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Statistical Analysis Plan

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

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LIST OF ABBREVIATIONS

Abbreviations pertain to the statistical analysis plan (SAP) only (not the tables, figures, and listings [TFLs]).

$\%AUC_{extrap}$	percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity
ADaM	Analysis Data Model
AE	adverse event
ANOVA	analysis of variance
$AR_{AUC0-\tau}$	observed accumulation ratio based on $AUC_{0-\tau}$
AR_{Cmax}	observed accumulation ratio based on C_{max} during the dosing interval
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 extrapolated to infinity
$AUC_{0-tlast}$	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
BID	twice a day
BLQ	below the limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL/F	apparent total clearance
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration during a dosing interval
COVID-19	coronavirus disease 2019
CRU	clinical research unit
CSR	clinical study report
CV	coefficient of variation
DMP	data management plan
ECG	electrocardiogram
eCRF	electronic case report form
GLSM	geometric least squares mean
ICH	International Council for/Conference on Harmonisation
ln	natural log
LSM	least squares mean
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
QD	once daily

QTcF	QT interval corrected for heart rate using Fridericia's formula
R^2-adj	adjusted coefficient for determination of exponential fit
SAP	statistical analysis plan
SD	standard deviation
SDV	source document verification
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
TID	three times a day
t_{max}	time of the maximum observed concentration
V_z/F	apparent volume of distribution during the terminal phase
WHODrug	World Health Organization Drug Dictionary
λ_z	apparent terminal elimination rate constant
λ_z Lower	start of exponential fit
λ_z N	number of data points included in the log-linear regression
λ_z Span Ratio	time period over which λ_z was determined as a ratio of $t_{1/2}$
λ_z Upper	end of exponential fit

1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 5.0 dated 16 September 2021) and electronic case report form (eCRF).

This SAP describes the planned analysis of the pharmacokinetic (PK), pharmacodynamic (PD), safety, and tolerability data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shells document.

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Kyorin Pharmaceutical Company Limited. A limited amount of information about this study (eg, objectives, study design) is given to help the reader's interpretation.

This SAP must be finalised prior to any unblinding of study data for analysis purposes (interim or final). Additionally, the SAP and TFL shells should be finalised prior to any programming activities commencing.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be agreed with Kyorin Pharmaceutical Company Limited and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E3 guideline *Structure and Content of Clinical Study Reports*, ICH E8 guideline *General Considerations for Clinical Trials*, and ICH E9 guideline *Statistical Principles for Clinical Trials*.[1,2,3]

The document history is presented in Appendix 1.

2. STUDY 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 PD 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 electrocardiogram (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.

3. STUDY ENDPOINTS

3.1. 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.

3.2. 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:

- $AUC_{0-\infty}$

- $AUC_{0\text{-tlast}}$
- 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:

- $AUC_{0\text{-}\tau}$
- $AUC_{0\text{-}\infty}$ (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:

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

Other PK parameters may also be added.

3.3. 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.

4. STUDY DESIGN

4.1. 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 coronavirus disease 2019 (COVID-19) risks.

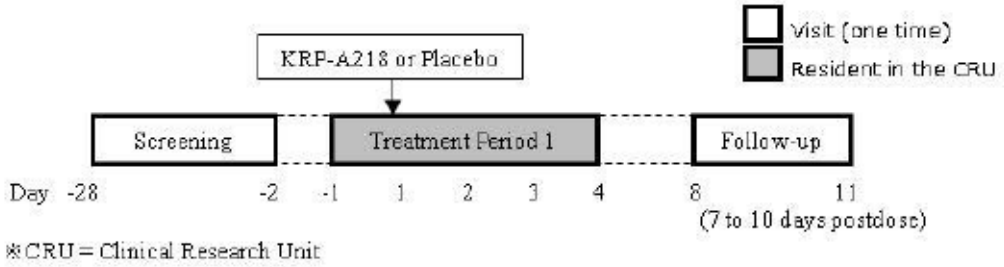
In each of Groups A1 to A5, 6 subjects will receive KRP-A218 and 2 subjects will receive placebo in accordance with a randomisation schedule. In Groups A1, A2b, and A3 to A5, all doses will be administered in the fasted state on the morning of Day 1. For Group A2a, Period 1, Day 1 doses will be administered 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 study treatment using a sentinel approach.

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).

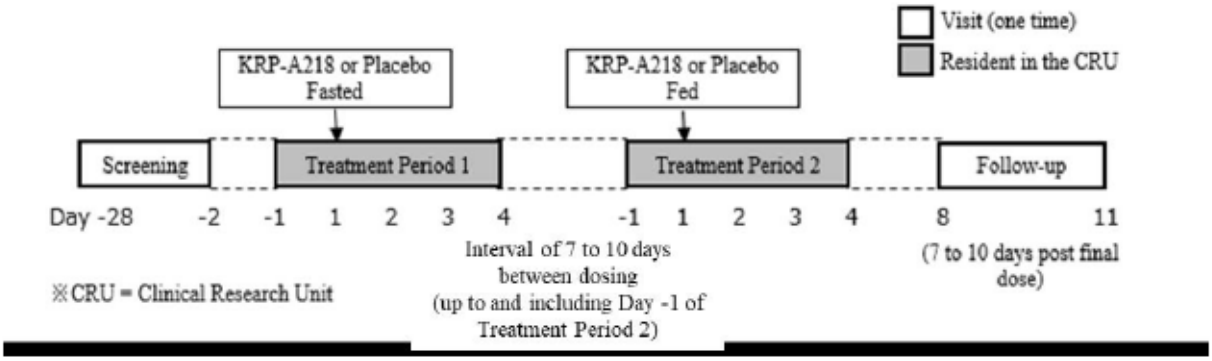
An overview of the study design is shown in Figure 1 and Figure 2, and the planned dose levels in Figure 5.

