- Days 1 and 11: single oral dose of KRP-A218
- Day 4: 2 × single oral doses of 200 mg itraconazole, approximately 12 hours apart
- Days 5 to 13: single oral doses of 200 mg itraconazole

The study days of dosing of itraconazole and KRP-A218 may be amended to extend the interval between the first dose of KRP-A218 and the first dose of itraconazole depending on the observed $t_{1/2}$ of CCI

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Subjects will be admitted into the study site on Day -1 and be confined to the study site until discharge on Day 14.

Subjects will return to the study site for a follow-up visit 7 to 10 days after the last dose of KRP-A218. The follow-up period may be extended depending on the observed $t_{1/2}$ of CCI .

The dietary state for dosing of KRP-A218 alone on Day 1 and KRP-A218 co-administered with itraconazole on Day 11 will be determined by comparing the PK data between fed and fasted state in Group A2a. Itraconazole on Days 4 to 10, 12 and 13 will be administered in the fasted state. On Day 11, if it is determined that KRP-A218 will be dosed in the fasted state, then KRP-A218 will be administered first and itraconazole will be administered second. If it is determined that KRP-A218 will be dosed in the fed state, then itraconazole will be dosed first; subjects will then receive breakfast at approximately 1 hour post itraconazole dose, and KRP-A218 will be dosed second following breakfast. The dose level of KRP-A218 will be confirmed based on the available safety, tolerability, and PK data in preceding Parts A and/or B of the study.

Number of Subjects:

Part A: 40 male subjects and 8 female subjects will be studied in 5 groups.

Part B: 40 male subjects will be studied in 4 groups.

Part C: 12 male subjects will be studied in 1 group.

Diagnosis and Main Criteria for Inclusion:

Healthy male and female subjects aged between 20 and 55 years (inclusive).

Investigational Products, Dose, And Mode of Administration Route:

Test Products: KRP-A218 1 mg tablet, and 10 mg tablet

Proposed Dose Levels:

Part A: Males: 1, 3 (fasted/fed), 6, 12, and a maximum dose of 24 mg of KRP-A218
Females: 3 mg of KRP-A218

Part B: Males: X, X, X, and X mg of KRP-A218 (over a period of 14 days)

Part C: Males: X mg of KRP-A218 (once on Days 1 and 11)

Administration Route: Oral

Reference Product and Mode of Administration Route (Parts A and B):

Reference Product: placebo tablet

Administration Route: Oral

Concomitant Drug, Dose Level, and Administration route (Part C):

Concomitant Drug: itraconazole 10 mg/mL oral solution

Proposed Dose Level: 200 to 400 mg of itraconazole (200 mg twice on Day 4 and 200 mg once daily on Days 5 to 13)

Administration Route: Oral

Duration of Subject Participation in the Study:

Planned Screening Duration: up to 27 days.

Planned Study Duration (Screening to Follow-up):

Part A: up to 39 days, or up to 50 days for food-effect evaluation.

Part B: up to 52 days.

Part C: up to 49 days.

Endpoints:

Safety:

Adverse events, body weight, clinical laboratory evaluations (haematology, clinical chemistry [with the exception of phospholipid-C], urinalysis, coagulation, faecal occult blood), 12-lead ECG parameters, vital signs (blood pressure, pulse rate, respiratory rate, and oral body temperature), Bristol Stool Chart, and physical examinations.

Pharmacokinetics:

Blood samples will be collected for the analysis of plasma concentrations of CCI, itraconazole, and hydroxy-itraconazole. Pharmacokinetic parameters will be derived by noncompartmental analysis.

For Parts A and C, the PK parameters derived from plasma concentrations of CCI will include: area under the concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration ($AUC_{0\text{-tlast}}$),AUC from time 0 extrapolated to infinity ($AUC_{0\text{-}\infty}$), maximum observed concentration (C_{max}), time of the maximum observed concentration (t_{max}), $t_{1/2}$, apparent total clearance (CL/F), and apparent volume of distribution during the terminal phase (V_z/F).

For Part B, the PK parameters of CCI will include: $AUC_{0\text{-}\infty}$, AUC over a dosing interval ($AUC_{0\text{-}\tau}$), $AUC_{0\text{-tlast}}$, C_{max}, minimum observed concentration (C_{min}), t_{max}, $t_{1/2}$, CL/F, V_z/F, observed accumulation ratio based on $AUC_{0\text{-}\tau}$ ($AR_{AUC0\text{-}\tau}$), and observed accumulation ratio based on C_{max} during the dosing interval (AR_{Cmax}).

For Part C, the PK parameters derived from plasma concentrations of itraconazole and hydroxy-itraconazole will include: $AUC_{0\text{-}\tau}$, C_{max}, and t_{max}

Other PK parameters may also be added.

Exploratory:

Metabolite Profiling:

Blood, urine, and faecal samples will be collected from 2 groups of male subjects in Part A, blood and urine samples will be collected from 1 group in Part B, and blood samples will be collected from 1 group in Part C.

Pharmacogenetic Analysis:

Blood samples will be collected from all subjects in Parts A to C.

Biomarker Analysis:

The analysis will be performed on residual blood and urine samples of exploratory metabolite profiling analysis in Parts A and B.

Phospholipid-C and Faecal Calprotectin Analysis:

Exploratory analysis of phospholipid-C in serum and faecal calprotectin will be performed on blood samples taken for safety clinical laboratory assessments and residual samples taken for faecal occult blood tests, respectively in Parts A to C.

Concentration-QTc Analysis:

Continuous ECG waveforms will be collected and stored in Part A (except Period 2 [fed state] in the food-effect arm).

Statistical methods:

Pharmacokinetics:

Individual plasma concentrations and PK parameters of CCI will be listed and summarised using descriptive statistics. Individual and mean concentration-time profiles for CCI will be presented graphically. Where data are available, CCI dose proportionality will be examined across the dose groups. The PK parameters will be analysed for dose proportionality using a power model approach and/or analysis of variance (ANOVA) model as appropriate. Where data are available, the effects of food at 1 dose level in Part A, and the assessment of the effect of co-administration of itraconazole on the PK of CCI in Part C will be investigated using mixed-model; the effect of sex at 1 dose level in Part A will be investigated using ANOVA. Individual plasma concentrations and PK parameters of itraconazole and hydroxy-itraconazole will be listed and summarised using descriptive statistics. Individual and mean concentration-time profiles for itraconazole and hydroxy-itraconazole will be presented graphically.

Safety:

Safety parameters will be listed and summarised using descriptive statistics. No formal statistical analysis of safety data is planned.

Exploratory:

Data associated with the exploratory metabolite profiling, biomarker analysis, pharmacogenetic analysis, and concentration-QTc analysis will be reported elsewhere.

Data associated with phospholipid-C and faecal calprotectin will be reported in the Clinical Study Report (CSR).

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
Alb	Albumin
ALP	alkaline phosphatise
ALT	alanine aminotransferase
ANOVA	analysis of variance
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 extrapolated to infinity
AUC_{0-24h}	area under the concentration-time curve from time 0 to 24 hours
$AUC_{0-tlast}$	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
$AUC_{0-\tau}$	area under the concentration-time curve over a dosing interval
BMI	body mass index
BUN	blood urea nitrogen
Ca	Calcium
CK	creatine kinase
Cl	Chloride
CL/F	apparent total clearance
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
COPD	chronic obstructive pulmonary disease
Cr	Creatinine
CRO	Contract Research Organization
CRU	clinical research unit
CSA	clinical study agreement
CYP	cytochrome P450
D-Bil	direct bilirubin
DDI	drug-drug interaction
DSS	Drug Safety Services
EC	Ethics Committee
EC_{50}	50% of maximum efficacious concentration
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
FSH	follicle-stimulating hormone
HDL-C	high-density lipoprotein cholesterol

HED	human equivalent dose
hERG	human ether-a-go-go-related gene
HRV	human rhinovirus
Ht	hematocrit
IB	Investigator's Brochure
I-Bil	indirect bilirubin
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
ITCZ	Itraconazole
IUD	intrauterine device
K	Potassium
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
MCH	mean cell haemoglobin
MCHC	mean cell haemoglobin concentration
MCV	mean cell volume
MRSD	maximum recommended starting dose
Na	sodium
NOAEL	no observed adverse effect level
P	inorganic phosphate
PI4K	phosphatidylinositol 4 kinase
PI4K2A	phosphatidylinositol 4 kinase type 2α
PI4K2B	phosphatidylinositol 4 kinase type 2β
PI4KB	phosphatidylinositol 4 kinase IIIβ
PK	pharmacokinetic(s)
PL	Phospholipid
PLT	Platelet
PT-INR	prothrombin time/international normalised ratio
QD	quaque die (once-daily)
QTcF	QT interval corrected for heart rate using Fridericia's method
$AR_{AUC0-\tau}$	observed accumulation ratio based on $AUC_{0-\tau}$
AR_{Cmax}	observed accumulation ratio based on C_{max} during the dosing interval
RBC	red blood cell
SAE	serious adverse event
$t_{1/2}$	apparent terminal elimination half-life
T-Bil	total bilirubin
T-CHO	total cholesterol
TG	Triglycerides

t_{max}	time of the maximum observed concentration
TMF	Trial Master File
TP	total protein
UA	uric acid
ULN	upper limit of normal
V_z/F	apparent volume of distribution
WBC	white blood cell
γ-GTP	gamma-glutamyl transferase

1. INTRODUCTION

1.1. Background

KRP-A218 is a novel orally active antiviral agent for positive-strand ribonucleic acid (RNA) viruses, discovered and synthesized by Kyorin Pharmaceuticals Co. Ltd., Japan, for the indication of human rhinovirus (HRV) infection. KRP-A218 is an adenosine triphosphate (ATP)-competitive and subtype specific inhibitor for phosphatidylinositol 4-kinase beta (PI4KB), known as a host cell factor required for the viral replication of HRVs and enteroviruses (EVs). KRP-A218 shows broad-spectrum antiviral activity against HRVs and EVs by PI4KB inhibition.

HRVs and EVs belong to the *Picornaviridae* family and they have been clustered into 7 groups: RV-A, B, C and EV-A, B, C, D.[1] HRV has more than 100 serotypes, which are highly prevalent respiratory pathogens traditionally associated with mild and self-limited upper respiratory tract infections (URTI; 'common cold'), and is the most commonly isolated virus as a causative virus for URTI.[2] Furthermore, HRV is known to cause more severe diseases of lower respiratory tract such as pneumonia and bronchiolitis in immunocompromised patients, infants, children, and elderly, and exacerbation of chronic respiratory diseases including asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease, and cystic fibrosis.[3, 4, 5] Especially, in immunocompromised patients such as hematopoietic cell transplantation (HCT) recipients and haematological malignancy patients, HRV is considered to be an important virus because HRV infection is not limited to URTI, it may progress to lower respiratory tract infection (LRTI) and cause death.[6, 7] Among immunocompromised patients, HCT recipients are the most studied about severity risk of HRV infection.[7, 8] The incidence of URTI by HRVs of HCT recipients is 22 to 25% [9, 10], and median duration of viral shedding was 3 weeks (prolonged shedding of at least 3 months occurred in 6 of 45 patients). The rate of progression to LRTIs is 17 to 32%.[11, 12, 13] The mortality rate is 41% when it deteriorates in LRTI.[7] Enterovirus also has more than 100 serotypes, and most infected people only have mild illness, like the common cold, hand-foot-mouth disease, and conjunctivitis. However, in infants, children, and people with decreased immunity, EV causes severe diseases including paralytic disease, meningitis, encephalitis and myocarditis.[14, 15] Currently, there are no approved antiviral agents for treatment of HRV and EV infection and efforts at vaccine development are hindered by the existence of more than 100 HRV and EV serotypes with high level sequence variability in the antigenic sites. In addition, the genetic variability within the HRV or EV species necessitates the development of broad-spectrum, pan HRV or EV antiviral drugs. Therefore, there is an unmet medical need for HRV and EV infection in the patients with risk to progress severe condition by those infections.

This first-in-human study has 2 purposes. One is to evaluate the safety, tolerability, and pharmacokinetics (PK) of CCI (the active ingredient in KRP-A218), and the other is to evaluate a drug-drug interaction (DDI). The PK of CCI will be evaluated following administration of single and multiple doses of KRP-A218. In the DDI study, the effect of co-administration of itraconazole on the PK of CCI will be evaluated, since the nonclinical study data suggested that CCI s a Cytochrome P450 (CYP) 3A4 substrate. Itraconazole has been chosen as it is recommended by the European Medicines Agency (EMA) [16] and the Food and Drug Administration (FDA) [17] as a suitable potent CYP3A4 inhibitor for use in DDI studies.

1.2. Nonclinical Development

The compound codes used throughout this section are presented below.

Drug Substance Codes	Description
CCI	Drug substance of KRP-A218
CCI	Active ingredient

The nonclinical program supporting initial clinical administration of KRP-A218 comprises a set of nonclinical pharmacology, safety pharmacology, absorption, distribution, metabolism and excretion (ADME), and toxicology (general toxicity and genotoxicity) studies.

CCI was found to be a highly potent (Inhibitory constant [Ki] value of 6.9 nmol/L), ATP-competitive, and a specific inhibitor of recombinant human PI4KB (50% inhibitory concentration [IC_{50}] value of 11 nmol/L, selectivity ratio for PI4KB over other phosphatidylinositol 4-kinases [PI4Ks] of ≥160), and demonstrated consistent potent and broad-spectrum antiviral activity against different HRV and EV serotypes (50% effective concentration [EC_{50}] values of 19 to 77 nmol/L). Primary pharmacology and ADME studies were performed with CCI, while dose levels for safety pharmacology and toxicology studies (including toxicokinetic interpretation) were calculated based on the free form of CCI. In vivo pharmacology studies showed that CCI suppressed viral infection in RV-A1B-infected corticosteroid-treated and coxsackievirus-B3 (CV-B3)-infected mouse models, with a minimum pharmacologically active oral dose of 1 mg/kg. In addition, CCI improved the survival rate in CV-B3-infected mice even when initially dosed starting 48 hours after infection at dose of 3 and 10 mg/kg/day. CCI was also effective against the viral load in lung of RV-A1B-infected mice at dose of 3 mg/kg and over.

Systemic exposure to CCI following single or repeated oral dosing with CCI was established in mouse, rat, dog, and monkey. There were no remarkable differences in exposure with repeated dosing and between the sexes, although values in females were slightly higher than in males for rats. Blood-plasma concentration ratio of CCI was similar across mouse, rat, dog, monkey, and human, with values of 0.909, 1.03, 0.933, 1.80, and 1.10, respectively, while plasma protein binding was 85.8, 75.6, 82.7, 79.7, and 88.4% in mouse, rat, dog, monkey, and human, respectively. CCI was metabolized by CYP3A, CYP2C9, CYP2C8, and CYP2D6. The contribution ratio for CCI metabolism was determined as ranging from 68.4 to 94.4% for CYP3A and was determined as ranging from 5.7 to 22.0% for CYP2C9. CCI generally had low potential for inhibition although slight time dependent inhibition was observed for CYP3A4 and it was shown to have a potential to induce CYP1A2, CYP2B6, CYP2C9, and CYP3A4.

