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Quotient Sciences

CLINICAL STUDY PROTOCOL

A Two-Part, Non-Randomised, Open Label Study to Evaluate the Effect of Itraconazole, Rifampicin, Rabeprazole and Omeprazole on the Pharmacokinetics of KD025

Quotient Study Number: QSC200311
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CONFIDENTIALITY AND GCP COMPLIANCE STATEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6 (R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 16.3 of this protocol.

Information taken from the study protocol may not be disseminated or discussed with a third party without the express consent of the sponsor.

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Nand Singh
Signature

26 SEP 2018
Date

Signatures for Sponsor

Sanjay Aggarwal, MD
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25-SEPT-2018

Date

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3 Synopsis

Sponsor: Kadmon Corporation, LLC	**Drug Substance:** KD025	**EudraCT No.:** 2018-000316-16

Title of Study: A Two-Part, Non-Randomised, Open Label Study to Evaluate the Effect of Itraconazole, Rifampicin, Rabeprazole and Omeprazole on the Pharmacokinetics of KD025

Principal Investigator: Nand Singh BSc, MD, DPM, MFPM

Study Centre:
Quotient Sciences, Mere Way, Ruddington Fields, Nottingham, NG11 6JS, UK

Objectives:

The primary objective of Part 1 of the study is:

- To determine the effect of itraconazole, rifampicin and rabeprazole on the pharmacokinetics (PK) of QD orally administered KD025, in healthy male subjects

The secondary objective of Part 1 of the study is:

- To provide additional information on the safety and tolerability of QD orally administered KD025, in healthy male subjects

The primary objective of Part 2 of the study is:

- To determine the effect of omeprazole on the PK of single day BID (every 12 hours [Q12h]) dose of KD025 administered orally, in healthy male subjects

The secondary objective of Part 2 of the study is:

- To provide additional information on the safety and tolerability of single day BID (Q12h) dose of KD025 administered orally, in healthy male subjects

Methodology:

This is a single centre, non-randomised, open label, two-part study.

Part 1

Part 1 is a single centre, non-randomised, 4-period sequential dose assessment in healthy male subjects. In each period, subjects will receive a single dose of the investigational medicinal product (IMP), KD025 Tablet, in the fed state. Additionally, in order to assess the effects of inhibition and induction of cytochrome P450 (CYP) 3A4 and the elevation of gastric pH on KD025 exposure, subjects will receive multiple doses of non-(N)IMP in Periods 2 to 4; a strong CYP3A4 inhibitor, itraconazole, in Period 2; a proton pump inhibitor (PPI), rabeprazole, in Period 3; and a strong CYP3A4 inducer, rifampicin, in Period 4:

Period	IMP/NIMP Dose
1	KD025 200 mg QD
2	itraconazole 200 mg QD for 7 days KD025 200 mg QD + itraconazole 200 mg QD on 8th day itraconazole 200 mg QD on 9th day
3	rabeprazole 20 mg BID for 3 days KD025 200 mg QD + rabeprazole 20 mg QD on 4th day
4	rifampicin 600 mg QD for 9 days KD025 200 mg QD on 10th day

QD: once daily; BID: twice daily

Study Design:

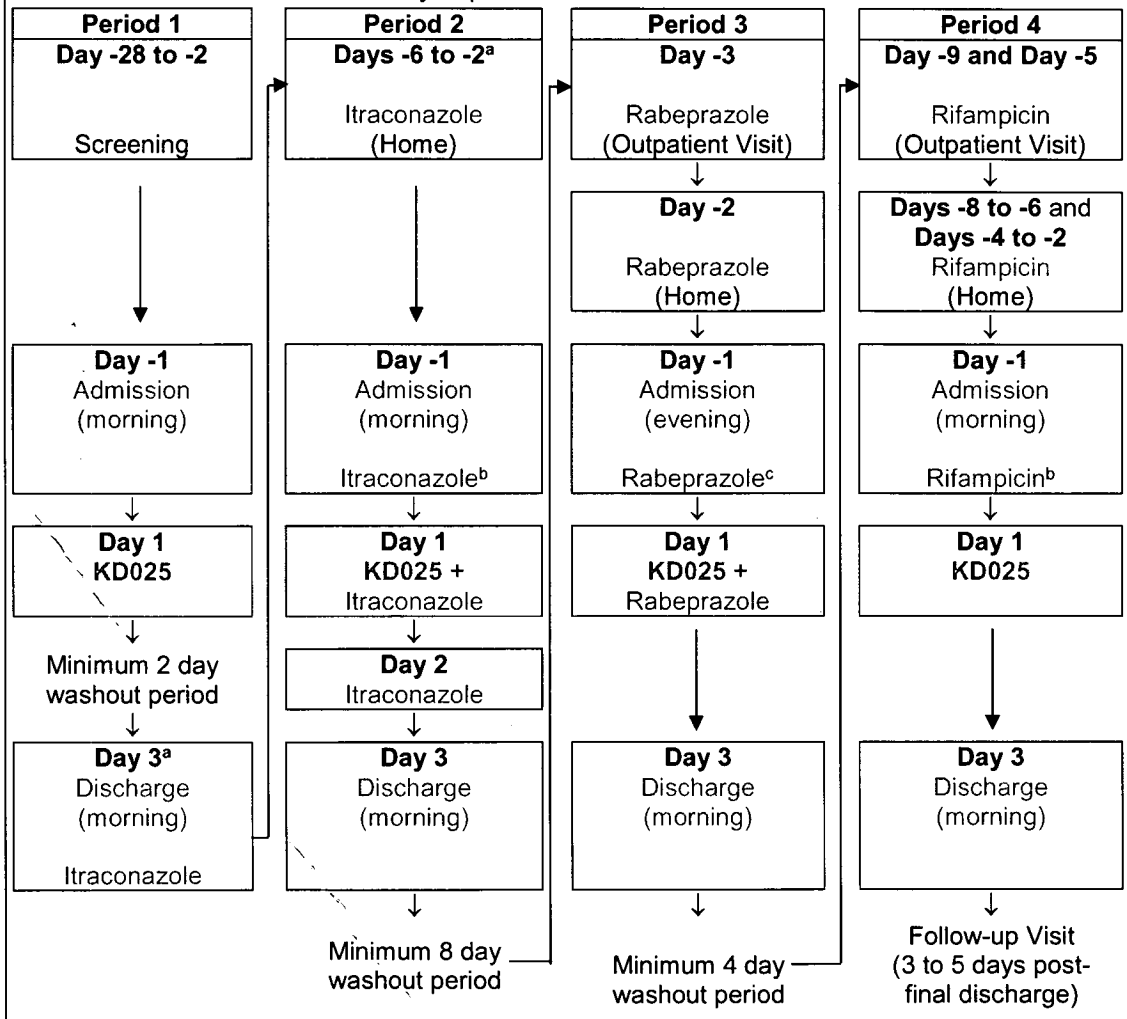
All subjects will undergo preliminary screening procedures to determine their eligibility for Part 1 of the study at the screening visit (Day -28 to Day -2 of Period 1). For each period, subjects will be admitted to the clinic on the day prior to IMP administration (Day -1) for

confirmation of eligibility and baseline procedures; morning admission for Periods 1, 2 and 4; evening admission for Period 3.