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

4.2. 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. On Day 14, the last dose will be the morning dose regardless of the dosing frequency (once daily [QD], twice a day [BID], three times a day [TID]).

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

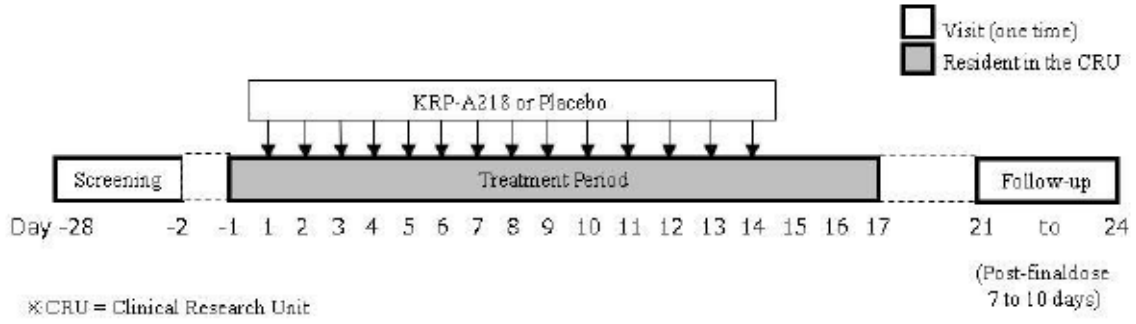
Based on the ongoing review of the safety, tolerability, and PK results, additional nonresidential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond 28 days after each final dosing occasion. All subjects may stay in the CRU even outside treatment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

All groups in Part B will receive the study treatment using a sentinel approach.

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

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

Figure 3: Study Schematic (Part B)



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

4.3. 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

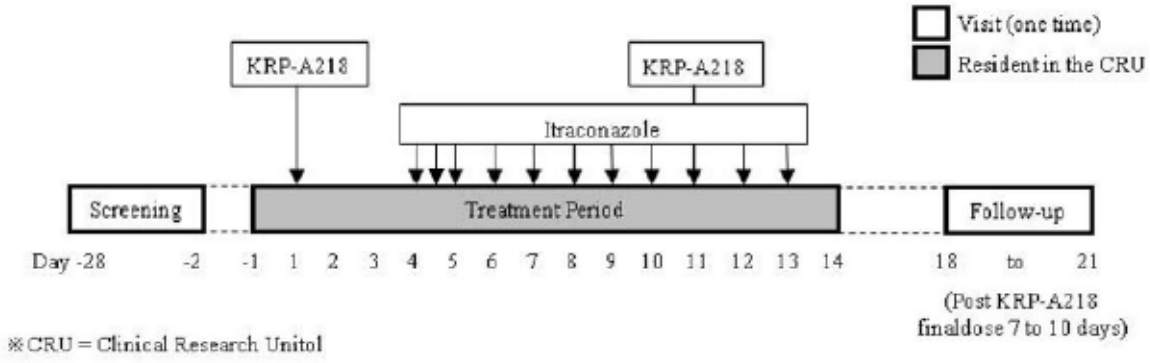
exceed 3 and will not extend beyond 28 days after each final dosing occasion. All subjects may stay in the CRU even outside treatment period due to COVID-19 risks.

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.

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

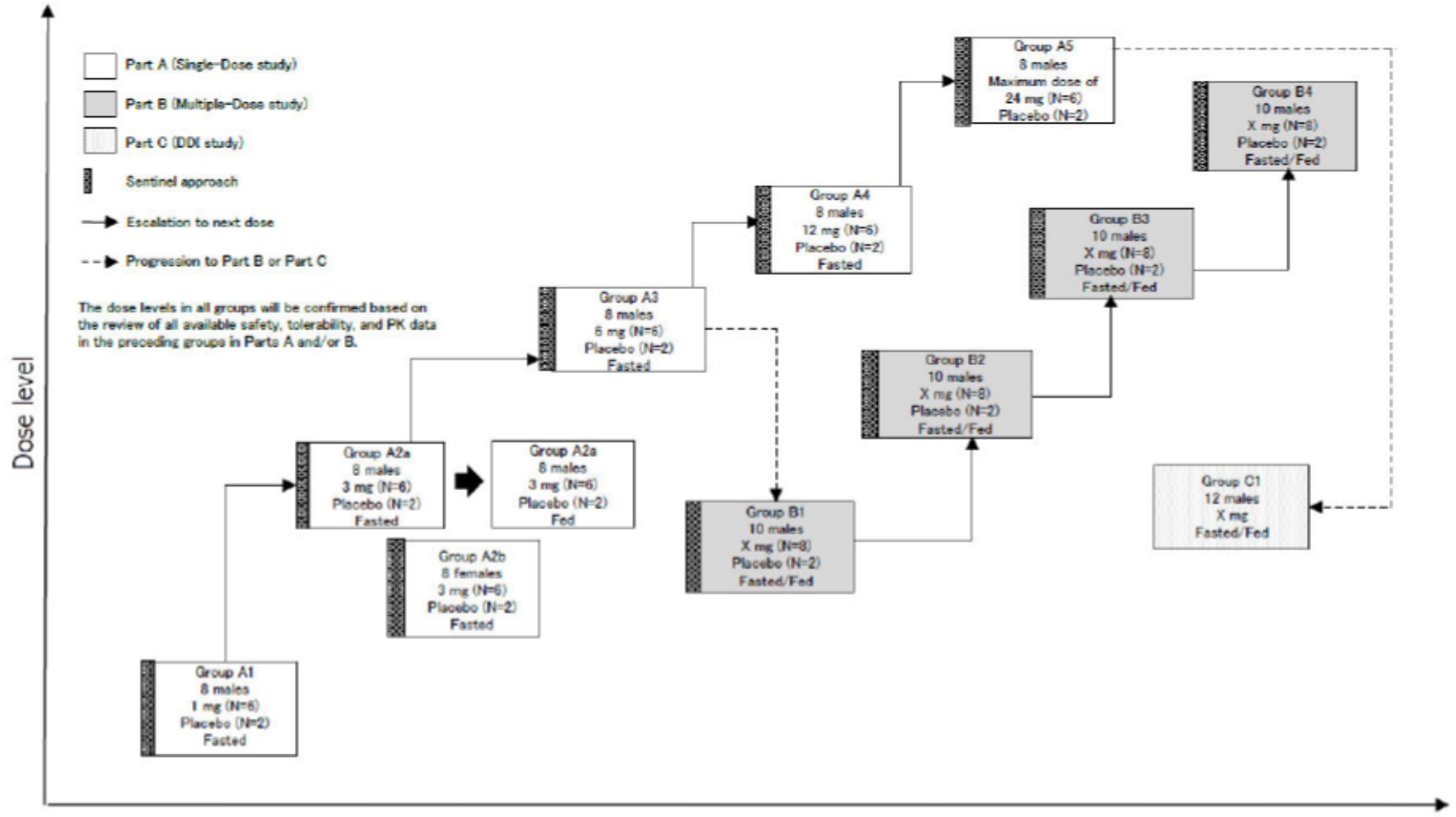
An overview of the study design is shown in Figure 4, and the planned dose levels in Figure 5.