A core battery of central nervous system, respiratory and cardiovascular (CVS) studies with CCI showed no safety concerns. CCI was shown to have no genotoxic potential from evaluation in a bacterial reverse mutation test, an in vitro chromosome aberrations assay in Chinese hamster lung cells and a bone marrow micronucleus study in rats. In a 2-week good laboratory practice (GLP) oral toxicology study in the rat, the no observed adverse effect level (NOAEL) of CCI was considered to be below 5 mg/kg/day for males (based on inflammatory cell infiltration in the lumen of the coagulating gland) and 5 mg/kg/day for

females (based on an increase in total cholesterol [T-CHO] and emperipolesis in the bone marrow in both sexes at ≥10 mg/kg/day). In a 2-week GLP oral toxicology study in the dog, the NOAEL of CCI was 2 mg/kg/day for both males and females, based on: abnormal stools, decreased bodyweight and decreased food consumption at ≥4 mg/kg/day; increased blood lipid system parameters (triglycerides, T-CHO, LDL-C, free cholesterol) and deviation enzymes at ≥4 mg/kg/day; and histopathological gastrointestinal (GI) changes in 1 female at 4 mg/kg/day (and 1 male and 1 female at 8 mg/kg/day), culminating in the death or early sacrifice of dogs given ≥6 mg/kg/day. In a non-pivotal 2-week toxicity study in male mice, the NOAEL of CCI was 10 mg/kg/day, based on: decreased body weights, cumulative body weight gain, and food consumption at 300 mg/kg/day; increased blood lipid system parameters (T-CHO, HDL-C, LDL-C) at ≥30 mg/kg/day; and histopathological changes in the stomach and small intestine at 300 mg/kg/day, culminating in the death or early sacrifice of mice given 300 mg/kg/day.

Toxicokinetic parameters determined from the pivotal 2-week repeat dose studies in rats and dogs are presented in Table 1 and Table 2.

Table 1: Summary of Toxicokinetic Parameters in 2-week Toxicity Study in Rat Given CCI

Dose level (mg/kg/day)	N (M/F)	Day	Male			Female		
			C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng·h/mL)
5	3/3	1	962	0.5	3610	1370	0.5	4910
	3/3	14	1220	0.5	3930	1600	0.5	4780
10	3/3	1	2130	1.0	8620	3220	0.5	12 500
	3/3	14	2010	1.0	8580	3490	0.5	10 700
20	3/3	1	4900	0.5	23 000	6220	0.5	30 200
	3/3	14	5110	0.5	20 900	7990	0.5	27 400
40	3/3	1	7960	0.5	51 600	9600	0.5	56 800
	3/3	14	8890	0.5	48 700	10 600	0.5	59 700

Mean (n = 3); AUC_{0-24h} = area under the concentration-time curve from time 0 to 24 hours; C_{max} = maximum concentration; T_{max} = time of maximum concentration; N (M/F): Number of animals (male/female)

Table 2: Summary of Toxicokinetic Parameters in 2-week Toxicity Study in Dog Given CCI

Dose level (mg/kg/day)	N (M/F)	Day	Male			Female		
			C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (ng·h/mL)
2	3/3	1	1450	0.8	8020	918	1.3	6000
	3/3	14	1450	0.7	9340	1350	0.8	8500
4	3/3	1	2780	1.7	19 900	2420	1.3	15 000
	3/3	14	3520	0.7	29 400	3120	0.8	19 900
6	3/3	1	4010	1.2	30 500	3820	1.0	27 900
	3/3	14	4420	1.0	35 000	5100	1.2	48 800
8	3/3	1	4840	1.3	35 800	5850	1.1	41 300
	3/3	14	4390	1.5	38 200	3310	2.0	34 700

Mean (n = 3); AUC_{0-24h} = area under the concentration-time curve from time 0 to 24 hours; C_{max} = maximum concentration; T_{max} = time of maximum concentration; N (M/F): Number of animals (male/female)

1.3. Summary of Clinical Experience

In this ongoing Phase 1 study, as of 27 August 2021, a total of 27 subjects have been dosed and have completed the study. Seven subjects have received 1 mg KRP-A218 or placebo under fasted conditions (Group A1), 8 male subjects have received 3 mg KRP-A218 or placebo under fasted and fed conditions (Group A2a), 4 female subjects have received 3 mg KRP-A218 or placebo under fasted conditions (Group A2b), and 8 subjects have received 6 mg KRP-A218 or placebo under fasted conditions (Group A3). For dose escalation decision, a minimum of 6 subject's data per group has been evaluated, including 7 subjects in Group A1 (1 mg), 6 subjects in Group A2a (3 mg), and 8 subjects in Group A3 (6 mg). There were no serious adverse events (SAEs), deaths, or no other significant adverse events (AEs). The AEs experienced by these subjects have included headache, loose stools, cold symptoms, aching lower legs, abdominal pain, stomach ache, drowsiness, blood visible when passing stool sample, and sore throat. All were transient and either mild or moderate in severity.

Preliminary PK parameters determined from the ongoing Phase 1 study are presented in Table 3.

Table 3: Geometric Mean (CV%) PK Parameters of CCI Following Single Oral Dose Administration of KRP-A218 to Healthy Subjects*

Parameter (units)	1 mg [Fasted]	3 mg [Fasted]	3 mg [Fed]	6 mg [Fasted]
$AUC_{0\text{-tlast}}$ (ng•h/mL)	198 (18.5)	540 (27.0)	570 (25.6)	1160 (28.4)
$AUC_{0\text{-}\infty}$ (ng•h/mL)	210 (18.6)	564 (30.1)	596 (28.0)	1230 (28.4)
$AUC_{0\text{-}24h}$ (ng•h/mL)	145 (19.5)	388 (21.4)	393 (19.1)	813 (27.9)
C_{max} (ng/mL)	11.9 (30.3)	29.8 (23.5)	29.5 (15.2)	60.3 (26.5)
t_{max}** (h)	3.00 (2.00–4.00)	3.50 (2.00-4.00)	3.50 (3.00-8.00)	3.50 (1.50-4.00)
$t_{1/2}$ (h)	18.2 (11.5)	15.2 (20.3)	14.8 (18.4)	16.9 (9.68)

Abbreviations: $AUC_{0\text{-}\infty}$ = area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}24h}$ = area under the concentration-time curve from time 0 to 24 hours; $AUC_{0\text{-tlast}}$ = area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max} = maximum observed concentration; CV% = coefficient of variation; PK = pharmacokinetic; $t_{1/2}$ = apparent terminal elimination half-life; t_{max} = time of the maximum observed concentration
* As per protocol, a minimum of 6 subjects (4 active subjects) data per group was evaluated for dose escalation decision.
** Median (min-max)

Following oral administration of KRP-A218, maximum concentrations of CCI were attained 3.0 to 3.5 hours postdose (median time to maximum observed concentration [t_{max}]), thereafter declining with a geometric mean half-life ($t_{1/2}$) of approximately 15 to 18 hours. Systemic exposure to CCI (maximum observed concentration [C_{max}] and area under the concentration-time curve from time 0 to 24 hours [$AUC_{0\text{-}24h}$]) increased in an approximate dose proportional manner over 1 to 6 mg KRP-A218. Administration of KRP-A218 following a high fat meal had no effect on the rate and extent of absorption of CCI

1.4. Study Rationale

This is the first time KRP-A218 will be administered to humans. The principal purposes of this study are to evaluate the safety and tolerability data when KRP-A218 is administered orally as single and multiple doses to healthy subjects. This information, together with the PK data, will help establish the doses and dosage regimen suitable for administration to patients. The study will also investigate the effects of food and sex on the PK of CCI prior to patient studies.

This first-in-human study also incorporates a DDI study. The initial target population of KRP-A218 includes immunocompromised patients, such as HCT recipients who require concomitant azole antifungal drugs to reduce the risk of fungal infection. Preclinical studies have shown that CYP3A4 is the major metabolic enzyme of CCI, and the presence and magnitude of DDI with CYP3A4 inhibitors, even if exploratory, should be confirmed early in development to understand the potential risk leading to dose adjustments or contraindications due to DDI. It is important to confirm the assessment of the impact of the combination of KRP-A218 and itraconazole, as an appropriate and potent CYP3A4 inhibitor, on PK as this will provide very important information for subsequent study design and dose selection for phase 2 and phase 3 studies.

1.5. Benefit-risk Assessment

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the investigational medicinal product (IMP), although there may also be some discomfort from collection of blood samples and other study procedures. More information about the known and expected risks and reasonably anticipated AEs associated with KRP-A218 may be found in the Investigator's Brochure (IB).[18]

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

Parts A and B:

The primary objective is:

- to evaluate the safety and tolerability of single and multiple oral doses of KRP-A218 in healthy subjects.

The secondary objectives are:

- to assess the PK of CCI (the active ingredient of KRP-A218) following single and multiple oral doses of KRP-A218 in healthy subjects.
- to assess the effect of food on the PK of CCI following a single oral dose of KRP-A218 in healthy male subjects.
- to assess the effect of sex on the PK of CCI following a single oral dose of KRP-A218.

The exploratory objectives are:

- to explore blood and urine samples for the metabolite profiles of CCI following single and multiple oral doses of KRP-A218 in healthy male subjects.
- to explore faecal samples for the metabolite profiles following a single oral dose of KRP-A218 in healthy male subjects.
- to explore blood and urine samples for pharmacodynamic biomarkers.
- to explore a potential effect of KRP-A218 on phospholipid-C in serum and faecal calprotectin.
- to collect blood samples for potential pharmacogenetic analyses.
- to collect continuous ECG waveforms for concentration-QTc analysis, following single oral doses of KRP-A218 in healthy subjects (Part A only).

Part C:

The primary objective is:

- to assess the effect of multiple doses of itraconazole (cytochrome P450 3A4 inhibitor) on the single-dose PK of CCI in healthy male subjects.

The secondary objectives are:

- to assess the safety and tolerability of single oral doses of KRP-A218 when co-administered with multiple oral doses of itraconazole in healthy male subjects.
- to assess the PK of itraconazole and its metabolite hydroxy-itraconazole when co-administered with KRP-A218 in healthy male subjects.

The exploratory objectives are:

- to explore blood samples for the metabolite profiles of CCI administered KRP-A218 alone and when co-administered with itraconazole in healthy male subjects.
- to explore a potential effect of KRP-A218 on phospholipid-C in serum and faecal calprotectin.
- to collect blood samples for potential pharmacogenetic analyses.

2.2. Endpoints

2.2.1. Primary Endpoints

For Parts A and B, the safety and tolerability endpoints are as follows:

- AEs
- body weight

- clinical laboratory evaluations (haematology, clinical chemistry [with the exception of phospholipid-C], urinalysis, coagulation, and faecal occult blood)
- 12-lead ECG parameters
- vital signs (blood pressure, pulse rate, respiratory rate, and oral body temperature)
- Bristol Stool Chart
- physical examinations

For Part C, the DDI (KRP-A218 alone versus co-administered with itraconazole) assessment, the PK endpoints will be the parameters derived from plasma concentrations of CCI on Days 1 and 11, which are as follows:

- area under the concentration-time curve (AUC) from time 0 extrapolated to infinity ($AUC_{0-\infty}$)
- AUC from time 0 to the time of the last quantifiable concentration ($AUC_{0-tlast}$)
- C_{max}
- t_{max}
- apparent terminal elimination half-life ($t_{1/2}$)
- apparent total clearance (CL/F)
- apparent volume of distribution during the terminal phase (V_z/F).

Other PK parameters may also be added.

2.2.2. Secondary Endpoints

For Part A, the single ascending dose, food (fed versus fasted dietary status at dosing), and sex (male versus female) PK parameters derived from plasma concentrations of CCI on Day 1 (including Day 1 in Treatment Period 2) are as follows:

- $AUC_{0-\infty}$
- $AUC_{0-tlast}$
- C_{max}
- t_{max}
- $t_{1/2}$
- CL/F
- V_z/F.

For Part B, the multiple ascending dose PK parameters derived from plasma concentrations of CCI on Days 1 and 14 are as follows:

- $AUC_{0-\tau}$
- $AUC_{0-\infty}$ (Day 1 only)

- $AUC_{0\text{-tlast}}$
- C_{max}
- minimum observed concentration (C_{min})
- t_{max}
- $t_{1/2}$
- CL/F
- V_z/F
- observed accumulation ratio based on $AUC_{0\text{-}\tau}$ ($AR_{AUC0\text{-}\tau}$)
- observed accumulation ratio based on C_{max} during the dosing interval (AR_{Cmax}).

For Part C, the safety and tolerability endpoints are as follows:

- AEs
- body weight
- clinical laboratory evaluations (haematology, clinical chemistry [with the exception of phospholipid-C], urinalysis, coagulation, and faecal occult blood)
- 12-lead ECG parameters
- vital signs (blood pressure, pulse rate, respiratory rate, and oral body temperature)
- Bristol Stool Chart
- physical examinations.

For Part C, the PK parameters derived from plasma concentrations of itraconazole and hydroxy-itraconazole on Day 11 are as follows:

- $AUC_{0\text{-}\tau}$
- C_{max}
- t_{max}.

Other PK parameters may also be added.

2.2.3. Exploratory Endpoints

For Parts A, B, and C, the exploratory endpoints that will be reported in the CSR for this study are:

- Phospholipid-C
- Faecal calprotectin

The endpoints associated with the exploratory metabolite profiling, biomarker analysis, pharmacogenetic analysis, and concentration-QTc analysis will be reported elsewhere, as applicable.

3. INVESTIGATIONAL PLAN

This Phase 1 study will consist of 3 parts, Parts A, B, and C. Part A will comprise a double-blind, randomised, placebo-controlled, single-dose, sequential-group, escalating-dose design, enrolling healthy male and female subjects (female subjects in Group A2b only). Part A will include a sex-effect (Groups A2a and A2b) which will investigate the effect of sex on PK of CCI by comparing PK parameters following dosing in females versus dosing in males. Part A will also include a food-effect Group A2a which will be a 2-period arm to investigate the effect of food on PK of CCI by comparing PK parameters following dosing in fed conditions versus dosing in fasted conditions.

Part B will comprise a double-blind, randomised, placebo-controlled, multiple-dose, sequential-group, escalating-dose design, enrolling healthy male subjects.

Part C will comprise an open-label, fixed-sequence, enrolling healthy male subjects to investigate the effect of multiple oral doses of itraconazole on the single oral dose PK of CCI in healthy male subjects.

3.1. Overall Study Design and Plan

3.1.1. Part A (Single Ascending Dose Study)

Part A will comprise a double-blind, randomised, placebo-controlled, single-dose, sequential-group, escalating-dose study incorporating a single-group, 2-period arm to investigate the effect of food on the PK of CCI Part A will also include a sex-effect arm (Groups A2a and A2b) which will investigate the effect of sex on PK of CCI by comparing PK parameters following dosing in females versus dosing in males. Overall, 48 subjects will be studied in 5 groups (Groups A1 to A5); Groups A1, and A3 to A5 will consist of 8 male subjects, and Group A2 will consist of 16 subjects split into 2 subgroups (Group A2a [male subjects only] and Group A2b [female subjects only]) that will consist of 8 subjects each.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only, except for Group A2a, where each subject will participate in 2 treatment periods where doses of KRP-A218 will be separated by an interval of 7 to 10 days (up to and including Day -1 of Treatment Period 2). The washout period may be extended depending on the observed $t_{1/2}$ of CCI Subjects will reside at the study site from Day -1 (the day before dosing) to Day 4 of each treatment period.

All subjects will return for a follow-up visit 7 to 10 days after their final dose. The follow-up period may be extended depending on the observed $t_{1/2}$ of CCI

Based on the ongoing review of the safety, tolerability, and PK results, additional nonresidential visits may be required. The number of additional visits per subject will not exceed 3 per period (as applicable) and will not extend beyond 28 days after each final dosing

occasion. All subjects may stay in the clinical research unit (CRU) outside treatment periods due to COVID-19 risks.