Prior to being admitted to the clinic in Periods 2 to 4, subjects will take multiple doses of the following NIMPs (see Part 1 overview below); itraconazole on Day 3 (Period 1; or Day -7 of Period 2 if washout period is extended) and continuing from Day -6 to -1 (Period 2); rabeprazole from Day -3 to -1 (Period 3); rifampicin from Day -9 to -1 (Period 4). Outpatient visits will take place on the mornings of Day -3 of Period 3 and Day -9 of Period 4, when the subjects will receive their morning dose of rabeprazole and rifampicin, respectively, and will be given sufficient supplies for home dosing. Subjects will also attend for an additional outpatient visit on the morning of Day -5 of Period 4 to receive their morning dose of rifampicin in the clinic, and will be given sufficient supplies for the remainder of the dosing period.

On the morning following admission for each period (Day 1), subjects will receive a single dose of IMP, either alone (Periods 1 and 4) or co-administered with NIMP (itraconazole in Period 2 [at the same time as IMP; fed state] and rabeprazole in Period 3 [2 h prior to IMP; fasted state]). In Period 2, a further dose of itraconazole will be administered on the day after IMP administration (Day 2). All subjects will remain on site until 48 h post-IMP dose for safety and PK assessments. There will be a minimum washout of 2, 8 and 4 days following completion of dosing in Periods 1, 2 and 3, respectively. A follow-up visit will take place 3 to 5 days post-final discharge.

An overview of Part 1 of the study is presented below:



[a] If the minimum washout period is extended, subjects will receive their first dose of itraconazole during a separate outpatient visit on Day -7 of Period 2
[b] Subjects will take itraconazole (Period 2)/rifampicin (Period 4) in the clinic after admission
[c] Subjects will take the evening dose of rabeprazole at home, prior to admission

Part 2

Part 1 is a single centre, non-randomised, 2-period sequential dose assessment in healthy male subjects.

In each period, subjects will receive a single day of BID dosing with IMP (KD025 tablet) in the fed state. Additionally, in order to assess the effect of a modest increase in gastric pH on the exposure of KD025, subjects will also receive multiple QD doses of the NIMP omeprazole, a PPI, in Period 2:

Period	IMP/NIMP Dose
1	KD025 200 mg BID (Q12h) on a single day only
2	omeprazole 20 mg QD for 3 days KD025 200 mg single day, BID (Q12h) + omeprazole 20 mg QD on 4th day

QD: once daily, BID: twice daily, Q12h: every 12 hours

Study Design

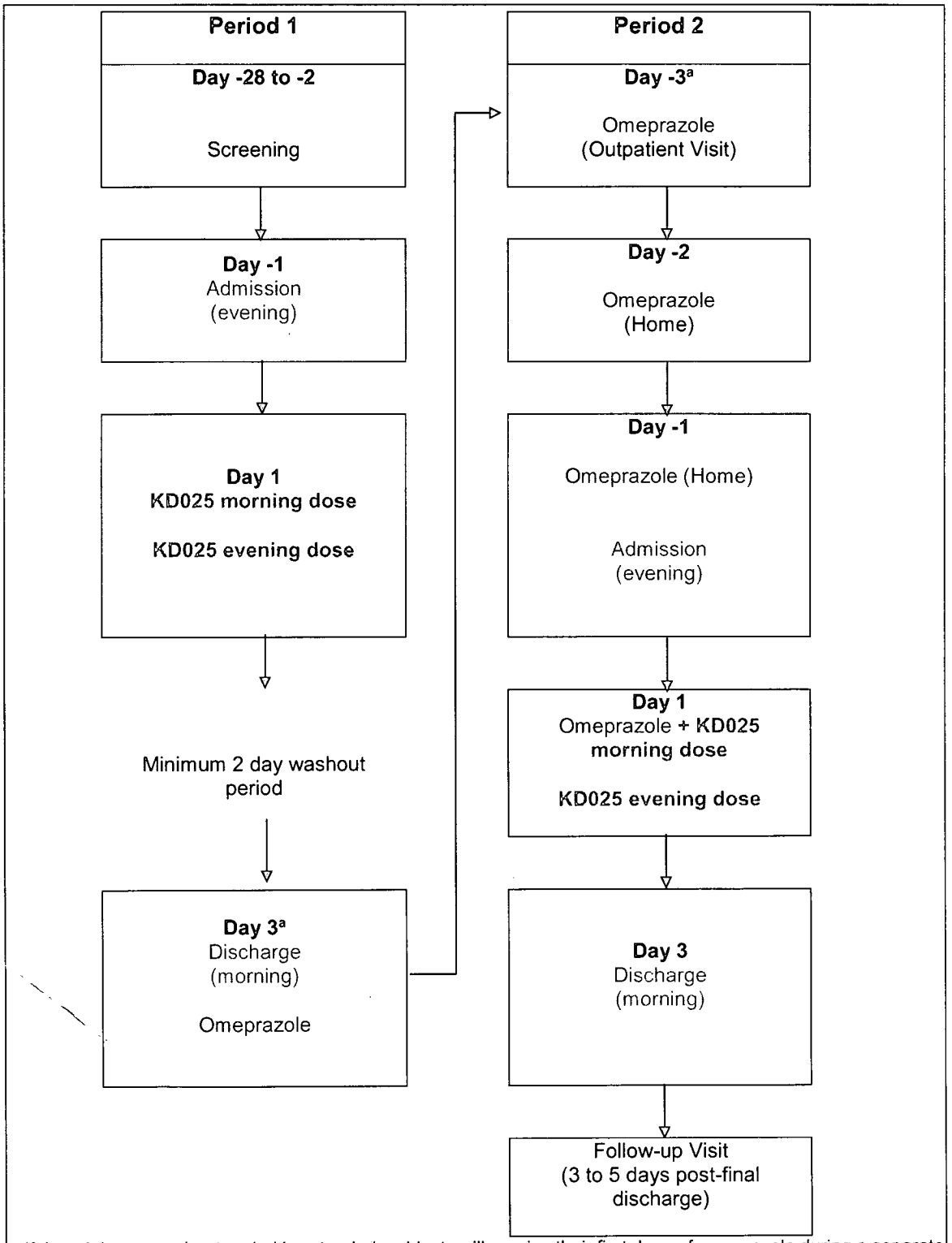
All subjects will undergo preliminary screening procedures to determine their eligibility for Part 2 of the study at the screening visit (Day -28 to Day -2 of Period 1). For each period, subjects will be admitted to the clinic on the evening of the day prior to IMP administration (Day-1) for confirmation of eligibility and baseline procedures.

Prior to being admitted to the clinic in Period 2, subjects will take single daily doses of NIMP. At discharge from Period 1, subjects will receive their first dose of omeprazole and will be given sufficient supplies for home dosing on Days -2 and -1, returning to the clinic for admission on the evening of Day -1. If the minimum washout period is extended due to logistics, subjects will receive their first dose of omeprazole during a separate outpatient visit on Day -3 of Period 2

On the day following admission for each period (Day 1), subjects will receive two doses of IMP (morning and evening, Q12h), either alone (Period 1) or with a NIMP (omeprazole) administered in the fasted state 2 h prior to planned morning IMP dose (Period 2). All IMP dosing will be in the fed state. All subjects will remain on site until 48 h post-IMP dose for safety and PK assessments. There will be a minimum washout of 2 days between dosing in Period 1 and starting dosing omeprazole in Period 2.

A follow-up visit will take place 3 to 5 days post-final discharge.

An overview of Part 2 of the study is presented below.