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

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



5. SAMPLE SIZE JUSTIFICATION

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.

6. STUDY TREATMENTS

6.1. Part A

The study treatment names and ordering to be used in the TFLs for Part A are presented in Table 1. The study treatment sequence names and ordering to be used in the TFLs for Part A are presented in Table 2.

Table 1: Presentation of Study Treatments in TFLs (Part A)

Group	Study Treatment	Order in TFLs
A1 to A8	Placebo[a]	1
A1	1 mg KRP-A218 (Fasted Male)	2
A2a	3 mg KRP-A218 (Fasted Male)	3
	3 mg KRP-A218 (Fed Male)	4
A2b	3 mg KRP-A218 (Fasted Female)	5
A3	6 mg KRP-A218 (Fasted Male)	6
A4	12 mg KRP-A218 (Fasted Male)	7
A5	24 mg KRP-A218 (Fasted Male)	8
A6[b]	XX mg KRP-A218 (Fasted Male)	9
A7[b]	XX mg KRP-A218 (Fasted Male)	10
A8[b]	XX mg KRP-A218 (Fasted Male)	11

[a] Placebo will be pooled across all groups, regardless of sex and the fasting condition
[b] Optional group, to be included if required

Table 2: Presentation of Study Treatment Sequences in TFLs (Part A; Food-effect Group Only)

Group	Study Treatment Sequence	Order in TFLs
A2a	Placebo (Fasted Male) / Placebo (Fed Male)	1
A2a	3 mg KRP-A218 (Fasted Male) / 3 mg KRP-A218 (Fed Male)	2

All TFLs will be based on actual treatments (eg, if subject was assigned to receive placebo but was wrongfully dosed with active treatment they would be summarised and listed under active treatment).

All dose levels described above are the potential dose levels, and therefore are subject to change. The TFLs will reflect the dose levels utilised in the study, and these will be displayed in increasing order.

All fasting conditions described above are the potential fasting conditions, and therefore are subject to change. The TFLs will reflect the fasting conditions utilised in the study.

The food-effect group described above is the potential food-effect group, and therefore is subject to change. The TFLs will reflect the food-effect group utilised in the study.

The sex-effect group described above is the potential sex-effect group, and therefore is subject to change. The TFLs will reflect the sex-effect group utilised in the study.

6.2. Part B

The study treatment names and ordering to be used in the TFLs for Part B are presented in Table 3.

Table 3: Presentation of Study Treatments in TFLs (Part B)

Groups	Study Treatment	Order in TFLs
B1 to B7	Placebo[a]	1
B1	XX mg KRP-A218 (QD[b])	2
B2	XX mg KRP-A218 (QD[b])	3
B3	XX mg KRP-A218 (QD[b])	4
B4	XX mg KRP-A218 (QD[b])	5
B5[c]	XX mg KRP-A218 (QD[b])	6
B6[c]	XX mg KRP-A218 (QD[b])	7
B7[c]	XX mg KRP-A218 (QD[b])	8

Abbreviations: QD = once daily; BID = twice a day; TID = three times a day
[a] Placebo will be pooled across all groups, regardless of sex, the fasting condition, or the dosing frequency
[b] The planned dosing frequency is QD, however the dosing frequency may be changed following review of data from Part A (eg, to BID or TID)
[c] Optional group, to be included if required

All TFLs will be based on actual treatments (eg, if subject was assigned to receive placebo but was wrongfully dosed with active treatment they would be summarised and listed under active treatment).

All dose levels described above are the potential dose levels, and therefore are subject to change. The TFLs will reflect the dose levels utilised in the study, and these will be displayed in increasing order.

If the fasting conditions vary across groups in Part B, then the active treatment labels will include the fasting status information (eg, 'XX mg KRP-A218 (QD) (Fasted)' or 'XX mg KRP-A218 (QD) (Fed)').

6.3. Part C

The study treatment names and ordering to be used in the TFLs for Part C are presented in Table 4. The study treatment sequence name and ordering to be used in the TFLs for Part C are presented in Table 5.

Table 4: Presentation of Study Treatments in TFLs (Part C)

Group	Study Treatment	Order in TFLs
C1	XX mg KRP-A218 Alone	1
	200 mg Itraconazole Alone	2
	XX mg KRP-A218 + 200 mg Itraconazole	3

Table 5: Presentation of Study Treatment Sequence in TFLs (Part C)

Group	Study Treatment Sequence	Order in TFLs
C1	XX mg KRP-A218 on Day 1; 200 mg Itraconazole (BID) on Day 4; 200 mg Itraconazole (QD) on Days 5 to 10; XX mg KRP-A218 + 200 mg Itraconazole (QD) on Day 11; 200 mg Itraconazole (QD) on Days 12 and 13	1

Abbreviations: QD = once daily; BID = twice a day

All TFLs will be based on actual treatment sequence. The 'Days X to Y' part of the treatment sequence labels will be kept unchanged even if a subject misses a dose on 1 or more days. Exact dosing regimen details including duration and days on which dose was received will be presented in the treatment administration listing only.