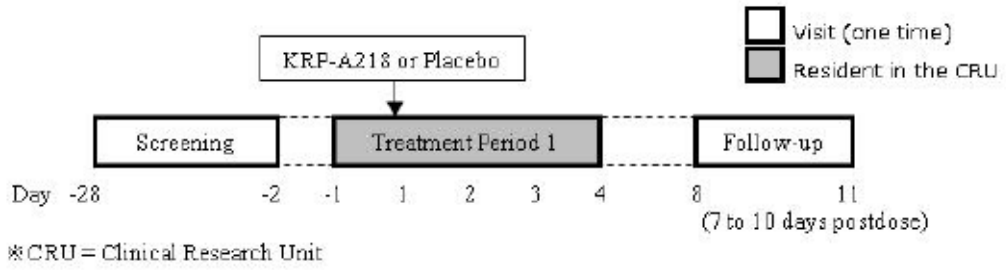
In each of Groups A1 to A5, 6 subjects will receive KRP-A218 and 2 subjects will receive placebo in accordance with a randomisation schedule. In Groups A1, A2b, and A3 to A5, all doses will be administered in the fasted state on the morning of Day 1. For Group A2a, Period 1, Day 1 doses will be administered in the fasted state and Period 2, Day 1 doses be will be given 30 minutes after starting a standard high-fat breakfast. Each subject in Groups A1, A2b, and A3 to A5 will receive only a single dose of KRP-A218 or placebo during the study. In Group A2a, subjects will have the same treatment in both periods, such that each subject will receive 2 single doses of KRP-A218 or placebo during the study.

All groups in Part A (with the exception of Group A2a in Treatment Period 2) will receive the IMP using a sentinel approach, as described in Section 5.3. Details regarding dose escalation are presented in Section 3.5.

An overview of the study design is shown in Figure 1 and Figure 2, and the planned dose levels in Figure 5.

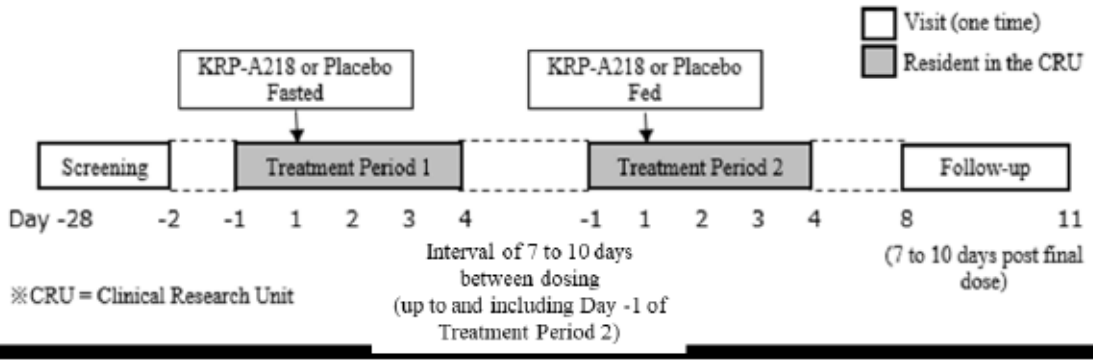
Schedules of Assessments is presented in Appendix 6.

Figure 1: Study Schematic (Part A; Groups A1, A2b [Female subjects Only], and A3 to A5)



The follow-up period may be extended depending on the observed $t_{1/2}$ of CCI

Figure 2: Study Schematic (Part A; Group A2a [Male subjects Only])



The washout and follow-up periods may be extended depending on the observed $t_{1/2}$ of CCI

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be up to 39 days (Groups A1, Group A2b [female subjects only], A3 to A5) or up to 50 days (Group A2a; male subjects only).

3.1.2. Part B (Multiple Ascending Dose Study)

Part B will comprise a double-blind, randomised, placebo-controlled, multiple-dose, sequential-group, escalating-dose design, enrolling healthy male subjects. Overall, 40 subjects will be studied in 4 groups (Groups B1 to B4), with each group consisting of 10 male subjects. Part B may start after completion of Group A3, at dose equal to or less than given in Groups A1 to A3.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only and reside at the CRU from Day -1 (the day before dosing) until the morning of Day 17 (following assessments at 72 hours after final dosing).

All subjects will return for a follow-up visit 7 to 10 days after their final dose. The follow-up period may be extended depending on the observed $t_{1/2}$ of CCI

In each of Groups B1 to B4, 8 subjects will receive KRP-A218 and 2 subjects will receive placebo in accordance with a randomisation schedule. The dietary state for dosing in Part B will be subject to review of the PK data from the fed/fasted comparison in Part A. For all subjects, dosing will occur on Days 1 to 14. The planned dosing frequency is once per day, however the dosing frequency in Part B may be changed following review of data from groups in Part A (Section 3.4). On Day 14, the last dose will be the morning dose regardless of the dosing frequency (QD, BID, TID).

The total daily dose administered will not exceed an exposure shown to be safe and well tolerated in Part A.

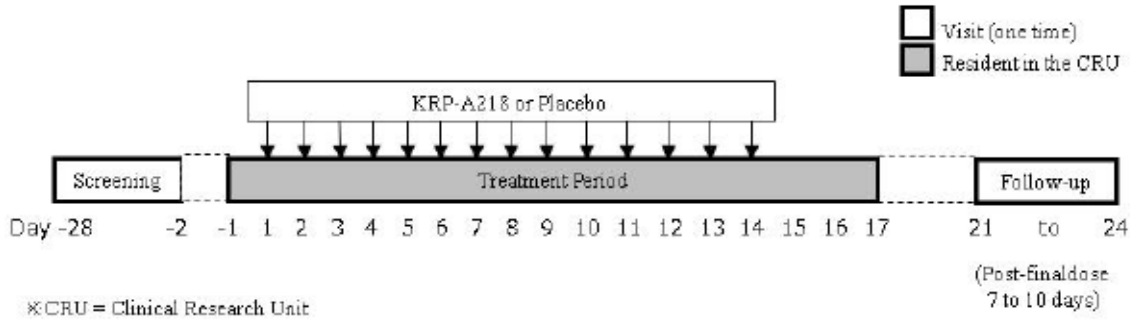
Based on the ongoing review of the safety, tolerability, and PK results, additional nonresidential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond 28 days after each final dosing occasion. All subjects may stay in the CRU even outside treatment period due to COVID-19 risks.

All groups in Part B will receive the IMP using a sentinel approach, as described in Section 5.3. Details regarding dose escalation are presented in Section 3.5.

An overview of the study design is shown in Figure 3, and the planned dose levels in Figure 5.

A Schedule of Assessments is presented in Appendix 6.

Figure 3: Study Schematic (Part B)



The follow-up period may be extended depending on the observed $t_{1/2}$ of CCI .

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be up to 52 days.

3.1.3. Part C (Drug-Drug Interaction Study)

Part C will comprise an open-label, fixed-sequence, enrolling healthy male subjects to investigate the effect of multiple oral doses of itraconazole on the single oral dose PK of CCI in healthy subjects. There will be 1 group; Group C1, consisting of 12 male subjects. Part C will start after completion of blinded safety, tolerability, and PK data review in Part A. All subjects will receive each of the following treatments:

- Days 1 and 11: single oral dose of KRP-A218
- Day 4: 2 × single oral doses of 200 mg itraconazole, approximately 12 hours apart
- Days 5 to 13: single oral doses of 200 mg itraconazole

The study days of dosing of itraconazole and KRP-A218 may be amended to extend the interval between the first dose of KRP-A218 and the first dose of itraconazole depending on the observed $t_{1/2}$ of CCI .

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Subjects will be admitted into the study site on Day -1 and be confined to the study site until discharge on Day 14.

Subjects will return to the study site for a follow-up visit 7 to 10 days after the last dose of KRP-A218. The follow-up period may be extended depending on the observed $t_{1/2}$ of CCI

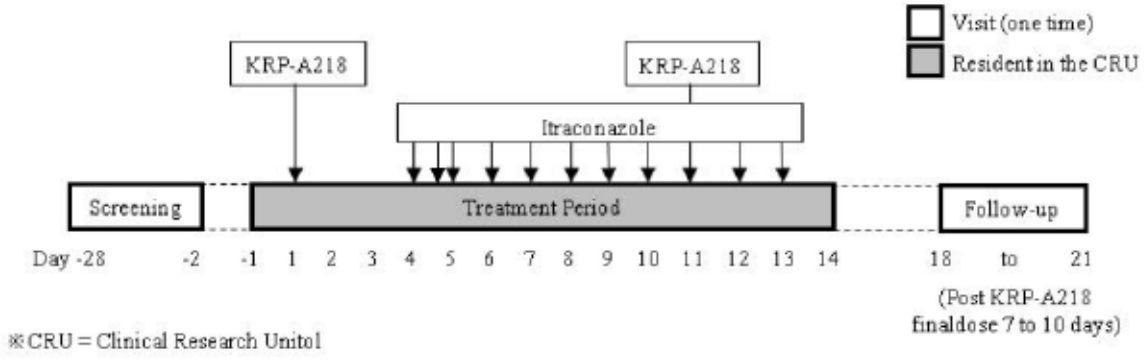
Based on the ongoing review of the safety, tolerability, and PK results, additional nonresidential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond 28 days after each final dosing occasion. All subjects may stay in the CRU even outside treatment period due to COVID-19 risks.

The dietary state for dosing of KRP-A218 alone on Day 1 and KRP-A218 co-administered with itraconazole on Day 11 will be determined by comparing the PK data between fed and fasted state in Group A2a. Itraconazole on Days 4 to 10, 12 and 13 will be administered in the fasted state. The dose level of KRP-A218 will be confirmed based on the available safety, tolerability, and PK data in preceding Parts A and/or B of the study.

An overview of the study design is shown in Figure 4, and the planned dose levels in Figure 5.

A Schedule of Assessments is presented in Appendix 6.

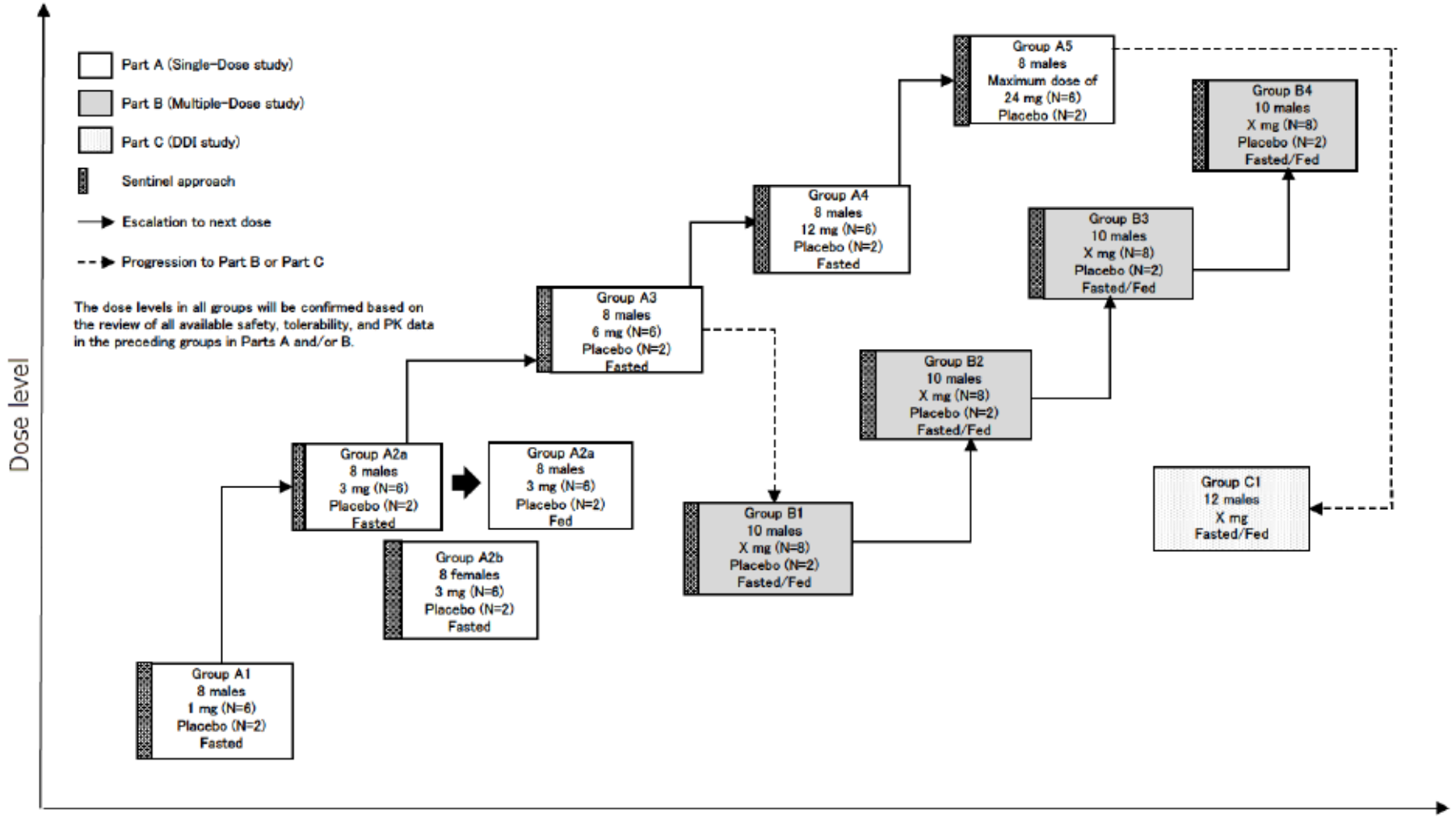
Figure 4: Study Schematic (Part C)



The study days of dosing of itraconazole and KRP-A218 may be amended to extend the interval between the first dose of KRP-A218 and the first dose of itraconazole depending on the observed $t_{1/2}$ of CCI In addition, the follow-up period may be extended depending on the observed $t_{1/2}$ of CCI

The total duration of study participation for each subject (from screening through follow-up visit) is anticipated to be up to 49 days.

Figure 5: Planned Dose Levels of KRP-A218 (Parts A, B, and, C)



3.2. Study Start and End of Study Definitions

The start of the study is defined as the date the first subject signs an informed consent form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

3.3. Additional Groups

Following review of the safety, tolerability, and PK data, additional dose groups (where systemic exposure is not expected to exceed that stated in the dose escalation stopping criteria as detailed in Section 3.7) may be added to the study. Up to 3 further groups of 8 subjects (6 KRP-A218 and 2 placebo) in Part A and 3 further groups of 10 subjects (8 KRP-A218 and 2 placebo) in Part B may be added. The requirement for additional groups will be agreed with the Sponsor and documented in the trial master file (TMF).

3.4. Discussion of Study Design, Including the Choice of Control Groups

For Parts A and B of the study, a sequential-group, ascending dose design has been chosen for safety reasons as KRP-A218 is in the early stages of clinical development, with Part A of the study being the first time it will be administered to humans. Oral doses have been chosen for each part of the study, as this is the intended clinical route of administration. A 2-period design has been chosen for the food-effect arm, as this gives a within subject assessment of the influence of food on the PK of CCI and so increases the power of the study for the given number of subjects.