[a] If the minimum washout period is extended, subjects will receive their first dose of omeprazole during a separate outpatient visit on Day -3 of Period 2. Otherwise, subjects will receive the first dose of omeprazole at discharge from Period 1.

Number of Subjects Planned:

Part 1

It is planned to enrol 40 subjects to ensure there are 34 evaluable subjects; defined as those subjects who have sufficient PK data to assess the primary objective of Part 1 of the study.

Up to 4 additional subjects may be enrolled in Part 1 of the study in order to achieve sufficient evaluable subjects per relevant comparison; the maximum number of subjects that may be dosed is 44. Any replacement subject will be required to complete the reference treatment period (Period 1) in addition to any further test periods (Period 2 to 4) not already completed by the replaced subject.

Part 2

It is planned to enrol 38 subjects to ensure there are 34 evaluable subjects; defined as those subjects who have sufficient PK data to assess the primary objective of Part 2 of the study.

Up to 4 additional subjects may be enrolled in Part 2 of the study in order to achieve sufficient evaluable subjects; the maximum number of subjects that may be dosed is 42.

Any replacement subject will be required to complete the reference treatment period (Period 1) in addition to Period 2.

Duration of Study:

Part 1

Subjects will receive a single dose of KD025 on 4 separate occasions, and multiple doses of itraconazole, rabeprazole and rifampicin, on separate occasions, for 9, 4 and 9 consecutive days, respectively.

The estimated duration from screening to discharge from Part 1 of the study is approximately 10 weeks.

Part 2

Subjects will receive a single day BID (Q12h) dose of KD025 on 2 separate occasions, and single doses of omeprazole for 4 consecutive days.

The estimated duration from screening to discharge from Part 2 of the study is approximately 7 weeks.

Main Inclusion Criteria:

Healthy males aged 18 to 55 years

Body weight ≥50 kg. Body mass index 18.0 to 32.0 kg/m^2 or, if outside the range, considered not clinically significant by the investigator.

Investigational Medicinal Product, Dose and Mode of Administration:

The following IMP will be used in this clinical study:

Investigational Medicinal Product	Dose and Route of Administration
KD025 Tablet	**Part 1** 200 mg (as 1 × 200 mg tablets) Oral **Part 2** 400 mg (1 x 200 mg tablet Q12h) Oral

All doses of KD025 will be administered in the fed state; a total of 240 mL water will be given immediately following oral administration.

Non-Investigational Medicinal Product, Dose and Mode of Administration:

The following NIMPs will be used in this clinical study:

Product and Product Licence Number	Active Component (Indication)	Dose and Route of Administration
Part 1		
Itraconazole 100 mg Capsules, hard; PL 20075/0900	itraconazole (fungal infections)	2 x 100 mg Capsule; Oral
Rabeprazole 20 mg Gastro-resistant Tablets; PL 30306/0254	rabeprazole sodium (gastroesophageal reflux disease)	1 x 20 mg Tablet; Oral
Rifadin 300 mg Capsules: PL 04425/5916R	rifampicin (antibiotic)	2 x 300 mg Capsule; Oral
Part 2		
Omeprazole 20 mg Gastro-resistant Tablets PL 14017/0042	omeprazole (gastroesophageal reflux disease)	1 x 20 mg Tablet; Oral

A total of 240 mL water (approximately) will be given immediately following oral administration.

Pharmacokinetic Assessments:

Part 1

Venous blood samples for PK assessments will be withdrawn at pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36 and 48 h post-IMP dose in each period.

Part 2

Venous blood samples for PK assessments will be withdrawn at pre-dose, and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 12.5, 13, 13.5, 14, 15, 16, 17, 18, 20, 22, 24, 36 and 48 h post-IMP morning dose in each period.

The plasma concentration data for KD025 and metabolites KD025m1 and KD025m2 will be analysed by Quotient Sciences using appropriate non-compartmental techniques to obtain, for Part 1, estimates of Cmax, AUC(0-last) and AUC(0-inf), and for Part 2, estimates of Cmax(first dose), Cmax(second dose), Tmax, AUC(0-12), AUC(12-24), AUC(0-24) AUC(0-last; first dose) and AUC(0-inf; first dose); additional parameters will be estimated where possible and appropriate.

Safety Assessments:

The following safety assessments will be performed at appropriate time points during the study:

- Physical examinations
- Safety laboratory tests (clinical chemistry, haematology and urinalysis)
- Vital signs
- Electrocardiograms
- Adverse events

Statistical Methodology:

Formal statistical analysis will be performed for KD025 and metabolites KD025m1 and KD025m2 PK parameters as follows:

- **Part 1:** Cmax, AUC(0-last) and AUC(0-inf)
- **Part 2:**
  - Primary: Cmax(first dose), Cmax(second dose) and AUC(0-24)
  - Secondary: AUC(0-12), AUC(12-24), AUC(0-last; first dose) and AUC(0-inf; first dose)

The PK parameters will undergo a natural logarithmic transformation and will be analysed using mixed effect modelling techniques. The mixed effects model will include terms for

treatment as a fixed effect and subject as a random effect. Adjusted geometric mean ratios (GMRs) and 90% confidence intervals (CIs) for the adjusted GMRs will be provided for the comparisons of interest, where the ratios are defined as test/reference. A separate model will be fitted for each comparison of interest and will only include subjects who complete both periods for the relevant comparison of interest.

Part 1

- Period 2 (KD025 + itraconazole) vs Period 1 (KD025 alone)
- Period 3 (KD025 + rabeprazole) vs Period 1 (KD025 alone)
- Period 4 (KD025 + rifampicin) vs Period 1 (KD025 alone)

If the 90% CIs for each of KD025 (parent only) Cmax, AUC(0-last) and AUC(0-inf) lie within the acceptance interval of 70.00% to 143.00%, then the absence of an effect on PK can be concluded for the comparison of interest.

Part 2

- Period 2 (KD025 + omeprazole) vs Period 1 (KD025 alone)

If the 90% CIs for each of KD025 (parent only) Cmax(first dose), Cmax(second dose) and AUC(0-24) lie within the acceptance interval of 70.00% to 143.00%, then the absence of an effect on PK can be concluded for the comparison of interest.

Sample Size and Power:

For the purposes of sample size calculation the following assumptions have been made:

- Estimates of intra-subject variability (CVw) of 50% and 40% for Cmax and AUC(0-last), respectively. Data obtained from previous food effect study (QCL117415, data on file)
- Two one-sided tests with a probability of type 1 error of 0.05 for PK endpoints Cmax and AUC(0-last), ie 90% CI to be calculated
- Acceptance interval of 70.00% to 143.00%
- 80% power assuming the true ratio is between 95.00% and 105.00%

Part 1

Based on the above assumptions, 40 subjects are to be dosed to achieve 34 evaluable subjects for Cmax (PK parameter with highest CVw value). Evaluable subjects are defined as those subjects who have sufficient PK data to assess the primary objective of Part 1 of the study.

Part 2

Based on the above assumptions, 38 subjects are to be dosed to achieve 34 evaluable subjects for Cmax (PK parameter with highest CVw value). Evaluable subjects are defined as those subjects who have sufficient PK data to assess the primary objective of Part 2 of the study.