7. DEFINITIONS OF POPULATIONS

Any protocol deviations, including those due to COVID-19 and related restrictions (see Section 8.1.1), will be considered prior to database lock for their importance and taken into consideration when assigning subjects to populations.

7.1. All Subjects Population

The all subjects population will include all subjects who signed the informed consent form and had any study assessment recorded in the database per the protocol.

7.2. Safety Population

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

7.3. 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 valid PK concentration.

7.4. Pharmacodynamic Population

The PD population will include all subjects who received at least 1 dose of study treatment (KRP-A218, Itraconazole, or Placebo) and have at least 1 valid postdose PD assessment.

8. STATISTICAL METHODOLOGY

8.1. General

Listings will be provided for all data captured in the database, with the exception of medical history. Listings will include all subjects assigned to the all subjects population and include data up to the point of study completion or discontinuation. Subjects are generally considered to have completed the study if they complete the scheduled follow-up visit (rather than early termination visit). Any subject who discontinues the study will be identified accordingly in the listings. Summaries and statistical analyses will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher if a new version is issued during the study).

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 (or higher if a new version is issued during the study) and CDISC ADaM Implementation Guide Version 1.1 (or higher if a new version is issued during the study). Pinnacle 21 Community Validator Version 3.1.2 (or higher if a new version is issued during the study) will be utilised to ensure compliance with CDISC standards.

For all statistical analyses, the hypothesis testing will be 2-sided and carried out on 0.05 significance level, unless specifically stated otherwise.

Caution should be used when interpreting results from the statistical analyses conducted in this study because the sample size is not based on power calculations.

Where reference is made to 'valid' data, this refers to non-missing data which meet the predetermined criteria (eg, are not flagged for exclusion).

Where reference is made to 'all calculations', this includes, but is not limited to, summary statistics, statistical analyses, baseline derivation, changes from baseline, and any parameter derivations.

All figures will be produced on linear-linear or discrete-linear scales, as applicable, unless specifically stated otherwise.

Any clock changes will be accounted for in the derivation of actual time postdose, adverse event (AE) duration, and AE onset time.

8.1.1. Handling of Data Quality Issues Due to Coronavirus Disease 2019 and Related Restrictions

Due to COVID-19 and related restrictions, there is a high risk for impact to data integrity, with the recognised potential for:

- Missed visits, caused by, for example,:

- Subject unable to travel to site due to restrictions, the need to quarantine, or COVID-19 infection
- Subject unwilling to go to site due to fear of COVID-19 infection
- Site postponing subject's visit due to investigator not being available (eg, if they have been dispatched to hospital handling COVID-19 infections)

- Site unable to replenish supply of investigational product
- Incomplete data entry by sites due to limited resources to support study or no access to source documents or to eCRF
- Outstanding source document verification (SDV) due to sponsor or country restrictions on remote SDV, or no or limited access to site(s) for on-site visits
- Unanswered queries

At the time of the reporting of the study results, all protocol deviations due to COVID-19 or related restriction will be assessed for their severity and impact on the analyses. If needed, appropriate statistical methods will be applied as a mitigating action (eg, data might be categorised into 2 analysis groups, with and without COVID-19 and related restrictions impact); however, this will exclude any imputations of the missing values. Any mitigating actions will be agreed with Kyorin Pharmaceutical Company Limited in advance and identified in the CSR.

8.1.2. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.
- If the number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.
- In general, as early termination data are not associated with any scheduled timepoint, they will be excluded from all calculations of summary statistics. Exceptions may be made where justified.

For categorical data the following rules will be applied:

- For ordered categorical data (eg, AE severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category.
- For non-ordered categorical data (eg, race), only those categories for which there is at least 1 subject represented will be included; unless specifically stated otherwise.

- Missing values will not be imputed, unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

8.1.3. Triplicate Readings

For vital signs data only, where triplicate readings are taken, the median of triplicate readings will replace the separate individual triplicate readings in all calculations.

For 12-lead ECG data only, where triplicate readings are taken, the mean of triplicate readings will replace the separate individual triplicate readings in all calculations.

In case of incomplete triplicate readings (eg, only 2 out of 3 readings were recorded), the mean and/or median will be calculated, as appropriate, based on the number of readings available.

8.1.4. Repeat and Unscheduled Readings

For vital signs and 12-lead ECG data only, any predose value recorded in addition to the original value or a postdose value recorded within 15 minutes of the original value will be defined as a repeat value; any postdose value recorded more than 15 minutes after the original value will be defined as an unscheduled value. For all other data types (eg, laboratory parameters), any value recorded in addition to the original value will be defined as an unscheduled value.

The original value will be replaced by the last associated repeat value in all calculations, with the exception of the 12-lead ECG outlier analysis (see Section 8.7.4).

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations, with the exception of the baseline derivation (see Section 8.1.5) and 12-lead ECG outlier analysis (see Section 8.7.4).

8.1.5. Definitions of Baseline and Change from Baseline

The baseline will be defined as the last value recorded prior to the first dose. If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to the first dose.

Individual changes from baseline will be calculated by subtracting the individual subject's baseline value from the value at the postdose timepoint.

The summary statistics for change from baseline will be derived from individual subjects' values (eg, mean change from baseline will be the mean of the individual changes from baseline for all subjects, rather than difference between the mean value at the postdose timepoint and mean value at baseline).

See Section 8.1.4 for more detail on handling repeat and unscheduled readings in the calculations. See Section 8.1.3 for more detail on handling of triplicate readings in the calculations.

8.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed.