It is the intent of Part B to dose subjects such that steady state plasma levels of CCI are achieved and maintained for several days. Based on the available nonclinical data, it is expected that this will be achieved following 3 days of once daily dosing; however, a full review of all the available safety, tolerability, and PK data from Part A will be performed to confirm the dose regimen for Part B. If the $t_{1/2}$ of CCI is longer than predicted by the nonclinical data, once-daily dosing may be more appropriate over 14 days (as steady state will take longer to achieve). The dose regimen will comprise no less than once every 3days and will not exceed 3-times daily dosing. The dosing duration will not exceed 14 consecutive days of dosing.

Details of the dosing regimen and duration used for Part B of the study will be documented in the TMF. An interval of 7 to 10 days between doses of KRP-A218 in the food-effect arm in Part A is considered adequate to prevent carryover of KRP-A218 but the interval may be extended depending on the observed $t_{1/2}$ of CCI

Parts A and B will be double-blind and placebo-controlled in order to avoid bias in the collection and evaluation of data during its conduct. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment related or simply reflect the study conditions.

Continuous 12-lead ECG monitoring will be included in this study in order to explore potential KRP-A218 effects on the QT interval, with a view of supporting a potential thorough QT study waiver.

For Part C of the study, the fixed-sequence design to be used is typical for interaction studies where a relatively small number of subjects are required, because it allows intrasubject comparisons and reduces intersubject variability. Part C of the study will be open-label because the endpoints are not considered to be subjective.

KRP-A218 will be administered as single doses in Part C, as single oral dose studies are usually performed for interaction studies for compounds with linear PK as found for KRP-A218. Itraconazole is the reference potent CYP3A inhibitor recommended in the EMA guideline [16], and among those noted in the FDA draft guideline [17]. The dose level of itraconazole was selected based on achievement of clinically probable CYP3A inhibition and the typical clinical dose (200 to 400 mg daily dose) of itraconazole.

Nonclinical data suggest that CCI is a CYP3A4 substrate. If a significant proportion of CCI metabolism in humans indeed proceeds through CYP3A4, the administration of itraconazole will significantly inhibit the metabolism of CCI, resulting in an increase in exposure of CCI.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

3.4.1. Dose Interval

Following thorough review of all available nonclinical data (pharmacological and toxicological), dosing in each group in Part A will be such that 2 subjects (1 KRP-A218 and 1 placebo) will be dosed at least 24 hours before the remaining 6 subjects. After dosing the first 2 subjects on a separate day, a minimum of a 5-minute dosing interval for the remaining 6 subjects in each dose-ascending group is considered acceptable. Continuation to dose the remaining 6 subjects will be at the Investigator's discretion.

For Part B, dosing at each dose level will be such that 2 male subjects (1 KRP-A218 and 1 placebo) will receive the IMP at least 7 days before the remaining 8 subjects. After dosing the first 2 subjects, a minimum of a 5-minute dosing interval for the remaining 8 subjects in each dose-ascending group is considered acceptable. Continuation to dose the remaining 8 subjects will be at the Investigator's discretion.

3.5. Selection of Doses in the Study

Based upon nonclinical data, no clinically important off-target effects are expected within the proposed exposure range.

In the pivotal 2-week toxicity studies in rats and dogs, the NOAEL was < 5 mg/kg/day for male rats, 5 mg/kg/day for female rats, and 2 mg/kg/day for dogs (both sexes), and in a non-pivotal 2-week toxicity study in mice, the NOAEL was 10 mg/kg/day for male mice. Inflammatory cell infiltration in the lumen of the coagulating gland in male rats was observed at ≥5 mg/kg/day. However, this finding is not considered to be relevant to human safety because the coagulating gland is an accessory sex gland in rats, not in humans, and the finding may be species specific as no related changes were seen in the dog or mouse. Furthermore, no other reproductive organ findings were noted in rats, and no adverse effects on male reproductive performance were observed in a preliminary male fertility study in rats. No other findings were observed in male rat at dose of 5 mg/kg. The maximum recommended

starting dose (MRSD) for a 60 kg subject, based on the most conservative human equivalent dose (HED) calculation among the treatment groups calculated from the most sensitive species, rat (lowest dose: 5 mg/kg/day [NOAEL not established for male rat]; HED: 48 mg/subject) is 4.8 mg/subject, including a 10-fold safety factor.[19] KRP-A218 shows pharmacological effects in mice from 1 mg/kg/day, which is equivalent to a HED of 4.9 mg for a 60 kg subject. The proposed starting dose of 1 mg includes an extra 5-fold safety factor, compared with the MRSD calculated from the 5 mg/kg/day for rats and the HED calculated from the 1 mg/kg/day for mice.

Due to the toxicity observed with respect to gastrointestinal effect that was observed in preclinical study in dogs,[18] the lower dose escalation increments should be selected. The highest clinical dose should be set so that proposed maximum individual exposure for dose escalation studies is capped to the exposure seen in the male rats at 5 mg/kg/day. The corresponding C_{max} and $AUC_{0\text{-}24h}$ values in male rats at the 5 mg/kg/day are 1220 ng/mL and 3930 ng•h/mL, respectively.

In a CV-B3 infected mouse model, the efficacy of CCI was observed in a dose dependent manner and CCI showed antiviral efficacy and improvement of survival rate.[18] Significant efficacy was observed at 1, 3, and 10 mg/kg; however, the predicted therapeutic range ($AUC_{0\text{-}24h}$) initially selected was 276 to 988 ng•h/mL, as 988 ng•h/mL (the $AUC_{0\text{-}24h}$ at 3 mg/kg) was lower than the exposure at the NOAEL in male rats whereas the mouse exposure at 10 mg/kg ($AUC_{0\text{-}24h}$ of 4920 ng•h/mL) was higher than the exposure at the NOAEL in male rats. Therefore, the therapeutic range initially proposed was a conservative estimate and the optimal clinical therapeutic range may exceed the $AUC_{0\text{-}24h}$ of 988 ng•h/mL.

Considering that the indication of KRP-A218 is HRV infection with a high risk of progressing to lower respiratory infection or other severe complications, it is necessary to achieve the expected exposure on the first day of administration. Based on the mean $AUC_{0\text{-}24h}$ observed in Groups A1 to A3 (Part A of this study), the expected clinical therapeutic dose that covers the $AUC_{0\text{-}24h}$ of 276 to 988 ng•h/mL on Day 1 is 2 to 8 mg (Table 4). To cover the estimated steady-state exposure of 8 mg with a single dose in this study, the mean exposure would need to be above 1730 ng•h/mL (mean $AUC_{0\text{-}24h}$*R) based on current human PK data.

Table 4: Observed and Estimated Human Exposure at Day 1 and Steady State

Dose (mg)	Mean $AUC_{0\text{-}24h}$ (ng·h/mL) (Day 1)	Mean $AUC_{0\text{-}24h}$*R (ng·h/mL) (Steady State)
1	145	NA
2*	271	434
3	388	NA
6	813	NA
8*	1080	1730

Abbreviations: $AUC_{0\text{-}24h}$ = area under the concentration-time curve from time 0 to 24 hours; NA = not available; R = accumulation ratio.
R = 1.6 (calculated using the geometric mean half life value from 6 mg KRP-A218)
* Estimated $AUC_{0\text{-}24h}$ values calculated based on the geometric mean $AUC_{0\text{-}24h}$ from 6 mg KRP-A218, assuming linearity across dose.

Moreover, considering the individual $AUC_{0\text{-}24h}$ values observed in Groups A1 to A3, it has been assumed that the maximum $AUC_{0\text{-}24h}$ may be in the range of approximately 2-fold the mean $AUC_{0\text{-}24h}$. Therefore, it is considered reasonable to set the dose escalation criteria at the NOAEL equivalent exposure (maximum $AUC_{0\text{-}24h}$ of 3930 ng•h/mL), which is approximately 2-fold of the estimated steady-state exposure at 8 mg (mean $AUC_{0\text{-}24h}$*R of 1730 ng•h/mL). In addition, based on safety data from this ongoing study at doses of 1 to 6 mg (Groups A1 to A3), no gastrointestinal findings of any concern have been observed.

Therefore, in this Phase 1 study, it is planned to investigate higher doses within the range up to the NOAEL (5 mg/kg in male rats: C_{max} 1220 ng/mL, $AUC_{0\text{-}24h}$ 3930 ng•h/mL) as the maximum exposure for individuals.

Exploring these higher doses in a Phase 1 study will allow AEs to be more closely monitored than in Phase 2 or 3 studies.[20] It will also allow the exploratory objective to collect data for concentration-QTc analysis to be more relevant as according to regulatory guidance, the QTc response should be characterised at a sufficiently high multiple of the clinically relevant exposure.[21, 22, 23]

CCI was metabolized by CYP3A, CYP2C9, CYP2C8, and CYP2D6, and the contribution ratio of CYP3A was determined as ranging from 68.4 to 94.4%. Because of the high contribution ratio for CYP3A, co-administration of KRP-A218 with drugs that induce or inhibit CYP3A may affect the exposure of CCI. The dose level in Part C will be selected based on PK profile in preceding Parts A and/or B.

The proposed IMP dose levels for Parts A, B, and C are shown in Table 5.

Table 5: Proposed Investigational Medicinal Product Dose Levels for Parts A, B, and C

Study Part	Group	Subject Numbers	Treatments	KRP-A218 Dose	Dietary State	Sex
Part A	A1	0101 – 0108	6 KRP-A218 2 placebo	1 mg	Fasted	Male
	A2a[a]	0109 – 0116	6 KRP-A218 2 placebo (2 doses)	3 mg	Fasted and Fed	Male
	A2b[a]	0117 – 0124	6 KRP-A218 2 placebo	3 mg	Fasted	Female
	A3	0125 – 0132	6 KRP-A218 2 placebo	6 mg	Fasted	Male
	A4	0133 – 0140	6 KRP-A218 2 placebo	12 mg	Fasted	Male
	A5	0141 – 0148	6 KRP-A218 2 placebo	maximum dose of 24 mg	Fasted	Male
Part B	B1	0201 – 0210	8 KRP-A218 2 placebo	X mg	Fasted/Fed[b]	Male
	B2	0211 – 0220	8 KRP-A218 2 placebo	X mg	Fasted/Fed[b]	Male

	B3	0221 – 0230	8 KRP-A218 2 placebo	X mg	Fasted/Fed [b]	Male
	B4	0231 – 0240	8 KRP-A218 2 placebo	X mg	Fasted/Fed [b]	Male
Part C	C1	0301 – 0312	12 KRP-A218 (2 doses)	X mg	Fasted/Fed [b]	Male

[a] Female subjects in Group A2b will participate in Treatment Period 1 only. Male subjects in Group A2a will be administered the same treatment in both treatment periods and will be in the fasted state in Treatment Period 1 and in the fed state in Treatment Period 2.
[b] The dietary state for dosing will be determined by comparing the PK data between the fed and fasted state in Group A2a.

For Part A, the planned first dose level is 1 mg. The dose level of the subsequent group will be set so that the predicted mean exposure does not exceed 5-fold the mean exposure of the previous group for predicted nonpharmacologically active dose, and 2-fold the mean exposure of the previous group for predicted pharmacologically active dose. The highest dose level will be guided by the review of safety, tolerability, and PK data from prior dose levels. In each group in Part A, predicted maximum systemic exposure (C_{max} and AUC_{0-24h}) of CCI in individual subjects will not exceed a C_{max} of 1220 ng/mL and/or an AUC_{0-24h} of 3930 ng•h/mL; i.e., systemic exposure will not exceed that seen in the male rat, which was the lowest systemic exposure that was seen at either 5 mg/kg/day in rats or the NOAEL of 2 mg/kg/day in dogs. Considering the predicted maximum systemic exposure and the observed maximum individual AUC_{0-24h} at 6 mg in Part A, the highest dose is estimated to be 17 mg (Table 6). Regardless of this estimate, the highest dose will be determined based on the review of the maximum AUC_{0-24h} value at the previous dose level; however, the maximum dose that will be administered in Part A will not exceed 24 mg, which is 2-fold the previous dose level.

Table 6: Estimated Human Exposure at Day 1

Dose (mg)	C_{max} (ng/mL)		AUC_{0-24h} (ng•h/mL)	
	Mean	Maximum	Mean	Maximum
6	60.3	95.7	813	1350
12*	121	191	1630	2700
17*	171	271	2300	3830

* C_{max} and AUC_{0-24h} were calculated based on geometric mean parameter values from 6 mg KRP-A218 in Part A, assuming linearity across dose.

For Part B, the dose levels, dosing regimen, and dietary status will be confirmed based on the review of all available safety, tolerability, and PK data in the preceding groups in Parts A and/or B. For all groups in Part B, selected dose levels will have a predicted mean steady-state exposure (C_{max} and AUC_{0-24h}) that does not exceed the mean exposure (C_{max} and AUC_{0-24h}) previously found generally safe and well tolerated in Part A. In addition, predicted maximum systemic exposure level (C_{max} and AUC_{0-24h}) of CCI in individual subjects that does not exceed the maximum exposure (C_{max} and AUC_{0-24h}) in individual subjects in the preceding groups in Part A and will not exceed a C_{max} of 1220 ng/mL and/or an AUC_{0-24h} of 3930 ng•h/mL; i.e., systemic exposure will not exceed that seen in the male rat, which was the lowest systemic exposure that was seen at either 5 mg/kg/day in rats.

For Part C, the dose level will be confirmed based on the review of all available safety, tolerability, and PK data in preceding Parts A and/or B. The actual dose level of KRP-A218 will be set so that the predicted mean exposure (C_{max} and AUC_{0-24h}) of CCI on co-administration of itraconazole will not exceed the mean exposure (C_{max} and AUC_{0-24h}) previously found generally safe and well tolerated in Part A and in addition, predicted maximum systemic exposure level (C_{max} and AUC_{0-24h}) of CCI on co-administration of itraconazole in individual subjects does not exceed the maximum exposure (C_{max} and AUC_{0-24h}) in individual subjects in Part A and will not exceed a C_{max} of 1220 ng/mL and/or an AUC_{0-24h} of 3930 ng•h/mL; i.e., systemic exposure will not exceed that seen in the male rat, which was the lowest systemic exposure that was seen at either 5 mg/kg/day in rats.

The actual dose levels will be determined based on emerging data.

Details of all doses administered in Parts A to C of the study will be documented in the TMF.

3.6. Dose Escalation

Doses will be administered in an escalating manner following satisfactory review by the Sponsor, Investigator, and Labcorp Drug Development Medical Monitor of the safety and tolerability data (up to 48 hours post last dose) and plasma PK data (up to 24 hours post last dose) from the previous lower dose level. Doses may be reduced and may be lower than the starting dose. There will be a minimum of 6 days between dose escalations to allow sufficient time for an adequate safety review.

Dose escalation in both Parts A and B will only occur if data from a minimum of 6 subjects have been reviewed from the previous lower dose group, such that data from a minimum of 4 subjects who have received KRP-A218 will be used to make the dose escalation decision.

The justification for this is as follows:

- Based upon nonclinical data, no clinically important off-target effects are expected within the proposed dose range.
- A minimum of 4 subjects receiving the active drug is considered sufficient to characterise the safety profile and PK response to KRP-A218.

Between each dose escalation, the Investigator will review all available data in a blinded manner to ensure it is safe to proceed with the planned dose escalation. An interim safety report, summarising results from all available safety assessments, will be sent to the Sponsor and Labcorp Drug Development Medical Monitor prior to the start of each successive group. Any clinically significant results will be discussed with the Sponsor before dose escalation continues. Interim PK data will also be reviewed in terms of dose escalation and to confirm that the study design remains appropriate. In the event of a disagreement between Sponsor and Investigator on the dose escalation decision, the decision of the Investigator will be upheld.