4 List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice daily
cGVHD	chronic graft versus host disease
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLcr	creatinine clearance
Cmax	maximal plasma concentration
CV%	coefficient of variation
CVw	intra-subject variability
CYP	cytochrome P450
EC	ethics committee
ECG	electrocardiogram
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GCP	good clinical practice
GERD	gastro-oesophageal reflux disease
GMR	geometric mean ratio
HbsAg	hepatitis B surface antigen
HCV Ab	hepatitis C virus antibody
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IPF	idiopathic pulmonary fibrosis
IL	interleukin
IMP	investigational medicinal product
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NIMP	non-investigational medicinal product
PI	principal investigator
PK	pharmacokinetic(s)

PPI	proton pump inhibitor
Q12h	every 12 hours
QD	once daily
QTc	corrected QT
QTcF	QT interval corrected using Fridericia's formula
RAP	Reporting and Analysis Plan
ROCK	Rho-associated protein kinases
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
Th17	T helper 17
Tregs	regulatory T cells
Tmax	time to maximal plasma concentration
ULN	upper limit of normal
WHO DDE	World Health Organisation Drug Dictionary Enhanced

5 Background Information

5.1 Introduction

An immune response is often a delicate balancing act protecting the integrity of the host organism from foreign invaders while restricting damage due to autoimmune reactivity [1]. Autoimmunity is a pathological condition characterised by humoral or cell-mediated immune responses against the body's own tissues, underlying diseases such as psoriasis, rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis. Patients who suffer from the more than 80 different types of autoimmune disorders are frequently treated with general immunosuppressive agents such as corticosteroids (eg prednisone) and nonsteroidal drugs (eg azathioprine, cyclophosphamide, methotrexate, sirolimus) that slow or stop the autoimmune attack, but do not allow for treatment discontinuation and can cause severe side effects such as infections and cancer [2]. Therefore, there is a need for effective and safe treatments for autoimmune disorders that produce remissions with fewer side effects. One approach is to develop therapies targeting specific immune cell subsets.

T helper 17 (Th17) cells are a subset of CD4+ T lymphocytes producing the cytokine interleukin (IL)-17 and are implicated in the pathogenesis of a number of autoimmune conditions [3]. Autoimmunity also involves alterations to regulatory T cells (Tregs). Tregs are a small (<5%) subset of CD4+ T lymphocytes that suppress activation of the immune system and play a critical role in maintaining immunological tolerance to self-antigens and inhibiting autoimmune responses [4]. Diminished suppressive function of Tregs contributes to the pathogenesis of many autoimmune disorders.

Rho-associated protein kinases (ROCKs) are members of the serine/threonine kinase family, often studied for their role in cell morphology, motility and shape through effects on the cytoskeleton [5][6]. Two ROCK isoforms have been identified, ROCK1 and ROCK2. Early work with nonspecific ROCK inhibitors suggested that both ROCK1 and ROCK2 are involved in Rho-mediated changes in the actin/myosin cytoskeletal network. More recent research has uncovered additional roles for ROCK signalling, particularly ROCK2, in conditions including autoimmune disease aggravated or caused by a Th17-polarised T-cell response [7], pulmonary fibrosis [8], and neurodegenerative conditions including Alzheimer's disease, in which ROCK2 contributes to overproduction of amyloid-β [9].

Rho GTPase-mediated signalling pathways play a central role in coordinating and balancing T cell mediated immune responses, including T cell receptor-mediated signalling, cytoskeletal reorganisation, and the acquisition of the appropriate T cell effector program [10]. Recent studies have demonstrated that aberrant activation of ROCK2 leads to induction of IL-17 and IL-21 via interferon regulatory factor 4-dependent mechanism [11]. Moreover, inhibition of ROCK effectively decreased IL-17 production in vivo and ameliorated the spontaneous development of arthritis, diabetes and lupus in mice. Additionally, ROCK activity was found to be up-regulated in patients with rheumatoid arthritis and systemic lupus erythematosus [12]. The specific inhibition of ROCK2 should therefore be examined for its potential as a therapy for autoimmune disorders.

KD025 (formerly called SLx-2119), (2-(3-(4-(1H-indazol-5-ylamino) quinazolin-2-yl) phenoxy)-N-isopropylacetamide-methane sulfonic acid salt) is an orally available ROCK2 selective inhibitor that is currently in Phase II clinical development for treating autoimmune and fibrotic disorders.

5.2 Investigational and Non-Investigational Medicinal Products

The investigational medicinal product (IMP) and non-investigational medicinal products (NIMPs), detailed in Table 1 and Table 2, respectively, will be used in this clinical study:

Table 1 Investigational Medicinal Product

Investigational Medicinal Product	Dose and Route of Administration
KD025 Tablet	200 mg (as 1 × 200 mg tablets) Oral

Table 2 Non-Investigational Medicinal Products

Product and Product Licence Number	Active Component (Indication)	Dose and Route of Administration
Part 1		
Itraconazole 100 mg Capsules, hard; PL 20075/0900	itraconazole (fungal infections)	2 x 100 mg Capsule; Oral
Rabeprazole 20 mg Gastro-resistant Tablets; PL 30306/0254	rabeprazole sodium (gastroesophageal reflux disease)	1 x 20 mg Tablet; Oral
Rifadin 300 mg Capsules: PL 04425/5916R	rifampicin (antibiotic)	2 x 300 mg Capsule; Oral
Part 2		
Omeprazole 20 mg Gastro-resistant Tablets PL 14017/0042	omeprazole (gastroesophageal reflux disease)	1 x 20 mg Tablet; Oral

All IMP/NIMPs will be reconciled and destroyed in accordance with the study-specific quality agreement and technical addendum.

5.3 Previous Study Findings

5.3.1 Nonclinical Data Summary

Nonclinical pharmacology studies demonstrate the potential of KD025 to have a therapeutic benefit in a number of indications, particularly in autoimmune disease through effects on Th17-type immune responses, and idiopathic pulmonary fibrosis (IPF) through anti-fibrotic mechanisms [13].

Solubility of KD025 is pH dependent ie, it is 100 µg/mL at pH 2.7, ~4 µg/mL at pH 6.5 and ~3 µg/mL at pH 7.4. The lower solubility at higher pH could potentially impact absorption of KD025 under physiological conditions.

KD025 plasma exposure generally increased with dose, was dose proportional or greater than dose proportional, and showed some accumulation. The elimination half-life of KD025 was variable in nonclinical studies with calculated values of approximately 2 h in mice, 1 to 7 h in rat and rabbit, and 1 to 3 h in dog.

KD025 undergoes first pass metabolism in all evaluated species after oral administration to form a ROCK2 active metabolite, KD025m1, and a metabolite that is relatively less active against ROCK2, KD025m2. Exposure levels for KD025m2, the only identified major metabolite in human subjects, in at least one species (rat) in the repeat-dose toxicology studies and both species (rat and rabbit) for embryo-foetal toxicity evaluation were sufficient to provide coverage relative to anticipated human exposure levels; therefore, KD025m2 is not considered a disproportionate human-only metabolite. In human liver microsomes, cytochrome P450 (CYP)-3A4 was the predominant CYP

isoform responsible for the metabolism of KD025, although other CYP or non-CYP mediated metabolism may also contribute.

KD025 primarily distributes to the adrenal gland, fur, gastrointestinal tract, kidney, and liver. No appreciable distribution to the brain has been detected. KD025 and KD025m1 are >99% bound to human, dog and rat plasma proteins; KD025m2 is >99% bound to human plasma protein.