A summary table by treatment for Parts A and B and by overall for Part C will be provided, based on the safety population.

Screen failure data summary table will be provided separately, based on the all subjects population.

8.3. Screening Demographics

The screening demographics including age, sex, race, ethnicity, height, body weight, and body mass index will be listed.

A summary table by treatment for Parts A and B and by overall for Part C will be provided, based on the safety population.

8.4. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to the first dose. Concomitant medication will be defined as medication that starts during or after the first dose or starts but does not end prior to the first dose.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Global, Format B3, Version March 2021 (or later if a new version is issued during the study; see the data management plan [DMP] for more details). Prior and concomitant medications will be listed.

8.5. Pharmacokinetic Assessments

8.5.1. Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma concentrations of CCI itraconazole and hydroxy-itraconazole using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.1 or higher):

Part A (Day 1), Part B (Day 1) and Part C (Days 1 and 11) (CCI

Parameter	Units[a]	Definition
$AUC_{0\text{-tlast}}$	ng*h/mL	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (t_{last})[b]
$DAUC_{0\text{-tlast}}$	ng*h/mL/mg	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (t_{last}) normalized by dose administered[e]
$AUC_{0\text{-}\tau}$	ng*h/mL	area under the concentration-time curve over a dosing interval (τ)[d]
$AUC_{0\text{-}\infty}$	ng*h/mL	area under the concentration-time curve from time 0 extrapolated to infinity[c]
$DAUC_{0\text{-}\infty}$	ng*h/mL/mg	area under the concentration-time curve from time 0 extrapolated to infinity normalized by dose administered[ce]
$\%AUC_{extrap}$	%	percentage of area under the concentration-time curve due to extrapolation from the last quantifiable concentration to infinity
C_{max}	ng/mL	maximum observed concentration
DC_{max}	ng/mL/mg	maximum observed concentration normalized by dose administered[e]
t_{max}	h	time of the maximum observed concentration
$t_{1/2}$	h	apparent terminal elimination half-life
CL/F	L/h	apparent total clearance
V_z/F	L	apparent volume of distribution during the terminal phase

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] The AUC will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).
[c] Based on the last observed quantifiable concentration
[d] Part B Day 1 only – not required for Parts A and C
[e] Not required for Part C

Part B (Day 14) (CCI [redacted]

Parameter	Units[a]	Definition
$AUC_{0\text{-tlast}}$	ng*h/mL	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (t_{last})[b]
$DAUC_{0\text{-tlast}}$	ng*h/mL/mg	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (t_{last}) normalized by dose administered
$AUC_{0\text{-}\tau}$	ng*h/mL	area under the concentration-time curve over a dosing interval (τ)
$DAUC_{0\text{-}\tau}$	ng*h/mL/mg	area under the concentration-time curve over a dosing interval (τ) normalized by dose administered
C_{max}	ng/mL	maximum observed concentration
DC_{max}	ng/mL	maximum observed concentration normalized by dose administered
C_{min}	ng/mL	minimum observed concentration during a dosing interval
t_{max}	h	time of the maximum observed concentration
$t_{1/2}$	h	apparent terminal elimination half-life
CL/F	L/h	apparent total clearance
V_z/F	L	apparent volume of distribution during the terminal phase
$AR_{AUC0\text{-}\tau}$		observed accumulation ratio based on $AUC_{0\text{-}\tau}$
AR_{Cmax}		observed accumulation ratio based on C_{max} during the dosing interval

The dosing interval τ is 24 hours.
[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] Area under the concentration-time curve will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).

Part C Day 11 (Itraconazole and Hydroxy-Itraconazole)

Parameter	Units[a]	Definition
$AUC_{0\text{-}\tau}$	ng*h/mL	area under the concentration-time curve over a dosing interval (τ)[b]
C_{max}	ng/mL	maximum observed concentration
t_{max}	h	time of the maximum observed concentration

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] The AUC will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).

Additional PK parameters may be determined where appropriate.

The PK analysis will be carried out where possible using the actual dose of KRP-A218 administered (mg) and actual postdose blood sampling times. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

The parameters C_{max}, C_{min}, and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

The accumulation ratios ($AR_{AUC0-\tau}$ and AR_{Cmax}) will be calculated as follows:

$AR_{AUC0-\tau} = AUC_{0-\tau}$ Day 14 / $AUC_{0-\tau}$ Day 1

$AR_{Cmax} = C_{max}$ Day 14 / C_{max} Day 1

8.5.1.1. Criteria for the Calculation of Apparent Terminal Elimination Rate Constant and Half-life

The start of the terminal elimination phase for each subject will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in concentrations.

The apparent terminal elimination rate constant (λ_z) will only be calculated when a reliable estimate can be obtained using at least 3 data points, preferably not including C_{max}, and the adjusted coefficient for determination of exponential fit (R^2-adj) of the regression line is $\geq$0.7. Parameters requiring λ_z for their calculation (eg, $AUC_{0-\infty}$, $t_{1/2}$, CL/F (single dose only), V_z/F) will only be calculated if the R^2-adj value of the regression line is $\geq$0.7.

The following regression-related diagnostic PK parameters will be determined where possible:

Parameter	Units	Definition
λ_z	1/h	apparent terminal elimination rate constant
λ_z Upper	h	end of exponential fit
λ_z Lower	h	start of exponential fit
λ_z N		number of data points included in the log-linear regression
λ_z Span Ratio		time period over which λ_z was determined as a ratio of $t_{1/2}$
R^2-adj		adjusted coefficient for determination of exponential fit

Where possible, the span of time used in the determination of λ_z (ie, the difference between λ_z Upper and λ_z Lower) should be $\geq$2 half-lives. If the λ_z Span Ratio is <2, the robustness of the $t_{1/2}$ values will be discussed in the CSR.

8.5.1.2. Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only 3 consecutive concentrations, at least 1 should follow C_{max}. An exception may be made for metabolites, where C_{max} may be the last timepoint.