3.7. Dose Escalation Stopping Criteria

The study will be halted if 1 or more subjects experience an SAE that is considered to be related to IMP or 2 or more subjects in the same group experience severe AEs that are

considered to be related to IMP. If, following an internal safety review, the Sponsor deems it appropriate to restart the study, this can be done following approval of a substantial protocol amendment.

For both Parts A and B, a consultation between the Investigator, Sponsor, and Labcorp Drug Development Medical Monitor will be held prior to dosing the next group. Dose escalation will stop if:

- Clinically relevant signs or symptoms of similar nature occur in 2 or more subjects in a group that, in the opinion of the Investigator, warrant stopping of dose escalation. In particular, the Investigator (or designee) should carefully monitor signs or symptoms below:
    - symptoms such as inappetence, abdominal distension, abdominal discomfort, abdominal pain, nausea and vomiting
    - signs/findings such as abdominal tenderness and decreased or absent peristaltic sounds
    - abnormal faeces such as diarrhea, hematochezia, and melena.
- Inappetence, abdominal distension, abdominal discomfort, abdominal pain, nausea and vomiting that prevent subjects from eating a meal on 3 or more occasions on 2 consecutive days in 1 or more subjects in a group.
- Diarrhea, defined as 7 or more episodes, rated as ≥5 on the Bristol Stool Chart, in 1 day for 2 consecutive days in 1 or more subjects in a group.
- Hematochezia and melena with visible blood that are considered to be caused by gastrointestinal bleeding in 1 or more subjects in a group.
- Clinically significant increases in liver function tests compared to baseline measurements, defined as AST, ALT, ALP, and/or γ-GTP ≥3 × the upper limit of normal (ULN) and/or T-Bil ≥2 × ULN (confirmed with repeat testing) in 2 or more subjects in a group.
- Maximum systemic exposure level of CCI in individual subjects in the next group predicted to exceed a C_{max} of 1220 ng/mL and/or an AUC_{0-24h} of 3930 ng•h/mL.

The dosing status of an individual subject may be unblinded to reviewers of the safety data if necessary for safety reasons or if pertinent to dose escalation decisions. The unblinded status will be kept to a minimum number of reviewers, based on pertinence to their role and relevant task. Further information on blinding can be found in Section 5.4.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the screening visit unless otherwise stated:

1. Male or female adults, between 20 and 55 years of age, inclusive.

2. Body weight ≥50 kg, with body mass index (BMI) between 18.0 and 30.0 kg/m2, inclusive.
3. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, and clinical laboratory evaluations (congenital nonhemolytic hyperbilirubinemia [eg, Gilbert's syndrome] is not acceptable) at Screening or Day -1 as assessed by the Investigator (or designee).
4. Females will not be pregnant or lactating, and females of childbearing potential will agree to use contraception and to not donate eggs (ova, oocytes) as detailed in Appendix 4. Males will agree to use contraception and to not donate sperm as detailed in Appendix 4. Females of nonchildbearing potential are defined as permanently sterile (ie, due to hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy), or postmenopausal, as defined in Appendix 4.
5. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the screening visit unless otherwise stated:

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, haematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the Investigator (or designee).
2. Clinically significant ECG abnormality at screening, including, but not limited to:
    a. QTcF >450 ms confirmed by repeat measurement
    b. QRS duration >110 ms confirmed by repeat measurement
    c. PR interval >220 ms confirmed by repeat measurement
    d. Findings which would make QTc measurements difficult of QTc data uninterpretable
    e. History of additional risk factors for torsades de pointes (eg, heart failure, hypokalemia, family history of long QT syndrome)
3. Clinically significant renal disease, nephrectomy, renal transplant, or creatinine clearance <60 mL/min/1.73 m^2 as calculated by using the Cockcroft-Gault equation:
    a. [1.23 × (140 – age) × [weight in kg)] ÷ (serum creatinine in µmol/L) – if male
    b. [1.04 × (140 – age) × (weight in kg)] ÷ (serum creatinine in µmol/L) – if female
4. Serum concentrations of TG, T-CHO, LDL-C that are above ULN, or serum concentration of HDL-C is below the lower limit of normal and are deemed clinically significant by the Investigator.
5. Positive pregnancy test at screening or Day -1 (female subjects).
6. Clinically significant impaired hepatic function at screening or Day -1 (confirmed by repeat); AST or ALT > 1.25 × ULN and / or T-Bil > 1.5 × ULN.

7. Unwilling or unable to eat high-fat breakfast; e.g. subject is vegetarian or has food allergies/ intolerances (for subjects recruited into Group A2a).
8. History of significant hypersensitivity, intolerance, or allergy to itraconazole. (Part C only)
9. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee).
10. History of stomach or intestinal surgery or resection including cholecystectomy that would potentially alter absorption and/or excretion of orally administered drugs (uncomplicated appendectomy and hernia repair will be allowed).
11. History of alcoholism or drug/chemical abuse within 2 years prior to Day -1.
12. Alcohol consumption of >14 units per week. One unit of alcohol equals 1/2 pint (285 mL) beer or lager, 1 glass (125 mL) of wine, or 1/6 gill (25 mL) of spirits.
13. Positive alcohol breath test result or positive urine drug and cotinine screen (confirmed by repeat) at Screening or Day -1.
14. Positive hepatitis panel and/or positive human immunodeficiency virus test.
15. Positive faecal occult blood test. For female subjects, the faecal occult blood test should be conducted at least 3 days after the completion of menstruation.
16. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 90 days prior to dosing.
17. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to dosing.
18. Use or intend to use any prescription medications/products within 14 days or 5 half-lives (whichever is longer) prior to dosing, unless deemed acceptable by the Investigator (or designee).
19. Use or intend to use strong or moderate CYP3A4 inhibitors or inducers within 14 days or 5 half-lives (whichever is longer) prior to dosing.
20. Use or intend to use strong CYP2C9, 2C8 and 2D6 inhibitors or inducers within 14 days or 5 half-lives (whichever is longer) prior to dosing.
21. Use or intend to use slow release medications/products considered to still be active within 14 days prior to dosing, unless deemed acceptable by the Investigator (or designee).
22. Use or intend to use any nonprescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant derived preparations within 7 days prior to dosing, unless deemed acceptable by the Investigator (or designee).
23. Use of tobacco or nicotine-containing products within 3 months prior to Day -1, or positive cotinine test at screening or Day -1.
24. Ingestion of poppy seed-, Seville orange-, or grapefruit-containing foods or beverages within 7 days prior to Day -1.
25. Consumption of caffeine- or xanthine-containing foods and beverages within 36 hours prior to Day -1.

26. Participation in strenuous exercised within 7 days prior to Day -1.
27. Receipt of blood products within 2 months prior to Day -1.
28. Donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, or platelets from 6 weeks prior to screening.
29. Poor peripheral venous access.
30. Subject does not have regular bowel habit. Regular bowel habit is defined as at least 1 bowel motion per day.
31. Have previously completed or withdrawn from this study or have previously received the IMP.
32. Administration or planned administration of a Coronavirus Disease 2019 (COVID 19) vaccine in the past 28 days prior to dosing until after the follow-up visit.
33. Subject is, in the opinion of the Investigator (or designee), unlikely to comply with the protocol or unsuitable to participate in this study for any reason.

4.3. Subject Number and Identification

Subjects will have a unique identification number used at screening. Subjects will be assigned a subject number prior to the first dosing occasion. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, in Part A subjects 0101, 0102, etc, in Part B subjects 0201, 0202, etc, and in Part C subjects 0301, 0302, etc,). Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus 1000 (eg, Subject 1101 replaces Subject 0101).

Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

4.4. Subject Withdrawal and Replacement

A subject is free to withdraw from the study at any time. In addition, a subject will be withdrawn if any of the following criteria are met:

- Change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects subject safety as determined by the Investigator (or designee)
- Noncompliance with the study restrictions that might affect subject safety or study assessments/objectives, as considered applicable by the Investigator (or designee)
- Any clinically relevant sign or symptom that, in the opinion of the Investigator (or designee), warrants subject withdrawal

If a subject is withdrawn from dosing, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the subject's electronic case report form (eCRF). If a subject is withdrawn from the study, efforts will be made to perform all follow-up assessments, if possible (Appendix 6). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the subject is in-house, these procedures should be performed before the subject is discharged from the clinic. The

Investigator (or designee) may also request that the subject return for an additional follow-up visit. All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilised.

Subjects who are withdrawn for reasons not related to study treatment may be replaced following discussion between the Investigator and the Sponsor. Subjects withdrawn as a result of AEs thought to be related to the study treatment will generally not be replaced.

4.5. Study Termination

The study may be discontinued at the discretion of the Investigator (or designee), or Sponsor if any of the following criteria are met:

- AEs unknown to date (ie, not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration)
- increased frequency, severity, and/or duration of known, anticipated, or previously reported AEs
- medical or ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- cancellation of drug development.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labelling

The IMPs include KRP-A218 1 mg tablet and 10 mg tablet and placebo tablet. The tablets all have the same appearance.

The IMPs will be supplied by the Sponsor (or designee), along with the batch numbers and Certificates of Analysis. A Certificate of Release authorized by a Qualified Person in the United Kingdom will also be issued for the IMP. A declaration of Good Manufacturing Practice equivalence issued by a Qualified Person in the United Kingdom will also be issued for the IMP. The IMP will be provided in a high-density polyethylene bottle in an aluminium bag with a desiccant and stored according to the instructions on the label.

All IMPs will be stored at ambient conditions between 1 to 30°C at the study site in a location that is locked with restricted access.

The bulk drug container and unit dose containers will be labelled in accordance with national laws and regulations. The IMPs will be transferred from bulk supplies into the subject's dose container by qualified clinical staff.

Tablets for the planned dose levels will be assembled as shown in Table 7.

Table 7: Tablet Assembly

Group	Dose Level (mg)	Number of Tablets to be Assembled		
		KRP-A218		Placebo
		1 mg tablets	10 mg tablets	
A1	1	1	-	1
A2	3	3	-	3
A3	6	6	-	6
A4	12	2	1	3
A5	maximum dose of 24	4	2	6
B1	X	X	-	X
B2	X	X	X	X
B3	X	X	X	X
B4	X	X	X	X
C1	X	X	-	-

In Part C, subjects will receive itraconazole as a concomitant drug.

Itraconazole (10 mg/mL oral solution) will be commercially sourced by Labcorp Clinical Research Unit Ltd. Every attempt will be made to source these supplies from a single lot/batch number. The Investigator (or designee) will record the lot/batch number, quantity, expiration date, and drug dispensed.

The storage conditions for itraconazole will be as indicated on the Summary of Product Characteristics. Each unit dose will be prepared by qualified clinical staff.

5.2. Study Treatment Administration

Each dose of KRP-A218 and placebo will be administered orally with approximately 240 mL of room temperature water. Every effort will be made to ensure that the times of administration of KRP-A218 for each individual subject are consistent throughout the treatment periods.

In Part A, all doses will be administered after an overnight fast of at least 10 hours, with the exception of Group A2a, where the dose given in Treatment Period 2, where KRP-A218 or placebo will be administered 30 minutes after starting a high-fat breakfast. The dietary status for dosing in Part B will be determined following review of the PK data from the fed/fasted comparison in Part A.

In Part C, each dose of KRP-A218 will be administered orally with approximately 240 mL of room temperature water. Itraconazole solution will be administered with no additional water. The dietary state for dosing of KRP-A218 alone on Day 1 and KRP-A218 co-administered with itraconazole on Day 11 will be determined by comparing the PK data between fed and fasted state in Group A2a. Itraconazole on Days 4 to 10, 12 and 13 will be administered in the fasted state. On Day 11, if it is determined that KRP-A218 will be dosed in the fasted state, then KRP-A218 will be administered first and itraconazole will be administered second. If it is determined that KRP-A218 will be dosed in the fed state, then itraconazole will be dosed first; subjects will then receive breakfast at approximately 1 hour post itraconazole dose, and KRP-A218 will be dosed second following breakfast.

Subjects will receive the IMP in numerical order while standing and will not be permitted to lie supine for 2 hours after dosing, except as necessitated by the occurrence of an AE and/or study procedures.

5.3. Randomisation

The randomisation code will be produced by the statistics department at Labcorp Drug Development using a computer-generated pseudo random permutation procedure.

In Part A, 2 subjects will be randomly assigned to receive placebo in each group, with the remaining 6 subjects randomly assigned to receive KRP-A218. Subjects in Group A2a will receive the same treatment in Treatment Periods 1 and 2. For all groups in Part A (with the exception of Group A2a in Treatment Period 2), sentinel dosing will occur whereby 2 subjects (1 active and 1 placebo) will be dosed on 1 day and, providing no safety concerns arise, the remaining 6 subjects will be dosed after at least 24 hours.

For Part B, 2 subjects will be randomly assigned to receive placebo in each group, with the remaining 8 subjects randomly assigned to receive KRP-A218. For all groups in Part B, sentinel dosing will occur whereby 2 subjects (1 active and 1 placebo) will be dosed on 1 day and, providing no safety concerns arise, the remaining 6 subjects will be dosed after at least 7 days.

Prior to the start of the study, a copy of the master randomisation code for Parts A and B of the study will be supplied in sealed envelopes to the Labcorp CRU pharmacy staff and the biopharmaceutical analyst at the bioanalytical laboratory.

Subjects in Part C will not be randomised, as this part of the study has an open-label, fixed treatment sequence.

5.4. Blinding

The blinding procedures outlined below will only be applicable to Parts A and B, as Part C is open-label.

The following controls will be employed to maintain the double-blind status of the study:

- The placebo tablets will be identical in appearance to KRP-A218.
- The Investigator and other members of staff involved with the study will remain blinded to the treatment randomisation code during the assembly procedure.
- Interim bioanalytical data will be provided to Labcorp CRU in a blinded manner.

To maintain the blind, the Investigator will be provided with a sealed randomisation code for each subject, containing details of their treatment. These individual sealed envelopes will be kept in a limited access area that is accessible 24 hours a day. In order to manage subject safety, to decision to proceed with dosing after sentinel dosing, or to support dose escalation decisions (in the event of possibly treatment related SAEs or severe AEs), the decision to unblind resides solely with the Investigator. Whenever possible, and providing it does not interfere with or delay any decision in the best interest of the subject, the Investigator will discuss the intended code break with the Sponsor. If it becomes necessary to break the code

during the study, the date, time, and reason will be recorded in the subject's source data and on the individual envelope and will be witnessed by a second person.

5.5. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each subject.
- At each dosing occasion, a predose and postdose inventory will be performed on the dose containers.

5.6. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for a review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused supplies will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

Subjects will refrain from use of any prescription or nonprescription medications/products during the study until the follow-up visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

Strong and moderate CYP3A4 inhibitors and inducers, and strong CYP2C9, 2C8 and 2D6 inhibitors and inducers are prohibited for at least 14 days or 5 half-lives prior to dosing (whichever is longer).

Paracetamol (up to 2 g/day for up to 3 consecutive days) is permitted at the discretion of the Investigator for the treatment of an AE. The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary in a medical emergency. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

Subjects will refrain from the use of hormone replacement therapy and oral, implantable, transdermal, injectable, or intrauterine hormonal contraceptives during the study until the follow-up visit.