To date, Good Laboratory Practice-compliant general toxicology/toxicokinetic studies of acute, subchronic (1 and 3 month), and chronic (6 month rat and 9 month dog) duration have been completed in rats and dogs. In addition, safety pharmacology studies evaluating human ether-a-go-go related gene (in-vitro), central nervous system (rat), respiratory (rat), and cardiovascular (dog) organ systems have been completed. Embryo-foetal toxicology (rat and rabbit) and fertility (rat) studies have also been completed. Furthermore, KD025 has been evaluated in a panel of studies evaluating drug genotoxicity and phototoxicity potential. Data from these nonclinical studies support a thorough understanding of the potential for safety-related effects of KD025 and have facilitated the development of the current clinical trial monitoring plan.

5.3.2 Clinical Data Summary

To date, 7 clinical studies have been completed, consisting of 6 Phase 1 clinical studies (SLx-2119-09-01, KD025-101, KD025-102, KD025-103, KD025-105, and KD025-106) in healthy subjects, and 1 Phase 2a study (KD025-205) in subjects with psoriasis vulgaris. Additionally, a Phase 2 study (KD025-206) in subjects with psoriasis vulgaris has been clinically completed; however, the clinical study report is pending. In addition to the completed studies, 3 Phase 2 studies are ongoing in subjects with chronic graft versus host disease (cGVHD; KD025-208), idiopathic pulmonary fibrosis (KD025-207) and psoriasis (KD025-211).

More than 300 subjects have received KD025 in completed studies with doses ranging from 20 to 1000 mg in single- and/or multiple-day dose regimens. Forty-eight subjects have received placebo. A total of 109 serious adverse events (SAEs) have been reported; 85 with the use of KD025, 22 with the use of placebo drug and 2 were blinded reports. The most common SAEs reported during use of KD025 were diarrhoea (4), nausea (3) and nasopharyngitis (3). No drug-related AEs have resulted in fatal outcomes.

To date, AEs most frequently reported with KD025 dosing include increased aspartate aminotransferase (AST) and increased alanine aminotransferase (ALT). Other commonly reported events include rash, pruritus, upper respiratory infection, joint aches and swelling, headache, fatigue, back pain, leg weakness, diarrhoea, nausea, vomiting, upper abdominal pain, increase in white blood cell count, catheter site infection, dizziness, and flatulence.

To date, 17 subjects in KD025 clinical trials have experienced liver-related AEs. Most of these events were considered to be at least possibly related to study drug. The majority of liver related AEs have been mild or moderate in intensity; 5 were severe. These events generally occurred after 16 to 36 days of KD025 administration, and all events were reversible. None of the liver-related AEs were determined to be SAEs.

The identified and potential risks noted in association with KD025 are balanced by the anticipated benefits that may be afforded to subjects with psoriasis vulgaris, IPF and cGVHD.

KD025 was the main analyte detected in all clinical studies, with maximal plasma concentration (Cmax) ranging from ~100 ng/mL (20 mg once daily [QD] in SLx-2119-09-01) to ~5300 ng/mL (500 mg twice daily [BID] in KD025-102), and median time to maximal plasma concentration (Tmax) ranging from ~2 h to ~8 h. Cmax and the area under the concentration-time curve (AUC) appear to be slightly greater than dose responsive over the 20 to 500 mg QD, but less than dose linear for doses > 500 mg. The half-life typically ranged from 4 h to 8 h, with a few reports greater than 8 h.

Two metabolites, KD025m1 and KD025m2, rapidly appeared in plasma and were readily eliminated. A major metabolite, KD025m2, was detected at Cmax levels ~20% that of parent and AUC approximately 15% that of parent. A minor metabolite, KD025m1, was detected at Cmax levels <5% of parent and AUC ~2% parent. Accumulation of KD025m2 was reported after multiple doses. KD025m1 did not accumulate.

In both Study KD025-105 (a fed/fasted crossover study with KD025 capsules) and Study KD025-106 (a fed/fasted crossover study with KD025 tablets), a high-fat meal given 30 minutes prior to KD025 oral administration had a significant effect on the pharmacokinetics (PK) of KD025. Plasma systemic exposure (Cmax and AUCs) of KD025 was approximately 2- to 3–fold higher under the fed state compared with the fasted state, and the median Tmax value was delayed by 0.5 to 2 h with food.

6 Rationale

6.1 Study Rationale

Preclinical data indicates that CYP3A4 plays a predominant role in the metabolism of KD025; therefore, drug-drug interactions will be investigated in this study to determine whether co-administration of KD025 with inhibitors or inducers of CYP3A4 results in altered exposure of KD025 and/or KD025m1 and KD025m2. In the present study, itraconazole and rifampicin will be used because they are classed as a strong inhibitor and inducer of CYP3A4, respectively.

In addition, the solubility of KD025 is pH dependent ie, it is 100 µg/mL at pH 2.7, ~4 µg/mL at pH 6.5 and ~3 µg/mL at pH 7.4. Thus, the impact of a proton pump inhibitor (PPI), on the exposure of KD025 will also be assessed. Rabeprazole, a recognised PPI, suppresses the secretion of gastric acid by noncompetitive blockade of the H+/K+-adenosine triphosphatase at the secretory surface of the gastric parietal cells and raises the intra-gastric pH above 3.0. As rabeprazole increases pH, co-administration of rabeprazole with KD025 could result in a decrease in exposure of KD025.

Preliminary results from Part 1 (n=21) show that the exposure of KD025 is decreased (by approximately 80%) in subjects when taking rabeprazole (20 mg BID). Part 2 of the study has been designed to assess the impact of omeprazole (20 mg QD) on KD025 exposure. Omeprazole is a PPI widely used in clinical settings for the treatment of gastro-esophageal reflux disease, and to manage upper GI involvement in patients with cGVHD and IPF. Omeprazole has a weaker anti-secretory effect on gastric acid than rabeprazole [14]. Co-administration of omeprazole with KD025 could result in a smaller decrease in exposure of KD025 than observed with rabeprazole. Therefore, omeprazole will allow assessment of a weaker PPI interaction with KD025.

6.2 Dose Rationale

6.2.1 KD025

KD025 in doses ranging from 20 to 1000 mg in single- and/or multiple-day dose regimens have generally been well tolerated. Single doses of 200 mg KD025 have been selected for Part 1 of this study. The 200 mg dose has been well tolerated as a single dose and in repeat dosing in healthy subjects and patients with psoriasis and cGVHD; repeat dosing at 400 mg QD has been well tolerated in patients with IPF. The 200 mg dose provides a clear PK profile, in the linear range, well above the lower limit of quantification, and is in the expected therapeutic range.

In Part 2, a BID (every 12 hours [Q12h]) 200 mg dose of KD025 has been selected, for a total of 400 mg per day on two separate occasions. The 400 mg dose has been well tolerated as a single dose and in repeat dosing in healthy volunteers and in patients with psoriasis and IPF. Repeat dosing of 200 mg BID has been well tolerated in patients with psoriasis and cGVHD [13].

6.2.2 Itraconazole

Itraconazole is recommended in the 2017 US Food and Drug Administration (FDA) Clinical Drug Interaction Studies guidance document as being a strong inhibitor of CYP3A4 [15]. From the literature, a dose of 200 mg QD for a duration of 4 days is commonly used to achieve clinically relevant inhibition of CYP3A4 [16][17][18]. Furthermore, a dose of 200 mg QD is the recommended clinical dosing regimen for itraconazole [19].