If the extrapolated area is >20%, $AUC_{0-\infty}$ (and derived parameters) may be excluded from the summary statistics and statistical analysis at the discretion of the sponsor or pharmacokineticist.

If $AUC_{0-\infty}$ cannot be determined reliably for all subjects and/or dose levels/treatments, an alternative AUC measure, such as AUC to a fixed timepoint or $AUC_{0-tlast}$, may be used in the statistical analysis of dose proportionality/food effect/sex effect.

If the τ PK blood sample is collected slightly early (i.e., the 24 hours sample), the actual sampling time of the τ sample may be used for the calculation of $AUC_{0-\tau}$. However, the $AUC_{0-\tau}$ parameter will be calculated if the τ sample is within 60 minutes of the nominal sampling time.

8.5.1.3. Criteria for Handling Concentrations Below the Limit of Quantification or Missing Concentrations for Pharmacokinetic Analysis

Plasma concentrations below the limit of quantification (BLQ) will be assigned a value of 0 before the first measurable concentration and thereafter BLQ concentrations will be treated as missing. The following rules apply to the specific situations defined below:

- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are considered to be a true characteristic of the profile of the drug.
- If a predose plasma concentration is missing, it will be set to 0 by default within Phoenix WinNonlin for the first dosing day of all parts of the study.
- For multiple dose part of the study (Day 14), if the analyte concentration at τ (24 hours postdose) is missing, this may be substituted with the predose concentration. Similarly, if the predose concentration is missing then this may be substituted with the concentration at τ. The PK parameters from any such profile will be listed but excluded from descriptive statistics and statistical analysis.

8.5.1.4. Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude the value from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in the CSR.

Any quantifiable predose concentration value on the first dosing day of all parts of the study will be considered treated as 0 for the PK analysis. The PK parameters from any such profile will be listed but excluded from descriptive statistics and statistical analysis.

8.5.2. Presentation of Pharmacokinetic Data

All PK concentrations and parameters will be listed.

Summary tables, arithmetic mean (+ standard deviation [SD]) figures, overlaying individual figures, and individual figures by treatment and time postdose will be provided for plasma

PK concentrations. All figures will be produced on both linear-linear and linear-logarithmic scales. The +SD bars will only be displayed on the linear-linear scale.

Summary tables by treatment will be provided for all PK parameters, with the exception of diagnostic regression-related PK parameters.

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 the median t_{max}.

If the actual time of sample collection deviates from the nominal time by more than ±10%, the plasma/serum/whole blood concentration will be flagged and excluded from the summary statistics. Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

For plasma/serum/whole blood concentration data, the following rules will apply:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.
- Arithmetic mean or median values that are BLQ will be presented as 0.

For PK parameters, the following rule will apply:

- Geometric mean and coefficient of variation (CV) will not be calculated for t_{max}.

8.5.3. Pharmacokinetic Statistical Methodology

8.5.3.1. Dose Proportionality Assessment (Parts A and B)

A statistical analysis will be conducted to investigate the dose proportionality of $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max} on profile day 1 in Part A, and $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\tau}$, and C_{max} on profile day 14 in Part B (only for plasma CCI

The analysis is planned to be conducted across full dose range, however if at the time of analysis there isn't sufficient data in some of the dose levels or the dose proportionality is not concluded for the full dose range, analysis across narrower dose range may be explored.

The PK parameters will be analysed using a power model[4] that will have the following form:

$$parameter = intercept \times dose^{\wedge}slope \times random\ error$$

Using the natural log (ln) transformation,[5] a power model can be expressed as a linear regression equation:

$$ln(parameter) = intercept + slope \times ln(dose) + random\ error$$

For dose proportionality, the slope of the regression line is equal to 1; for dose independence, it is equal to 0.

For each PK parameter separately, a pooled estimate (across all doses) of slope, corresponding 95% confidence interval (CI), and between-subject CV will be calculated. Figures (on the logarithmic-logarithmic scale) containing individual values, the power model line (95% CI), and the dose proportionality line (defined as the power model line with slope of 1) will be created for each PK parameter. Additionally, figures (on the logarithmic-linear scale) containing individual values and geometric means will be created for each corresponding PK parameter normalised by dose administered.

The lack of fit test will be conducted for the statistical assessment of linearity assumption, and thus appropriateness of a power model. The lack of fit model will be the same as the power model fitted, but with dose included as an additional fixed effect. The statistical assessment will rule the linearity assumption acceptable if the diagnostic plots appear reasonable and the lack of fit 2-sided p-value >0.05 (dose effect is not significant at the 0.05 level of significance). The assessment of linearity assumption may also occur via visual examination of the figures by the pharmacokineticist. This assessment may override the statistical assessment; where this occurs, it will be detailed in the CSR.

If the assumption of linearity is ruled acceptable and the 95% CI for the slope spans 1, it will be deemed that there is no statistical basis to conclude a lack of proportionality.

If the assumption of linearity is ruled unacceptable for any PK parameter, its corresponding PK parameter normalised by dose administered will be ln-transformed and analysed using an analysis of variance (ANOVA) model.[6] The model will include dose as a factor.

For each PK parameter separately, the geometric least squares mean (GLSM) for each dose, p-values for the overall, and pairwise dose comparisons will be calculated. Residual plots will be produced to assess the adequacy of the model(s) fitted.