6.2. Diet

While confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study related activities. Subjects will be fasted at least 6 hours before collection of blood samples for clinical laboratory evaluations (haematology, clinical chemistry).

On the days with intensive PK assessments (Day 1 for Part A, Days 1 and 14 for Part B, and Days 1 and 11 for Part C), meals will be identical for each group with the exception of the high-fat breakfast in Treatment Period 2 for subjects in Group A2a.

6.2.1. Part A

With the exception of Treatment Period 2 for subjects in Group A2a, on Day 1 in Part A, subjects will be fasted for at least 10 hours prior to dosing until 4 hours after dosing, after which time a meal will be provided (lunch times on Day 1 will be staggered between subjects to ensure this). With the exception of water given with the dose, subjects will not be allowed fluids from 1 hour prior, until 2 hours after dosing. Meals will be provided as appropriate at other times. Other than the fluid restrictions on dosing days, water will be freely available at all times.

Subjects in Group A2a will consume a high-fat breakfast (contents are detailed in Table 8) before dosing in Treatment Period 2. Subjects should start this meal 30 minutes prior to administration of the IMP. Study subjects should finish this meal in 30 minutes or less. The IMP should be administered 30 minutes after start of the meal.

Table 8: High-fat Breakfast Content

High-fat Breakfast
120 g fried eggs (2 eggs) in vegetable oil
50 g bacon (2 rashers)
72 g toasted white bread (2 slices)
13 g butter (2 pats)
108 g hash brown (3 each)
240 g whole milk
Total calories: 973 kcal

This high-fat meal contains the equivalent of approximately 150 protein calories, 250 carbohydrate calories, and 500 to 600 fat calories.

6.2.2. Part B

Subjects will receive the IMP on Days 1 to 14. The dietary state for dosing in Part B will be subject to review of the PK data from the fed/fasted comparison in Part A. The time interval between meals and dosing will be determined by the PK data from Part A and will be documented in the TMF. If the IMP is administered in the fasted state, subjects will be fasted for at least 10 hours prior to dosing. For Days 1 and 14, subjects will be fasted until 4 hours

after dosing, after which time a meal will be provided (lunch times will be staggered between subjects to ensure this). With the exception of water given with the dose, subjects will not be allowed fluids from 1 hour prior to dosing until 2 hours after dosing. Meals will be provided as appropriate. Other than these fluid restrictions, water will be freely available at all times.

6.2.3. Part C

Subjects will receive KRP-A218 alone on Day 1 and KRP-A218 co-administrating with itraconazole on Day 11. The dietary state for dosing of KRP-A218 alone on Day 1 and KRP-A218 co-administered with itraconazole on Day 11 will be determined by comparing the PK data between fed and fasted state in Group A2a. The time interval between meals and dosing of KRP-A218 will be determined by the PK data from Part A and will be documented in the TMF. If KRP-A218 is administered in the fasted state on Days 1 and 11, subjects will be fasted for at least 10 hours prior to dosing until at least 4 hours after dosing, after which time a meal will be provided (lunch times will be staggered between subjects to ensure this). On Day 4, itraconazole will be administered twice, approximately 12 hours apart, in the fasted state. Itraconazole on Days 5 to 10, 12 and 13 will be administered in the fasted state. With the exception of water given with KRP-A218, subjects will not be allowed fluids from 1 hour prior to dosing until 2 hours after dosing on Days 1 and 11. Meals will be provided as appropriate. Other than these fluid restrictions on Days 1 and 11, water will be freely available at all times.

6.3. Other Restrictions

6.3.1. Foods and Beverages

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to Day -1 until after the follow-up visit.

Caffeine- and xanthine-containing foods and beverages will not be allowed from 36 hours before Day -1 until discharge (in each treatment period, where applicable) and from 10 hours prior to the follow-up visit until after the follow-up visit.

Consumption of alcohol will not be permitted from 48 hours prior to Day -1 until discharge (in each treatment period, where applicable) and from 48 hours prior to the follow-up visit until after the follow-up visit. Up to 4 units/day (male) and 3 units/day (female) of alcohol are permitted from discharge until 48 hours before the follow-up visit (Day -1 for Treatment Period 2 in Group A2a).

6.3.2. Smoking

Subjects will not be permitted to use tobacco- or nicotine-containing products within 3 months prior to Day -1 until after the follow-up visit.

6.3.3. Exercise

Subjects are required to refrain from strenuous exercise from 7 days before Day -1 until after the follow-up visit and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.3.4. Blood Donation

Subjects are required to refrain from donation of blood from 3 months prior to screening, plasma from 2 weeks prior to screening, and platelets from 6 weeks prior to screening until 3 months after the follow-up visit.

7. STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same time point.

The highest priority procedures will be performed closest to the nominal time. The order of priority for scheduling procedures around a time point is (in descending order of priority):

- dosing
- blood samples for PK and exploratory metabolite profiling
- any other procedures (safety ECGs will be scheduled before vital signs measurements [except body temperature]; vital signs measurements [except body temperature] will be scheduled before blood sampling)

7.1. Pharmacokinetic Assessments

7.1.1. Pharmacokinetic Sample Collection and Processing

Blood samples (approximately 1 × 2-mL sample per scheduled time) for PK analysis of CCI and blood samples (approximately 1 × 2-mL sample per scheduled time) for PK analysis of itraconazole and its metabolite hydroxy-itraconazole will be collected by venepuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 6. Furthermore, up to 3 additional blood samples may be taken from each subject per treatment period in Part A, and up to 6 additional blood samples may be taken from each subject in Parts B and C, with the maximum volume of blood withdrawn per subject will not exceed the limit detailed in Appendix 3. Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the TMF. Blood samples taken from subjects who received placebo will not be analysed.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

7.1.2. Pharmacokinetic Analytical Methodology

Plasma concentrations of CCI, itraconazole, and hydroxy-itraconazole will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

7.2. Exploratory Assessments

7.2.1. Sample Collection and Processing for Exploratory Metabolite Profiling

For subjects in Groups A2a, A5, B1, and C1, blood samples (approximately 1 × 2 mL sample per scheduled time) will be collected by venepuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 6. The maximum volume of blood withdrawn per subject will not exceed the limit detailed in Appendix 3. Any changes to the scheduled times of blood sampling for metabolite profiling will be agreed with the Sponsor and documented in the TMF. Blood samples taken from subjects who received placebo will not be measured.

For subjects in Groups A2a and A5, predose spot urine and faecal samples and 24-hour urine and faecal samples will be collected into pre-weighed polyethylene containers over the time intervals indicated in the Schedule of Assessments in Appendix 6. Faecal samples will be collected, as far as possible. For subjects in Groups B1, predose spot urine and 24-hour urine samples will be collected into pre-weighed polyethylene containers over the time intervals indicated in the Schedule of Assessments in Appendix 6. Urine and faecal samples taken from subjects who received placebo will not be measured.

Procedures for collection, processing, and shipping of blood, urine, and faecal samples for metabolite profiling will be detailed in a separate document.

7.2.2. Methodology for Exploratory Metabolite Profiling Analysis

The analytical methods for exploratory metabolite profiling analysis may be provided in a separate document and will not form part of the Clinical Study Report for this study.

7.2.3. Sample Collection and Processing for Pharmacogenetic Analysis

Blood samples (approximately 1 × 10-mL sample) will be collected by venepuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 6. The maximum volume of blood withdrawn per subject will not exceed the limit detailed in Appendix 3.

Subjects will only be required to provide a single sample for pharmacogenetic analysis during the course of the study. In the case that a pharmacogenetic sample is collected whilst a subject is standby for the sentinel group but is not then dosed as a sentinel a second pharmacogenetic sample is not required if that subject is subsequently enrolled in the main group.

7.2.4. Methodology for Pharmacogenetic Analysis

If pharmacogenetic analysis is undertaken, the analytical methods may be provided in a separate document and will not form part of the Clinical Study Report for this study.

7.2.5. Sample Collection and Processing for Exploratory Biomarker Analysis

Exploratory biomarker analysis in blood and urine will be performed on residual samples of exploratory metabolite profiling in Parts A and B.

7.2.6. Sample Collection and Processing for Analysis of Phospholipid-C and Faecal Calprotectin

Exploratory analysis of phospholipid-C in serum and faecal calprotectin will be performed on blood samples taken for safety clinical laboratory assessments and residual samples taken for faecal occult blood tests, respectively. Faecal calprotectin measurements will only be performed during the respective treatment period.

7.2.7. Methodology for Exploratory Biomarker Analysis

If exploratory biomarker analysis is undertaken, the analytical methods may be provided in a separate document and will not form part of the Clinical Study Report for this study.

7.2.8. Continuous 12-lead Electrocardiogram Monitoring

Continuous 12-lead ECG monitoring using a digital recorder will take place at the times indicated in the Schedule of Assessments in Appendix 6. Continuous 12-lead ECG monitoring may be added to Part B; if added, the details will be documented and filed in the eTMF.

All continuous 12-lead ECG data collected will be archived without extraction or analysis and will not be reported in the scope of this study.

Environmental distractions (eg, television, radio, conversation) should be avoided during ECG recording, where possible.

7.3. Safety and Tolerability Assessments

7.3.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each subject will be monitored from the time of signing the ICF to final discharge from the study. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as "how have you been feeling since you were last asked?", at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

Any AEs and remedial action required will be recorded in the subject's source data. The nature, time of onset, duration, and severity will be documented, together with an Investigator's (or designee's) opinion of the relationship to study treatment.

Adverse events recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the Investigator (or designee) to have stabilised. This will be completed at the Investigator's (or designee's) discretion.

7.3.2. Clinical Laboratory Evaluations

Clinical laboratory evaluations are listed in Appendix 2. Total blood sampling volumes for an individual subject is shown Appendix 3.

Blood, urine and faecal samples will be collected for clinical laboratory evaluations (including clinical chemistry, haematology, urinalysis, coagulation, and faecal occult blood test) at the times indicated in the Schedule of Assessments in Appendix 6. Blood samples for clinical laboratory evaluations will be collected after at least 6-hour fast. Faecal samples in treatment periods will be collected as far as possible. If the latest result during the treatment period is positive, faecal samples will be collected for faecal occult blood test at the follow-up visit, as far as possible. If subjects collect faecal samples at home, the sample within 24 hours before the designated time point is acceptable. For female subjects, faecal samples at screening and the follow-up visit should be collected at least 3 days after the completion of menstruation.

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

Subjects will be asked to provide urine samples for drugs of abuse screen and cotinine test, and will undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 6.

For all female subjects, serum and/or urine pregnancy tests and follicle-stimulating hormone test will be performed at the times indicated in the Schedule of Assessments in Appendix 6, as applicable.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

7.3.3. Bristol Stool Chart

The form of faeces will be assessed by clinical staff using the Bristol Stool Chart when collecting faecal samples for faecal occult blood test in treatment periods (see Schedule of Assessments in Appendix 6). The form of faeces may also be assessed at other times if judged to be clinically appropriate.

7.3.4. Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 6. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

For Day 1 predose in each treatment period in Parts A to C and Day 11 predose in Part C, blood pressure, pulse rate, and respiratory rate will be measured in triplicate at approximately 2-minute intervals. The median value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges. Oral body temperature will be measured singly.

Subjects should be supine for at least 5 minutes before blood pressure and pulse rate measurements.

7.3.5. 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 6. Single 12-lead ECGs will be repeated once if either of the following criteria apply:

- QTcF value >500 msec
- QTcF change from the baseline (predose) is >60 msec.

Additional 12 lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12 lead ECG.

Day 1 predose 12-lead ECGs in each treatment period in Parts A to C and Day 11 predose in Part C will be measured in triplicate at approximately 2-minute intervals. The mean value will be used as the baseline value in the data analysis. All subsequent measurements will be performed singly and repeated once if outside the relevant clinical reference ranges.

7.3.6. Physical Examination

A full physical examination or symptom-directed physical examination will be performed by Investigator (or designee) at the time points specified in the Schedule of Assessments in Appendix 6.

7.3.7. Abdominal Examination

An abdominal examination will be performed in Parts A and B by Investigator (or designee) and will include inspection, auscultation, palpation and percussion of the abdomen. The abdominal examination will be performed at the times indicated in the Schedule of Assessments in Appendix 6.

When the physical examination and the abdominal examination are scheduled at the same day, the abdominal examination may be performed as part of the physical examination.

7.3.8. Height, Body Weight, and BMI

Height and body weight (in underclothes and with shoes off) will be recorded at the times indicated in the Schedule of Assessments in Appendix 6. The BMI is calculated using metric units with the formula provided below.

BMI should be derived as:

Metric: BMI=body weight (kg)/height $(m)^2$

8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

No formal statistical assessment, in terms of sample size, has been conducted as this is the first time KRP-A218 is being administered to humans. However, the number of subjects in Parts A, B, and C is common in early clinical pharmacology studies/DDI studies, and is considered sufficient to achieve the objectives of the study.

8.2. Analysis Populations

8.2.1. Pharmacokinetic Population

The PK population will include all subjects who received at least 1 dose of active study treatment (KRP-A218 or itraconazole) and have at least 1 quantifiable PK concentration. A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2-times t_{max}.

8.2.2. Safety Population

The safety population will include all subjects who received at least 1 dose of study treatment (KRP-A218, placebo, or itraconazole).

8.3. Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual plasma concentration data, using commercial software such as Phoenix® WinNonlin®. Plasma concentrations and PK parameters of CCI, itraconazole, and hydroxy-itraconazole will be listed and summarised by treatment group using descriptive statistics. Individual and mean concentration-time profiles for CCI and itraconazole and hydroxy-itraconazole for each treatment group will also be presented graphically.

Where data are available, dose proportionality of CCI will be examined across dose groups. The PK parameters will be analysed for dose proportionality using a power model approach and/or analysis of variance (ANOVA) model, as appropriate. Where data are available, the effect of food at 1 dose level in Part A, and the interaction between KRP-A218 alone and co-administered with itraconazole in Part C will be investigated using mixed-model; the effect of sex at 1 dose level in Part A will be investigated using ANOVA.

Data handling procedures will be documented in the Statistical Analysis Plan.

8.4. Exploratory Metabolite Profiling Analysis

Data obtained from the exploratory metabolite profiling analysis may be reported elsewhere and will not form part of the Clinical Study Report for this study.

8.5. Pharmacogenetic Analysis

If pharmacogenetic analysis is undertaken, results may be reported elsewhere and will not form part of the Clinical Study Report for this study.

8.6. Exploratory Biomarker Analysis

If exploratory biomarker analysis is undertaken, results may be reported elsewhere and will not form part of the Clinical Study Report for this study.

8.7. Concentration-QTc Analysis

If concentration-QTc analysis is undertaken, results may be reported elsewhere and will not form part of the Clinical Study Report for this study.

8.8. Safety Analysis

Safety parameters will be listed and summarised using descriptive statistics. No formal statistical analysis of safety data is planned. Each AE will be coded using the Medical Dictionary for Regulatory Activities.

8.9. Interim Analysis

There is no planned interim analysis for this study.

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

Assessment of Severity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- **Severe**: Interrupts usual activities of daily living, or significant affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The Investigator will make a determination of the relationship of the AE to the study drug using a four-category system according to the following guidelines:

- **Not Related**: The AE is definitely caused by the subject's clinical state or the study procedure/conditions.
- **Unlikely Related**: The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- **Possibly Related**: The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the subject's clinical state or the study procedures/conditions.
- **Related**: The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow-up with subjects who have AEs. Any subject who has an ongoing AE that is possibly related or related to the IMP or study procedures at the follow-up visit will be followed up, where possible, until resolution or until the unresolved AE is judged by the Investigator (or designee) to have stabilised. This will be completed at the Investigator's (or designee's) discretion. Any subject who has an ongoing

AE that is not related or unlikely related to the IMP or study procedures at the follow-up visit can be closed out as ongoing at the Investigator's discretion.