However, itraconazole has time dependent kinetics, thus after 15 days of multiple dosing at 100 mg and 200 mg QD or 200 mg BID, there is greater accumulation than would be predicted from the single dose kinetics, and the half-life is increased from around 15 to 25 h following single dosing, to around 35 to 40 h after multiple dosing [20]. Thus a dosing duration of 9 days was selected as a duration which would result in a clinically relevant inhibition of CYP3A4 with consideration given to the multiple dose kinetics of itraconazole.

Dosing of itraconazole in Period 2 will continue on Day 1 of dosing with KD025, and on Day 2, ie during the washout phase of KD025, in order to maintain CYP3A4 inhibition during the elimination phase of KD025.

6.2.3 Rabeprazole

Rabeprazole, a potent PPI, suppresses the secretion of gastric acid by noncompetitive blockade of the H+/K+-adenosine triphosphatase at the secretory surface of the gastric parietal cells and raises the intra-gastric pH above 3.0. Rabeprazole has demonstrated anti-secretory activity, following single doses in healthy volunteers and patients with gastro-oesophageal reflux disease (GERD), but has less anti-secretory activity than esomeprazole on Days 1 and 5 after multiple doses in volunteers and patients with GERD. Rabeprazole has a rapid onset of action (within 4 h), and achieves maximal or near maximal effect after a single dose. After 3 to 5 days of single doses of rabeprazole, the intra-gastric pH is approximately 4 in healthy subjects. The effects of rabeprazole on acid secretion persist for several days after ceasing treatment [21].

Sodium rabeprazole (immediate release form) is rapidly absorbed, with peak plasma concentrations occurring approximately 3.5 h after administration. The oral bioavailability of rabeprazole is unaffected by food. Rabeprazole displayed dose proportional PK over the dose range of 10 to 80 mg following single oral doses in healthy volunteers. Rabeprazole is largely excreted via the urine, and the elimination half-life is approximately 1 h.

The recommended starting dose of sodium rabeprazole for patients with GERD or hypersecretory syndromes is 20 to 60 mg per day [22]. For the short duration of this drug interaction study, the proposed dose of rabeprazole is 20 mg BID for a total dose of 40 mg per day for 3 consecutive days, followed by a QD dose prior to IMP.

6.2.4 Rifampicin

Rifampicin is recommended in the 2017 FDA Clinical Drug Interaction Studies guidance document as being a strong inducer of CYP3A4 [15]. A dosing regimen for rifampicin of 600 mg QD for between 5 to 9 days has been modelled and shown to result in steady state induction of CYP3A4 activity [23]. This is also a clinically relevant dosing regimen [24] and therefore is considered to be an appropriate dosing regimen in this study. Rifampicin is also an inhibitor of the organic anion transporter protein; therefore, rifampicin will be dosed on Days -9 to -1 (Period 4), but not on Day 1 when KD025 will be administered. This is to avoid any confounding effects that may occur in data interpretation should KD025 be a substrate for the organic anion transporter protein in addition to CYP3A4 [15].

6.2.5 Omeprazole

Omeprazole has a weaker anti-secretory effect on gastric acid than rabeprazole and supresses gastric acid secretion by noncompetitive blockade of the H+/K+ adenosine triphosphatase at the secretory surface of the gastric parietal cell. Omeprazole has demonstrated anti-secretory effects in healthy volunteers and patients with GERD [25], but has less of an anti-secretory effect than rabeprazole on Day 1 and 8 following multiple doses in health subjects [14]. Omeprazole has a rapid onset of action, within one hour, and achieves the maximum effect within 2 h. Following discontinuation, secretory activity returns to normal over 3 to 5 days.

Omeprazole is rapidly absorbed, with peak plasma levels of omeprazole occurring within 1 to 2 h after administration. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. The AUC of omeprazole increases with repeated administration. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. Omeprazole is largely excreted (80%) via urine, and the elimination half-life is less than 1 h [26].

The recommended starting dose of omeprazole for patients varies between 20 mg to 60 mg once daily depending on indication [26]. For the short duration of this study, the recommended dose is 20 mg QD for 4 days.

6.3 Population Rationale

The European Medicines Agency (EMA) propose to include subjects in the age group 18 to 55 years with normal weight who are non smokers without a history of alcohol or drug abuse. The latter criteria are proposed to avoid interaction on drug metabolism and to avoid non compliance. In order to avoid any interaction with other medication, no co medication will be allowed.

As this is a Phase I study assessing the bioavailability, PK and safety of KD025, the most relevant population is healthy volunteers, as recommended by the FDA [27] and the EMA guidelines [28].

The purpose of this study is to show a difference between the applied conditions, and therefore it is an advantage to enrol a relatively homogeneous population and to minimise variability. Healthy male subjects, aged 18 to 55 years, will be therefore be enrolled.

Formal rat and rabbit embryo-foetal developmental toxicology studies with KD025 demonstrated potential for embryo-foetal toxicity and/or malformations at clinically relevant exposures. Therefore subjects with pregnant partners will be excluded from this study.

6.4 Risks and Benefits

6.4.1 Potential Risks associated with KD025

KD025 has generally been well tolerated across the clinical studies conducted. No drug-related AEs have resulted in fatal outcomes. The most common AEs associated with KD025 administration are liver-related, specifically increased ALT and AST levels. Subjects will receive single doses of KD025 in this study and will be closely monitored throughout the study for any changes in liver enzymes, and no subject with a history or presence of hepatic disease or ALT/AST values > the upper limit of normal (ULN) will be enrolled in the study (see Section 9.3).

Other commonly reported events include rash, pruritus, upper respiratory infection, joint aches and swelling, headache, fatigue, back pain, leg weakness, diarrhoea, nausea, vomiting, upper abdominal pain, increase in white blood cell count, catheter site infection, dizziness, and flatulence.

6.4.2 Potential Risks associated with Non-Investigational Medicinal Products

6.4.2.1 Itraconazole

The full reference safety information for itraconazole (Itraconazole 100 mg Capsules, hard) is provided in the Summary of Product Characteristics [19]. The most common side effects reported include: nausea, abdominal pain and rash. Rarely, itraconazole has been associated with serious hepatotoxicity, including liver failure and death.

6.4.2.2 Rabeprazole

The full reference safety information for rabeprazole (Rabeprazole 20 mg Gastro-resistant Tablets) is provided in the Summary of Product Characteristics [22]. The most common side effects reported include: infections, insomnia, headache, dizziness, aches, cough, pharyngitis, rhinitis, non-specific pain, back pain, effects on stomach or gut (flatulence, nausea, vomiting, diarrhoea, abdominal pain, benign fundic gland polyps and constipation), asthenia or influenza-like symptoms. Other side effects may include serious hypersensitivity (face swelling, dyspnoea or hypotension).

6.4.2.3 Rifampicin

The full reference safety information for rifampicin (Rifadin 300 mg Capsules) is provided in the Summary of Product Characteristics [24]. Common side effects include gastrointestinal reactions such as anorexia, nausea, vomiting, diarrhoea and abdominal discomfort. Skin reactions such as itching or flushing with or without a rash, as well as

urine discolouration (orange or reddish colour) have been observed. Additionally, hepatitis may also occur and liver function tests will be closely monitored in this study. Other rare side effects include acute renal failure, thrombocytopenia and haemolytic anaemia.