Examples of the SAS code that will be used are as follows:

Power Model Analysis

```
proc mixed data = <data in> alpha = 0.05;
 by parcat1n parcat1 pkday paramn param;
 model lpk = ldose / cl residual ddfm = kr2;
 ods output solutionf = <data out>;
run;
```

Power Model Analysis (Between-subject Variability)

```
proc mixed data = <data in> covtest alpha = 0.05;
 by parcat1n parcat1 pkday paramn param;
 class ldose;
 model lpk = ldose / cl residual ddfm = kr2;
 ods output covparms = <data out>;
run;
(Note: Pooled Geometric CV (%) = 100*(sqrt(exp(estimate)-1)))
```

Power Model Analysis (Lack of Fit Test)

```
proc mixed data = <data in>;
 by parcat1n parcat1 pkday paramn param;
 class dose;
 model lpk = ldose dose / htype = 1 ddfm = kr2;
```

```
 ods output tests1 = <data out>;
run;
```

ANOVA Model Analysis

```
proc mixed data = <data in> alpha = 0.05;
 by parcat1n parcat1 pkday paramn param;
 class dose;
 model ldnpk = dose / cl residual ddfm = kr2;
 lsmeans dose / cl pdiff;
 ods output lsmeans = <data out>;
 ods output diffs = <data out>;
 ods output tests3 = <data out>;
run;
```

8.5.3.2. Food Effect Assessment (Part A)

A statistical analysis will be conducted to investigate the food effect on the treatment by comparing '3 mg KRP-A218 (Fed Male)' (test treatment) to '3 mg KRP-A218 (Fasted Male)' (reference treatment).

The ln-transformed[5] $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max} on profile day 1 in Part A (only for plasma CCI will be analysed using a mixed model.[7] The model will include actual treatment as fixed effect and subject as a random effect.

For each PK parameter separately, the least squares mean (LSM) for each treatment, difference in LSMs between the fed and fasted treatments, and corresponding 90% and 95% CIs will be calculated; these values will then be back-transformed to give the GLSM, ratio of GLSMs, and corresponding 90% and 95% CIs.

Additionally, the pooled estimate (across treatments) of the within-subject CV will be calculated, and residual plots will be produced to assess the adequacy of the model(s) fitted.

Examples of the SAS code that will be used are as follows:

Mixed Model Analysis

```
proc mixed data = <data in>;
 by parcat1n parcat1 pkday paramn param;
 class trtan usubjid;
 model lpk = trtan / cl residual ddfm = kr2;
 lsmeans trtan / cl pdiff = control('1') alpha = 0.1;
 lsmeans trtan / cl pdiff = control('1') alpha = 0.05;
 random intercept / subject = usubjid;
 ods output lsmeans = <data out>;
 ods output diffs = <data out>;
 ods output covparms = <data out>;
run;
```

8.5.3.3. Sex Effect Assessment (Part A)

A statistical analysis will be conducted to investigate the sex effect on the treatment by comparing '3 mg KRP-A218 (Fasted Female)' (test treatment) to '3 mg KRP-A218 (Fasted Male)' (reference treatment).

The ln-transformed[5] $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max} on profile day 1 in Part A (only for plasma CCI will be analysed using an ANOVA model.[6] The model will include actual treatment as a factor.

For each PK parameter separately, the LSM for each treatment, difference in LSMs between the test and reference treatments, and corresponding 90% and 95% CIs will be calculated; these values will then be back-transformed to give the GLSM, ratio of GLSMs, and corresponding 90% and 95% CIs.

Additionally, the pooled estimate (across treatments) of the between-subject CV will be calculated, and residual plots will be produced to assess the adequacy of the model(s) fitted.

Examples of the SAS code that will be used are as follows:

ANOVA Model Analysis

```
proc mixed data = <data in>;
 by parcat1n parcat1 pkday paramn param;
 class trtan;
 model lpk = trtan / cl residual ddfm = kr2;
 lsmeans trtan / cl pdiff = control('1') alpha = 0.1;
 lsmeans trtan / cl pdiff = control('1') alpha = 0.05;
 ods output lsmeans = <data out>;
 ods output diffs = <data out>;
 ods output covparms = <data out>;
run;
```

8.5.3.4. Drug-drug Interaction Assessment (Part C)

A statistical analysis will be conducted to investigate the drug-drug interaction on the PK of KRP-A218 by comparing 'XX mg KRP-A218 + 200 mg Itraconazole' (test treatment) to 'XX mg KRP-A218' (reference treatment).

The ln-transformed[5] $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, and C_{max} in Part C (only for plasma CCI will be analysed using a mixed model.[7] The model will include actual treatment as fixed effect and subject as a random effect.

For each PK parameter separately, the LSM for each treatment, difference in LSMs between the test and reference treatments, and corresponding 90% CI will be calculated; these values will then be back-transformed to give the GLSM, ratio of GLSMs, and corresponding 90% CI.

Additionally, the pooled estimate (across treatments) of the within-subject CV will be calculated, and residual plots will be produced to assess the adequacy of the model(s) fitted.

Examples of the SAS code that will be used are as follows:

Mixed Model Analysis

```
proc mixed data = <data in>;
  by parcat1n parcat1 paramn param;
  class trtan usubjid;
  model lpk = trtan / cl residual ddfm = kr2;
```

```
  lsmeans trtan / cl pdiff = control('1') alpha = 0.1;
  random intercept / subject = usubjid;
  ods output lsmeans = <data out>;
  ods output diffs = <data out>;
  ods output covparms = <data out>;
run;
```

8.6. Pharmacodynamic Assessments

8.6.1. Pharmacodynamic Analysis

Data associated with serum phospholipid-C concentrations and faecal calprotectin will be reported in the TFLs.

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

8.6.2. Presentation of Pharmacodynamic Data

All serum phospholipid-C data and their changes from baseline will be listed.

Summary tables and boxplots by treatment and timepoint will be provided for all serum phospholipid-C data and their changes from baseline.

All faecal calprotectin data will be listed only.

Values recorded as $<x$, $\leq x$, $>x$, or $\geq x$ will be displayed in the listings as recorded. For the derivation of listing flags, all calculations, and presentation in the figures, $<x$ and $\leq x$ values will be set to half of x whereas $>x$ and $\geq x$ values will be set to x.

8.6.3. Pharmacodynamic Statistical Methodology

No inferential statistical analyses are planned.

8.7. Safety and Tolerability Assessments

8.7.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 (or higher if a new version is issued during the study; see the DMP for more details).