Adverse Drug Reactions

All noxious and unintended responses to any dose of IMP (ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility [ie, 'related' or 'possibly related']) should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, IB for an unapproved IMP).

Serious Adverse Events

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

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 subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, will be reported to the Sponsor.

<u>Definition of Life-threatening</u>

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

<u>Definition of Hospitalization</u>

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at the CRU. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs and should be recorded on a Clinical Assessment Form and added to the eCRF. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

Labcorp Drug Development Patient Safety Services (PSS) Europe, Maidenhead, UK (to confirm), are responsible for coordinating the reporting of SAEs in accordance with the European Directive 2001/20/EC.

The Investigator will complete an SAE report form and forward it by facsimile or email to PSS immediately (within 24 hours) upon becoming aware of an SAE.

The responsibilities of Labcorp Drug Development PSS include the following:

- Prepare an AE reporting plan prior to the start of the study. Where this plan differs from the applicable CRU standard operating procedure on SAE reporting, the AE reporting plan will always take precedence.
- Receive and review SAE report forms from the CRU and inform the Sponsor of the SAE within 1 business day of the initial notification to PSS. Patient Safety Services will delete any information from the SAE report forms that may identify the subject.
- Write case narratives and enter the case into Labcorp Drug Development's safety database as defined in the AE reporting plan.
- Produce appropriate reports of all Suspected Unexpected Serious Adverse Reactions and forward to the Ethics Committee, Medicines and Healthcare Products Regulatory Agency, Principal Investigator, and the Sponsor within the timeframes stipulated in the Clinical Trials Directive Guideline (ENTR/CT 3).

The responsibility for reporting SAEs will be transferred to the Sponsor 28 days after the end of the study.

Pregnancy

Pregnancy (maternal or paternal exposure to study treatment) does not meet the definition of an AE. However, to fulfil regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and foetus.

Appendix 2: Clinical Laboratory Evaluations

Clinical chemistry	Aspartate aminotransferase, Alanine aminotransferase, Alkaline phosphatase, Lactate dehydrogenase, Gamma glutamyl transferase, Total bilirubin, Direct bilirubin, Unconjugated bilirubin, Creatine kinase, Total protein, Triglycerides, Total cholesterol, Low-density lipoprotein cholesterol, High-density lipoprotein cholesterol, Phospholipid C[a], Albumin, Blood urea nitrogen, Creatinine[b], Creatinine clearance[c, d], Uric acid, Sodium, Potassium, Chloride, Calcium, Inorganic phosphate, Glucose
Haematology	White blood cell (WBC) count, WBC differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), Red blood cell count, Mean cell volume, Mean cell haemoglobin, Mean cell haemoglobin concentration, Haemoglobin, Hematocrit, Platelet count
Coagulation	Prothrombin time/international normalised ratio, Activated partial thromboplastin time, Fibrinogen
Urinalysis	Specific gravity, pH, Ketones, Blood, Glucose, Protein, Urobilinogen, Microscopic examination
Serology[c]	Anti-hepatitis B surface antibody, Hepatitis B surface antigen, Hepatitis C antibody, Human immunodeficiency (HIV 1 and HIV 2) antibodies
Drug and cotinine screen[e]	Including but not limited to: Amphetamines/methamphetamines, Barbiturates, Benzodiazepines, Cocaine (metabolite), Cotinine, Methadone, Phencyclidine, Opiates, Tetrahydrocannabinol/cannabinoids, Tricyclic antidepressants
Breath test[e]	Alcohol breath test
Hormone panel females only	Follicle-stimulating hormone[f] Serum pregnancy test (human chorionic gonadotropin)[f] Urine pregnancy test[g]
Faecal test	Faecal occult blood test, faecal calprotectin[a]

a To be analysed as an exploratory endpoint only.
b Serum creatinine will be used to calculate creatinine clearance using the Cockcroft-Gault formula.
c Screening only.
d Assessed using the Cockcroft-Gault formula.
e Screening and Day -1 only.
f Performed at screening for all females.
g Performed for all females at Day -1 and follow-up. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn from each subject in Part A.

	Volume per blood sample (mL)	Maximum number of blood samples			Total amount of blood (mL)		
		A1, A2b (f), A3, A4	A5	A2a (m)	A1, A2b (f), A3, A4	A5	A2a (m)
Haematology, Clinical chemistry, and Coagulation [a, b]	9.3	5	5	8	46.5	46.5	74.4
Serology	3.5	1	1	1	3.5	3.5	3.5
CCI pharmacokinetics	2	16	16	32	32	32	64
Metabolite profiling	2	-	7	7	-	14	14
Pharmacogenetics	10	1	1	1	10	10	10
Total:					92	106	165.9

Abbreviations: f = females; m= males.
[a] Includes blood collected for follicle-stimulating hormone and serum pregnancy testing at screening from subjects in Group A2b.
[b] Includes a 1.8 mL sample for activated partial thromboplastin time, prothrombin time/international normalised ratio, and fibrinogen.

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

The following blood volumes will be withdrawn from each subject in Part B.

	Volume per blood sample (mL)	Maximum number of blood samples		Total amount of blood (mL)	
		B1	B2 to B4	B1	B2 to B4
Haematology, Clinical chemistry, and Coagulation[a]	9.3	9	9	83.7	83.7
Serology	3.5	1	1	3.5	3.5
CCI pharmacokinetics	2	40	40	80	80
Metabolite profiling	2	8	-	16	-
Pharmacogenetics	10	1	1	10	10
Total:				193.2	177.2

[a] Includes a 1.8 mL sample for activated partial thromboplastin time, prothrombin time/international normalised ratio, and fibrinogen.

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

The following blood volumes will be withdrawn from each subject in Part C.

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
		C1	C1
Haematology, Clinical chemistry, and Coagulation[a]	9.3	8	74.4
Serology	3.5	1	3.5
CCI pharmacokinetics	2	32	64
Itraconazole and hydroxy-itraconazole pharmacokinetics	2	16	32
Metabolite profiling	2	14	28
Pharmacogenetics	10	1	10
Total:			211.9

[a] Includes a 1.8 mL sample for activated partial thromboplastin time, prothrombin time/international normalised ratio, and fibrinogen.

If extra blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed 500 mL.

Appendix 4: Contraception Guidance

Definitions

Women of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Nonchildbearing Potential:

1. Surgically sterile: females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy be reported medical history and/or medical records. Surgical sterilisation to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to screening.
2. Postmenopausal: Females at least 45 years of age with amenorrhoea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥40 mIU/mL at screening. The amenorrhoea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhoea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-oestrogens, or selective oestrogen receptor modulators.

Fertile Male: a male that is considered fertile after puberty.

Infertile Male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Subjects

Female subjects who are of nonchildbearing potential will not be required to use contraception. Female subjects of childbearing potential must be willing to use a highly effective method of birth control in conjunction with male barrier contraception (i.e. male condom with spermicide) from the time of signing the ICF until 90 days after the follow-up visit. Hormone-releasing intrauterine device (IUD) and oral, implantable, transdermal, or injectable hormonal methods of contraception are not acceptable, since the contraceptive effects may not be sufficient due to the possibility of CYP3A4 induction by CCI
Highly effective methods of contraception include:

- Male sterilisation (performed at least 90 days prior to the screening visit), with verbal confirmation of surgical success (for female subjects on the study, the vasectomised male partner should be the sole partner for that subject)
- Bilateral tubal ligation or occlusion (performed at least 90 days prior to the screening visit)

Female subjects should refrain from donation of eggs (ova, oocytes) from check-in (Day -1) until 90 days after the follow-up visit.

Male Subjects

Male subjects (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception from Day -1 until 90 days after the follow-up visit. In addition to the list of highly effective methods of contraception above, other acceptable methods of contraception for female partners include:

- Hormone-releasing IUD. Steel or copper IUDs are not acceptable
- Established use of oral, implantable, transdermal, or injectable hormonal method of contraception associated with inhibition of ovulation
- Established use of progesterone only oral contraception, where inhibition of ovulation is not the primary mode of action

Double-barrier methods, such as male condom with spermicide along with female partner use of a female condom, diaphragm, cap, or sponge are not acceptable.

An acceptable second method of contraception for male subjects is vasectomy that has been performed at least 90 days prior to the screening visit, with verbal confirmation of surgical success.

For male subjects (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the time of the first dose until 90 days after the follow-up visit. Male subjects are required to refrain from donation of sperm from check-in until 90 days after the follow-up visit.

Sexual Abstinence and Same-sex Relationships

Subjects who practice true abstinence, because of the subject's lifestyle choice (ie, the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a subject who is abstinent at the time of signing the ICF becomes sexually active they must agree to use contraception as described previously.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents must be submitted to an Ethics Committee (EC) by the Investigator and reviewed and approved by the EC before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the subjects or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects or any nonsubstantial changes, as defined by regulatory requirements.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with CRU personnel, subjects will sign the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. A copy of the ICF will be given to the subject.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all

identifiable information from individual subjects or Investigator will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her study-related data may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- Labcorp Drug Development is responsible for the data management of this study including quality checking of the data. Predefined, agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in the study site archive for at least 5 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will also be entered into a 21 CFR Part A1-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Labcorp Drug Development electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled subject, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

Publications will be addressed in a separate agreement.

Appendix 6: Schedule of Assessments

Table 9: Schedule of Assessments-Part A (Groups A1, A2b, and A3 to A5; Single-Dose)

	Screening	Treatment Period 1																		Follow-up (7 to 10 Days Postdose)[r]
Day	-28 to -2	-1	1													2		3	4	
Time Postdose (h)			pre	0	0.25	0.5	0.75	1	1.5	2	3	4	6	8	12	24	36	48	72	
Informed consent	X																			
Inclusion/exclusion criteria	X	X																		
Demographic data	X																			
Medical history	X	X[a]																		
Urinary drug and cotinine screen	X	X																		
Alcohol breath test	X	X																		
Serology	X																			
Follicle-stimulating hormone[b]	X																			
Pregnancy test[c]	X	X																		X
Height	X																			
IMP administration																				
KRP-A218 or placebo				X[d]																
Pharmacokinetics																				
Blood sampling for the PK of CCI			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Exploratory analyses																				
Blood sampling for metabolite profiling[e]			X			X		X		X		X		X		X				
Urine and Faecal collection for metabolite profiling[e,f]		<----X---->	<----------X----------><----X----><---X-->																	
Pharmacogenetics			X																	
Continuous 12-lead ECG[g]			←----------X----------→																	
Safety and tolerability																				
Adverse event recording	<---------->																			
Prior/concomitant medication monitoring	<---------->																			
Body weight	X	X																	X[h]	
Haematology, clinical chemistry, coagulation, and urinalysis[i]	X	X														X[h]			X[h]	X
Faecal occult blood test[j]	X	<----X---->	<----------X----------><----X----><---X-->																	X[k]
Bristol Stool Chart[l]		<----X---->	<----------X----------><----X----><---X-->																	

Table 9: Schedule of Assessments-Part A (Groups A1, A2b, and A3 to A5; Single-Dose)

	Screening	Treatment Period 1																		Follow-up (7 to 10 Days Postdose)[t]
Day	-28 to -2	-1	1													2		3	4	
Time Postdose (h)			pre	0	0.25	0.5	0.75	1	1.5	2	3	4	6	8	12	24	36	48	72	
Blood pressure, pulse rate, and respiratory rate[m]	X	X	X[n]					X		X		X		X	X	X[h]		X[h]	X[h]	X
Oral body temperature	X	X	X													X[h]		X[h]	X[h]	X
12-lead ECG for safety assessment[o]	X	X	X[n]			X		X		X		X		X	X	X[h]		X[h]	X[h]	X
Physical examination		X[p]																	X[q,r]	X[p]
Abdominal examination		X									X					X[s]		X[s]	X[r]	

[a] Interim medical history.
[b] Female subjects only.
[c] Female subjects only. Serum pregnancy test at screening and urine pregnancy test at all other timepoints. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
[d] Subjects will be fasted for at least 10 hours prior to dosing until 4 hours after dosing, after which time a meal will be provided.
[e] Collected in Group A5 only.
[f] Spot urine and faecal samples will be collected any time prior to dosing in the treatment period. 24-hour urine and faecal samples will be collected on 0 to 24, 24 to 48, and 48 to 72 hours postdose. Faecal samples will be collected, as far as possible.
[g] A continuous 12-lead ECG will be obtained from 2 hours predose to 24 hours postdose. The 15-minute predose posture restriction (supinely or semi-recumbently resting in an undisturbed environment) for continuous ECG monitoring will be performed in triplicate within the first 2 hours prior to dosing. Postdose 15-minute posture restrictions for continuous ECG monitoring will be performed at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours postdose. Additional posture restrictions may be performed if deemed necessary after the review of PK data at the dose escalation review meetings.
[h] From waking-up to before breakfast.
[i] Subjects will be fasted at least 6 hours before collection.
[j] Faecal occult blood test will be performed once each during the following sampling periods: Screening, Day -1 to prior to dosing, 0 to 24, 24 to 48, and 48 to 72 hours postdose. On screening, faecal samples will be collected to confirm eligibility for enrollment. For the other sampling periods, faecal samples will be collected as far as possible.
[k] If the latest result during the treatment period is positive, faecal samples will be collected for faecal occult blood test at the follow-up visit (within -2 day), as far as possible.
[l] To be assessed when collecting faecal samples for faecal occult blood test during the treatment period.
[m] Subjects should be supine for at least 5 minutes before blood pressure and pulse rate measurements.
[n] To be measured in triplicate at approximately 2-minute intervals.
[o] To be recorded after the subject has been supine and at rest for at least 5 minutes.