6.4.2.4 Omeprazole

The full reference safety information for omeprazole (Omeprazole 20 mg Gastro-Resistant Tablets) is provided in the Summary of Product Characteristics [26]. The most common side effects (1-10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting. Another common side effect is fundic gland polyps (benign). Uncommon (≥1/1,000 to <1/100) side effects include: increased liver enzymes, dermatitis, pruritus, rash, urticarial, fracture of the hip, wrist or spine, malaise and peripheral oedema.

6.4.3 Other Considerations

During cannulation, more than one attempt may be needed to insert the cannula in a vein of a subject and it is possible that bruising and/or inflammation may be experienced at the site of cannulation.

Electrocardiogram stickers on the subjects' chests and limbs may cause some local irritation and may be uncomfortable to remove but subjects will be closely monitored to ensure any local irritation does not persist.

There is no benefit to the subjects from taking part in this study. The development of a ROCK2-selective small molecule drug has the potential for effectiveness in multiple disease indications and will be of benefit to the wider community.

The overall risk benefit balance is therefore considered to be acceptable.

7 Objectives and Endpoints

7.1 Objectives

7.1.1 Primary Objective

The primary objective of Part 1 of the study is:

- To determine the effect of itraconazole, rifampicin and rabeprazole on the pharmacokinetics (PK) of QD orally administered KD025, in healthy male subjects

The primary objective of Part 2 of the study is:

- To determine the effect of omeprazole on the PK of a single day BID (Q12h) dose of KD025 administered orally, in healthy male subjects

7.1.2 Secondary Objective

The secondary objective of Part 1 of the study is:

- To provide additional information on the safety and tolerability of QD orally administered KD025 in healthy male subjects

The secondary objective of Part 2 of the study is:

- To provide additional information on the safety and tolerability of a single day BID (Q12h) dose of KD025 administered orally, in healthy male subjects

7.2 Endpoints

7.2.1 Primary Endpoint

The primary endpoint of Part 1 of the study is:

- A comparison of the PK profile of KD025 Tablets (QD) when co-administered with itraconazole, rifampicin and rabeprazole, compared to when administered alone, by assessing the following primary PK parameters for KD025, KD025m1 and KD025m2: Cmax, AUC(0-last) and AUC(0-inf), at a minimum.

The primary endpoint of Part 2 of the study is:

- A comparison of the PK profile of KD025 Tablets (BID; Q12h) when co-administered with omeprazole compared to administration of KD025 alone by assessing the following PK parameters for KD025, KD025m1 and KD025m2: Cmax(first dose), Cmax(second dose) and AUC(0-24).

7.2.2 Secondary Endpoint

The secondary endpoint of Part 1 of the study is:

- Assess the safety and tolerability of KD025 (QD) by evaluating the following: safety laboratory tests, vital signs, electrocardiograms (ECGs), physical examinations and AEs

The secondary endpoint of Part 2 of the study is:

- Assess the safety and tolerability of BID (Q12h) dosing of KD025 by evaluating the following: safety laboratory tests, vital signs, ECGs, physical examinations and AEs

8 Study Design

8.1 Study Plan

This is a single centre, non-randomised, open label, two-part study.

8.1.1 Study Plan Part 1

Part 1 is a single centre, non-randomised, 4-period sequential dose assessment in healthy male subjects. In each period, subjects will receive a single dose of IMP, KD025 Tablet, in the fed state. Additionally, in order to assess the effects of inhibition and induction of CYP3A4 and the elevation of gastric pH on KD025 exposure, subjects will receive multiple doses of NIMP in Periods 2 to 4; a strong CYP3A4 inhibitor, itraconazole, in Period 2; a PPI, rabeprazole, in Period 3; and a strong CYP3A4 inducer, rifampicin, in Period 4:

Period	IMP/NIMP Dose
1	KD025 200 mg QD
2	itraconazole 200 mg QD for 7 days KD025 200 mg QD + itraconazole 200 mg QD on 8th day itraconazole 200 mg QD on 9th day
3	rabeprazole 20 mg BID for 3 days KD025 200 mg QD + rabeprazole 20 mg QD on 4th day
4	rifampicin 600 mg QD for 9 days KD025 200 mg QD on 10th day

QD: once daily; BID: twice daily; details of the IMP and NIMPs are provided in Section 5.2.

It is planned to enrol 40 subjects to ensure there are 34 evaluable subjects; defined as those subjects who have sufficient PK data to assess the primary objective of Part 1 of the study.

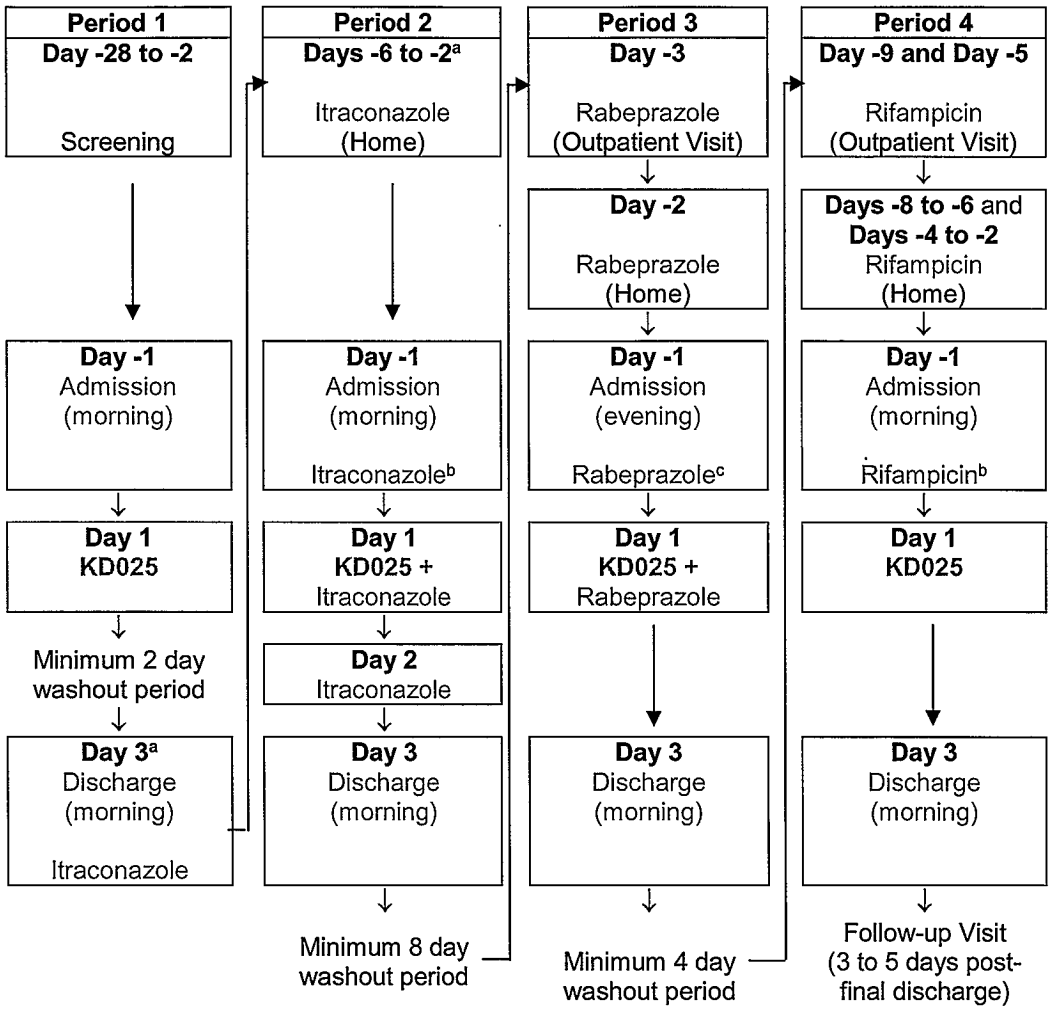
All subjects will undergo preliminary screening procedures to determine their eligibility for Part 1 of the study at the screening visit (Day -28 to Day -2 of Period 1). For each period, subjects will be admitted to the clinic on the day prior to IMP administration (Day -1) for confirmation of eligibility and baseline procedures; morning admission for Periods 1, 2 and 4; evening admission for Period 3.