A treatment-emergent adverse event (TEAE) will be defined as an AE that starts during or after the first dose, or starts prior to the first dose and increases in severity after the first dose.

A treatment-related TEAE will be defined as a TEAE with a relationship of possibly related or related to the study treatment, as determined by the investigator.

For Group A2a in Part A, the assignment of TEAEs to treatments will be as follows:

- A TEAE that starts or increases in severity during or after Period 1, Day 1 dosing and prior to Period 2, Day 1 dosing will be assigned to '3 mg KRP-A218 (Fasted Male)'.
- A TEAE that starts or increases in severity during or after Period 2, Day 1 dosing will be assigned to '3 mg KRP-A218 (Fed Male)'.

For Part C, the assignment of TEAEs to treatments will be as follows:

- A TEAE that starts or increases in severity during or after Day 1 dosing and prior to Day 4 dosing will be assigned to 'XX mg KRP-A218 Alone'.
- A TEAE that starts or increases in severity during or after Day 4 dosing and prior to Day 11 dosing will be assigned to '200 mg Itraconazole Alone'.
- A TEAE that starts or increases in severity during or after Day 11 dosing will be assigned to 'XX mg KRP A218 + 200 mg Itraconazole'.

All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of the last associated dose for TEAEs only. Where the last associated dose is referring to the last dose received prior to the start of a TEAE.

The frequency of subjects with TEAEs and the number of TEAEs will be summarised for the following categories:

- TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- TEAEs by severity and treatment
- Treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- Treatment-related TEAEs by severity and treatment

The frequency of subjects will be summarised separately for TEAEs and treatment-related TEAEs by the following:

- System organ class, preferred term, and treatment
- Preferred term and treatment

For the AE data the following rules will apply:

- For the derivation of treatment-emergent status (applicable to all AEs): If the start date/time of an AE is incomplete or missing, an AE will be assumed to not be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started after the first dose.

- For the derivation of treatment-related status (applicable to TEAEs only): If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to not be a treatment-related TEAE.

- For the derivation of onset time (applicable to TEAEs only): If the start date/time of a TEAE is missing, onset time will not be calculated. If the start date/time of a TEAE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of the last associated dose is 01MAY2019/08:00 and recorded start date/time of a TEAE is 03MAY2019, then the minimum possible onset time will be calculated by assuming a TEAE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing). If the start date of a TEAE is the same as the date of the last associated dose but the start time of a TEAE is missing, an onset time will be presented as '≥00:00:01'. Any clock changes will be accounted for in the derivation.

- For the derivation of duration (applicable to all AEs): If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming an AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing). Any clock changes will be accounted for in the derivation.

- For the calculation of TEAE summary statistics: If the severity of a TEAE is missing, that TEAE will be counted under the 'missing' category.

- For the calculation of TEAE summary statistics: If a subject experienced multiple TEAEs with the same preferred term for the same treatment, this will be counted as 1 TEAE for that treatment under the maximum severity recorded.

8.7.2. Clinical Laboratory Parameters

All clinical laboratory parameters and their changes from baseline will be listed, as applicable; any value outside the clinical reference range will be flagged. Separate listings will be provided for any parameter for which there is any individual subject value outside the respective clinical reference range.

Summary tables and boxplots by treatment and timepoint for Parts A and B and by timepoint for Part C will be provided for clinical chemistry, haematology, and coagulation parameters and their changes from baseline, as applicable.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags, all calculations, and presentation in the figures, <x and ≤x values will be set to half of x whereas >x and ≥x values will be set to x.

8.7.3. Vital Signs Parameters

All vital signs parameters and their changes from baseline will be listed; any value outside the clinical reference range will be flagged.

Summary tables and boxplots by treatment and timepoint for Parts A and B and by timepoint for Part C will be provided for all vital signs parameters and their changes from baseline.

8.7.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters and their changes from baseline will be listed; any value outside the clinical reference range will be flagged.

Summary tables and boxplots by treatment and timepoint for Parts A and B and by timepoint for Part C will be provided for all 12-lead ECG parameters and their changes from baseline.

An outlier analysis will be performed for QT interval corrected for heart rate using Fridericia's formula (QTcF). The analysis will include all individual original, repeat, and unscheduled postdose values.

The maximum postdose values will be summarised by treatment for all Parts according to the following categories:

- ≤450 ms
- >450 and ≤480 ms (all instances flagged in the listing)
- >480 and ≤500 ms (all instances flagged in the listing)
- >500 ms (all instances flagged in the listing)

The maximum increases from baseline will be summarised by treatment for all Parts according to the following categories:

- ≤30 ms
- >30 and ≤60 ms (all instances flagged in the listing)
- >60 ms (all instances flagged in the listing)

8.7.5. Bristol Stool Chart and Faecal Occult Blood Test

All Bristol stool chart and faecal occult blood test data will be listed.

Summary tables by treatment for Parts A and B and by overall for Part C will be provided for all Bristol stool chart and faecal occult blood test data. Additionally, summary tables by treatment and timepoint for Parts A and B and by timepoint for Part C will be provided for all Bristol stool chart scale and faecal occult blood test data.

8.7.6. Other Assessments

Medical history will not be listed.

All other safety and tolerability assessments not detailed in the above sections will be listed only.

8.7.7. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

9. INTERIM ANALYSES

No interim analyses are planned.

10. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

There were no significant changes from the protocol-specified analyses.

11. REFERENCES

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4. Gough K, Hutchinson M, Keene O, et al. Assessment of dose proportionality: report from the statisticians in the pharmaceutical industry/Pharmacokinetics UK Joint Working Party. *Drug Inf J*. 1995;29(3):1039-1048.

5. Keene ON. The log transformation is special. *Stat Med*. 1995;14(8):811-819.

6. Snedecor GW, Cochran WG. *Statistical Methods*. 8th ed. Ames, IA: Iowa State University Press, 1989.

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12. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.

NA = not applicable