[p] Full physical examination.
[q] Symptom-directed physical examination.
[r] Prior to discharge.
[s] To be performed at approximately the same time as on Day 1.
[t] The follow-up period may be extended depending on the observed $t_{1/2}$ of [redacted]

Table 10: Schedule of Assessments-Part A (Group A2a; Single-Dose) [Screening to Treatment Period 1]

	Screening	Treatment Period 1																		
Day	**-28 to -2**	**-1**	**1**													**2**		**3**	**4**
Time Postdose (h)			**pre**	**0**	**0.25**	**0.5**	**0.75**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**72**
Informed consent	X																		
Inclusion/exclusion criteria	X	X																	
Demographic data	X																		
Medical history	X	X[a]																	
Urinary drug and cotinine screen	X	X																	
Alcohol breath test	X	X																	
Serology	X																		
Height	X																		
IMP administration																			
KRP-A218 or placebo				X[b]															
Pharmacokinetics																			
Blood sampling for the PK of CCI			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exploratory analyses																			
Blood sampling for metabolite profiling			X			X		X		X		X		X		X			
Urine and Faecal collection for metabolite profiling[c]		<----X---->	<----------X----------><----X----><----X---->																
Pharmacogenetics			X																
Continuous 12-lead ECG[d]			<----------X---------->																
Safety and tolerability																			
Adverse event recording	<---------->																		
Prior/concomitant medication monitoring	<---------->																		
Body weight	X	X																	X[e]
Haematology, clinical chemistry, coagulation, and urinalysis[f]	X	X														X[e]			X[e]
Faecal occult blood test[g]	X	<----X---->	<----------X----------><----X----><----X---->																
Bristol Stool Chart[h]		<----X---->	<----------X----------><----X----><----X---->																
Blood pressure, pulse rate, and respiratory rate[i]	X	X	X[j]					X		X		X		X	X	X[e]		X[e]	X[e]
Oral body temperature	X	X	X													X[e]		X[e]	X[e]
12-lead ECG for safety assessment[k]	X	X	X[j]			X		X		X		X		X	X	X[e]		X[e]	X[e]
Physical examination		X[l]																	X[m, n]
Abdominal examination		X									X					X[o]		X[o]	X[n]

Table 10: Schedule of Assessments-Part A (Group A2a; Single-Dose) [Washout to Follow-up visit]

Day	Washout (interval of 7 to 10 days between dosing)[r]	Treatment Period 2																		Follow-up (7 to 10 Days Postdose)[r]
		-1	1													2		3	4	
Time Postdose (h)			pre	0	0.25	0.5	0.75	1	1.5	2	3	4	6	8	12	24	36	48	72	
Inclusion/exclusion criteria		X																		
Urinary drug and cotinine screen		X																		
Alcohol breath test		X																		
IMP administration																				
KRP-A218 or placebo				X[p]																
Pharmacokinetics																				
Blood sampling for the PK of CCI			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety and tolerability																				
Adverse event recording	<----------																			---------->
Prior/concomitant medication monitoring	<----------																			---------->
Body weight		X																	X[e]	
Haematology, clinical chemistry, coagulation, and urinalysis[f]		X														X[e]			X[e]	X
Faecal occult blood test[g]		<----X---->	<----------X----------><----X----><--X-->																	X[q]
Bristol Stool Chart[h]		<----X---->	<----------X----------><----X----><--X-->																	
Blood pressure, pulse rate, and respiratory rate[i]		X	X[j]					X		X		X		X	X	X[e]		X[e]	X[e]	X
Oral body temperature		X	X													X[e]		X[e]	X[e]	X
12-lead ECG for safety assessment[k]		X	X[j]			X		X		X		X		X	X	X[e]		X[e]	X[e]	X
Physical examination		X[l]																	X[m,n]	X[l]
Abdominal examination		X									X					X[o]		X[o]	X[n]	

[a] Interim medical history.

[b] Subjects will be fasted for at least 10 hours prior to dosing until 4 hours after dosing, after which time a meal will be provided.

[c] Spot urine and faecal samples will be collected any time prior to dosing in Treatment Period 1. 24-hour urine and faecal samples will be collected on 0 to 24, 24 to 48, and 48 to 72 hours postdose. Faecal samples will be collected, as far as possible.

[d] A continuous 12-lead ECG will be obtained from 2 hours predose to 24 hours postdose. The 15-minute predose posture restriction (supinely or semi-recumbently resting in an undisturbed environment) for continuous ECG monitoring will be performed in triplicate within the first 2 hours prior to dosing. Postdose 15-minute posture restrictions for continuous ECG monitoring will be performed at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours postdose. Additional posture restrictions may be performed if deemed necessary after the review of PK data at the dose escalation review meetings.

[e] From waking-up to before breakfast.

[f] Subjects will be fasted for at least 6 hours before collection.

[g] Faecal occult blood test will be performed once each during the following sampling periods: Screening, Day -1 to prior to dosing, 0 to 24, 24 to 48, and 48 to 72 hours postdose in Treatment Period 1, and Day -1 to dosing, 0 to 24, 24 to 48, and 48 to 72 hours postdose in Treatment Period 2. On screening in Treatment Period 1, faecal samples will be collected to confirm eligibility for enrollment. For the other sampling periods, faecal samples will be collected as far as possible.
[h] To be assessed when collecting faecal samples for faecal occult blood test in treatment periods.
[i] Subjects should be supine for at least 5 minutes before blood pressure and pulse rate measurements.
[j] To be measured in triplicate at approximately 2-minute intervals.
[k] To be recorded after the subject has been supine and at rest for at least 5 minutes.
[l] Full physical examination.
[m] Symptom-directed physical examination.
[n] Prior to discharge.
[o] To be performed at approximately the same time as on Day 1.
[p] Subjects will receive the IMP at the same time as Day 1 in Treatment Period 1 and 30 minutes after starting a high-fat breakfast.
[q] If the latest result during the treatment period is positive, faecal samples will be collected for faecal occult blood test at the follow-up visit (within -2 day), as far as possible.
[r] The interval between dosing is up to and including Day -1 of Treatment Period 2. The washout and follow-up periods may be extended depending on the observed $t_{1/2}$ of CCI

Table 11: Schedule of Assessments-Part B (Multiple-Dose) [Screening to Day 1]

	Screening	Treatment Period													
Day	**-28 to -2**	**-1**	**1**												
Time Postdose(h)			**Pre**	**0**	**0.25**	**0.5**	**0.75**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**
Informed consent	X														
Inclusion/exclusion criteria	X	X													
Demographic data	X														
Medical history	X	X[a]													
Urinary drug and cotinine screen	X	X													
Alcohol breath test	X	X													
Serology	X														
Height	X														
IMP administration															
KRP-A218 or placebo[b]				X[c]											
Pharmacokinetics															
Blood sampling for the PK of [redacted]			X		X	X	X	X	X	X	X	X	X	X	X
Exploratory analyses															
Blood sampling for metabolite profiling[d]			X												
Urine collection for metabolite profiling[d,e]		<----X---->													
Pharmacogenetics			X												
Safety and tolerability															
Adverse event recording	<---------->														
Prior/concomitant medication monitoring	<---------->														
Body weight	X	X													
Haematology, clinical chemistry, coagulation, and urinalysis[f]	X	X													
Faecal occult blood test[g]	X	<----X---->		<----------X---------->											
Bristol Stool Chart[h]		<----X---->		<----------X---------->											
Blood pressure and pulse rate, and respiratory rate[i]	X	X	X[j]					X				X		X	X
Oral body temperature	X	X	X												
12-lead ECG for safety assessment[k]	X	X	X[j]					X				X		X	X
Physical examination		X[l]													
Abdominal examination		X									X				

Table 11: Schedule of Assessments-Part B (Multiple-Dose) [Day 2 to Day 13]

	Treatment Period											
Day	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Time Postdose(h)	**24**	**48**	**72**	**96**	**120**	**144**	**168**	**192**	**216**	**240**	**264**	**288**
IMP administration												
KRP-A218 or placebo[b]	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics												
Blood sampling for the PK of [CCI]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]
Safety and tolerability												
Adverse event recording	<----------											---------->
Prior/concomitant medication monitoring	<----------											---------->
Body weight						X[o]						
Haematology, clinical chemistry, coagulation, and urinalysis[f]		X[o]		X[o]		X[o]			X[o]			
Faecal occult blood test[g]	----><----------	X	----------><----------		X	----------><----------			X	----------><----------		X----------
Bristol Stool Chart[q]	----><----------	X	----------><----------		X	----------><----------			X	----------><----------		X----------
Blood pressure and pulse rate, and respiratory rate[i]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]
Oral body temperature	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]
12-lead ECG for safety assessment[k]	X[o]	X[o]		X[o]		X[o]			X[o]			
Physical examination						X[l]						
Abdominal examination	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]

Table 11: Schedule of Assessments-Part B (Multiple-Dose) [Day 14 to Follow-up visit]

	Treatment Period																	Follow-up (7 to 10 Days Post Final Dose)[f]
Day	**14**													**15**		**16**	**17**	
Time Postdose (h)	**Pre**	**0**	**0.25**	**0.5**	**0.75**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	
IMP administration																		
KRP-A218 or placebo[b]		X[c]																
Pharmacokinetics																		
Blood sampling for the PK of CCI	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Exploratory analyses																		
Blood sampling for metabolite profiling[d]	X			X		X		X		X		X		X				
Urine collection for metabolite profiling[d,e]		<----------X---------->																
Pharmacogenetics																		
Safety and tolerability																		
Adverse event recording	<---------->																	
Prior/concomitant medication monitoring	<---------->																	
Body weight	X																X[q]	
Haematology, clinical chemistry, coagulation, and urinalysis[f]	X																X[q]	X
Faecal occult blood test[g]	--->	<----------X---------->																X[r]
Bristol Stool Chart[a]	--->	<----------X---------->																
Blood pressure and pulse rate, and respiratory rate[i]	X					X				X		X	X	X[q]		X[q]	X[q]	X
Oral body temperature	X													X[q]		X[q]	X[q]	X
12-lead ECG for safety assessment[k]	X					X				X		X	X	X[q]			X[q]	X
Physical examination																	X[m,s]	X[l]
Abdominal examination									X[p]					X[p]		X[p]	X[s]	

[a] Interim medical history.
[b] Subjects will receive the IMP once daily at the same time as Day 1 in the fasted state (at least 10 hours).
[c] Subjects will be fasted until 4 hours after dosing, after which time a meal will be provided.
[d] Collected in Group B1 only.
[e] Spot urine sample will be collected any time prior to dosing. 24-hour urine samples will be collected on 0 to 24 hours postdose on Day 14.
[f] Subjects will be fasted at least 6 hours before collection.

[g] Faecal occult blood test will be performed once each during the following sampling periods: Screening, Day -1 to prior to dosing, 0 to 24, 24 to 96, 96 to 168, 168 to 240 hours postdose on Day 1, 240 hours postdose on Day 1 to 0 hours on Day 14, and 0 to 72 hours postdose on Day 14. On screening, faecal samples will be collected to confirm eligibility for enrollment. For the other sampling periods, faecal samples will be collected as far as possible.
[h] To be assessed when collecting faecal samples for faecal occult blood test in the treatment period.
[i] Subjects should be supine for at least 5 minutes before blood pressure and pulse rate measurements.
[j] To be measured in triplicate at approximately 2-minute intervals.
[k] To be recorded after the subject has been supine and at rest for at least 5 minutes.
[l] Full physical examination.
[m] Symptom-directed physical examination.
[n] Immediately before dosing.
[o] From waking-up to before dosing.
[p] To be performed at approximately the same time as on Day 1.
[q] From waking-up to before breakfast.
[r] If the latest result during the treatment period is positive, faecal samples will be collected for faecal occult blood test at the follow-up visit (within -2 day), as far as possible.
[s] Prior to discharge.
[t] The follow-up period may be extended depending on the observed $t_{1/2}$ of CCI

Table 12: Schedule of Assessments-Part C (DDI) [Screening to Day4]

	Screening	Treatment Period 1																	
Day	-28 to -2	-1	1												2		3	4
Time Postdose (h)			Pre	0	0.25	0.5	0.75	1	1.5	2	3	4	6	8	12	24	36	48	72
Informed consent	X																		
Inclusion/exclusion criteria	X	X																	
Demographic data	X																		
Medical history	X	X[a]																	
Urinary drug and cotinine screen	X	X																	
Alcohol breath test	X	X																	
Serology	X																		
Height	X																		
KRP-A218 and itraconazole administration[r]																			
KRP-A218				X[b]															
Itraconazole																			X[d]
Pharmacokinetics																			
Blood sampling for the PK of CCI			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]
Exploratory analyses																			
Blood sampling for metabolite profiling of CCI			X			X		X		X		X		X		X			
Pharmacogenetics			X																
Safety and tolerability																			
Adverse event recording	<----------																		---------->
Prior/concomitant therapies monitoring	<----------																		---------->
Body weight	X	X																	X[f]
Haematology, clinical chemistry, coagulation, and urinalysis[g]	X	X														X[f]			X[f]
Faecal occult blood test[h]	X	<---X--->	<----------								X						><--------X--------->		
Bristol Stool Chart[i]		<---X--->	<----------								X						><--------X--------->		
Blood pressure and pulse rate, and respiratory rate[j]	X	X	X[k]					X				X		X	X	X[f]		X[f]	X[f]
Oral body temperature	X	X	X													X[f]		X[f]	X[f]
12-lead ECG for safety assessment[l]	X	X	X[k]					X				X		X	X	X[f]		X[f]	X[f]
Physical examination		X[m]																	

Table 12: Schedule of Assessments-Part C (DDI) [Day 5 to Follow-up visit]

	Treatment Period																			Follow-up (7 to 10 Days Post-IMP Final Dose)[q]
Day	**5 to 9**	**10**	**11**													**12**		**13**	**14**	
Time Postdose (h)			**Pre**	**0**	**0.25**	**0.5**	**0.75**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	
KRP-A218 and itraconazole administration[r]																				
KRP-A218				X[b,c]																
Itraconazole	X[d]	X[d]		X[b,c]												X[d]		X[d]		
Pharmacokinetics																				
Blood sampling for the PK of CCI			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood sampling for the PK of itraconazole and hydroxy-itraconazole			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Exploratory analyses																				
Blood sampling for metabolite profiling of CCI			X			X		X		X		X		X		X				
Safety and tolerability																				
Adverse event recording	<----------																			---------->
Prior/concomitant therapies monitoring	<----------																			---------->
Body weight		X																	X[f]	
Haematology, clinical chemistry, coagulation, and urinalysis[g]		X														X[f]			X[f]	X
Faecal occult blood test[h]		<--X-->		<----------						X						---------->	<--------X-------->			X[o]
Bristol Stool Chart[i]		<--X-->		<----------						X						---------->	<--------X-------->			
Blood pressure and pulse rate, and respiratory rate[j]			X[k]					X				X		X	X	X[f]		X[f]	X[f]	X
Oral body temperature			X													X[f]		X[f]	X[f]	X
12-lead ECG for safety assessment[l]			X[k]					X				X		X	X	X[f]		X[f]	X[f]	X
Physical examination		X[m]																	X[n,p]	X[m]

[a] Interim medical history.

[b] Subjects will be fasted for at least 10 hours prior to dosing until at least 4 hours after dosing, after which time a meal will be provided. On Day 11, subjects will receive the IMP at the same time as Day 1.

[c] If it is determined that KRP-A218 will be dosed in the fasted state, then KRP-A218 will be administered first and itraconazole will be administered second. If it is determined that KRP-A218 will be dosed in the fed state, then itraconazole will be dosed first; subjects will then receive breakfast at approximately 1 hour postdose.

[d] To be administered in the fasted state.
[e] Immediately before dosing.
[f] From waking-up to before breakfast.
[g] Subjects will be fasted at least 6 hours before collection.
[h] Faecal occult blood test will be performed once each during the following sampling periods: Screening, Day -1 to prior to dosing, 0 to 24 and 24 to 72 hours postdose on Day 1, Day 10 to 0 hours on Day 11, and 0 to 24 and 24 to 72 hours postdose on Day 11. On screening, faecal samples will be collected to confirm eligibility for enrollment. For the other sampling periods, faecal samples will be collected as far as possible.
[i] To be assessed when collecting faecal samples for faecal occult blood test in the treatment period.
[j] Subjects should be supine for at least 5 minutes before blood pressure and pulse rate measurements.
[k] To be measured in triplicate at approximately 2-minute intervals.
[l] To be recorded after the subject has been supine and at rest for at least 5 minutes.
[m] Full physical examination.
[n] Symptom-directed physical examination.
[o] If the latest result during the treatment period is positive, faecal samples will be collected for faecal occult blood test at the follow-up visit (within -2 day), as far as possible.
[p] Prior to discharge.
[q] The follow-up period may be extended depending on the observed $t_{1/2}$ of CCI
[r] The study days of dosing of itraconazole and KRP-A218 may be amended to extend the interval between the first dose of KRP-A218 and the first dose of itraconazole depending on the observed $t_{1/2}$ of CCI