Prior to being admitted to the clinic in Periods 2 to 4, subjects will take multiple doses of the following NIMPs; itraconazole on Day 3 (Period 1; or Day -7 of Period 2 if washout period is extended) and continuing from Day -6 to -1 (Period 2); rabeprazole from Day -3 to -1 (Period 3); rifampicin from Day -9 to -1 (Period 4). Outpatient visits will take place on the mornings of Day -3 of Period 3 and Day -9 of Period 4, when the subjects will receive their morning dose of rabeprazole and rifampicin, respectively, and will be given sufficient supplies for home dosing. Subjects will also attend for an additional outpatient visit on the morning of Day -5 of Period 4 to receive their morning dose of rifampicin in the clinic, and will be given sufficient supplies for the remainder of the dosing period.

On the morning following admission for each period (Day 1), subjects will receive a single dose of IMP, either alone (Periods 1 and 4) or co-administered with NIMP (itraconazole in Period 2 [at the same time as IMP; fed state] and rabeprazole in Period 3 [2 h prior to IMP; fasted state]). In Period 2, a further dose of itraconazole will be administered on the day after IMP administration (Day 2). All subjects will remain on site until 48 h post-IMP dose for safety and PK assessments. There will be a minimum washout of 2, 8 and 4 days following completion of dosing in Periods 1, 2 and 3, respectively. A follow-up visit will take place 3 to 5 days post-final discharge.

The Part 1 study design is presented in Figure 1.

Figure 1 Part 1 Study Sequence



[a] If the minimum washout period is extended, subjects will receive their first dose of itraconazole during a separate outpatient visit on Day -7 of Period 2
[b] Subjects will take itraconazole (Period 2)/rifampicin (Period 4) in the clinic after admission
[c] Subjects will take the evening dose of rabeprazole at home, prior to admission

8.1.2 Study Plan Part 2

Part 2 is a single centre, non-randomised, 2-period sequential dose assessment in healthy male subjects. In each period, subjects will receive a single day of BID dosing with IMP (KD025 tablet) in the fed state. Additionally, in order to assess the effect of a modest increase in gastric pH on the exposure of KD025, subjects will also receive multiple QD doses of the NIMP omeprazole, a PPI, in Period 2:

Period	IMP/NIMP Dose
1	KD025 200 mg BID (Q12h) on a single day
2	omeprazole 20 mg QD for 3 days KD025 200 mg single day, BID (Q12h) + omeprazole 20 mg QD on 4th day

QD: once daily, BID: twice daily, Q12h: every 12 hours
Details of the IMP and NIMPs are provided in Section 5.2

It is planned to enrol 38 subjects to ensure there are 34 evaluable subjects, defined as those subjects who have sufficient PK data to assess the primary objective of Part 2 of the study.

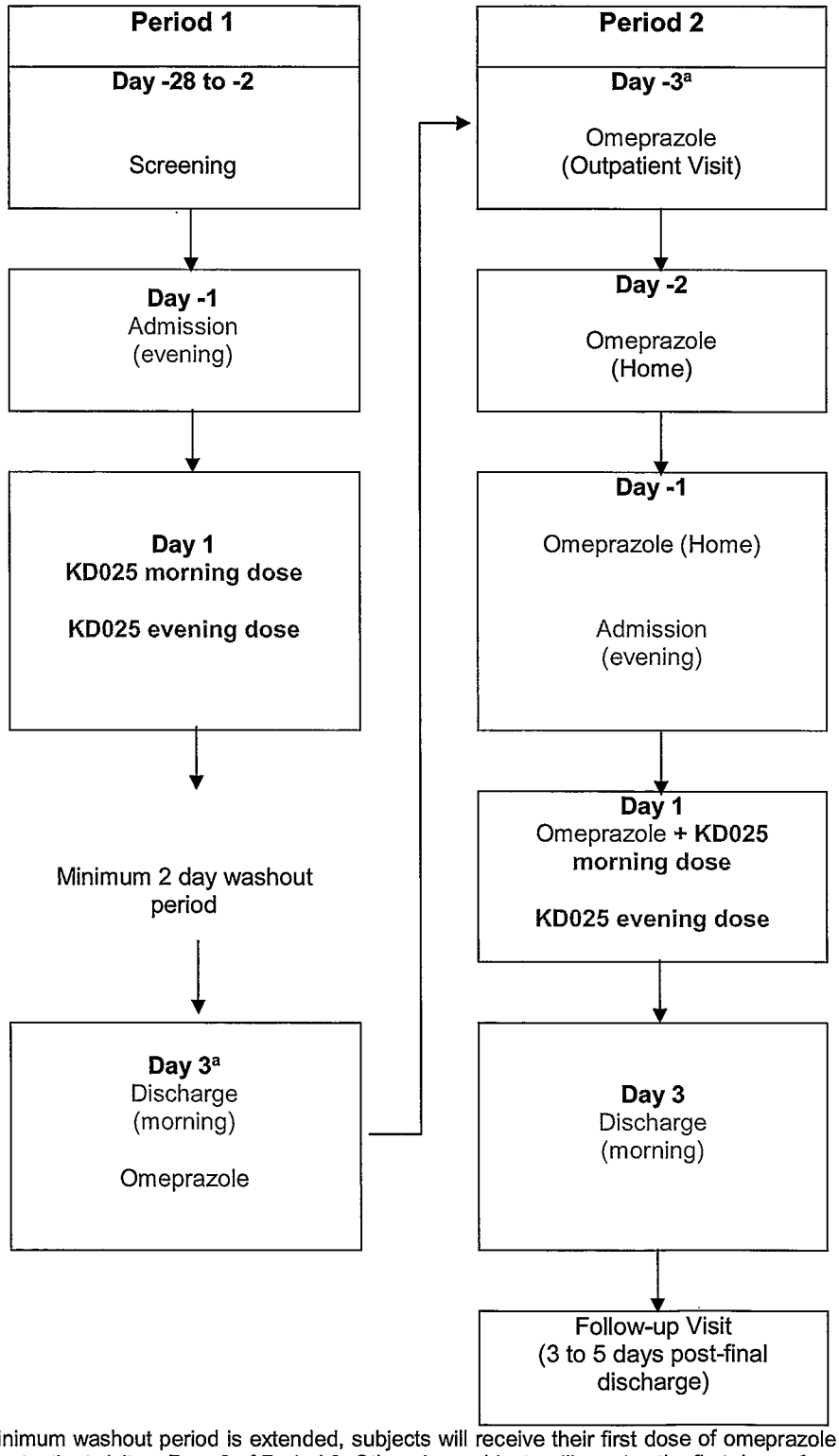
All subjects will undergo preliminary screening procedures to determine their eligibility for the study at the screening visit (Day -28 to Day -2 of Period 1). For each period, subjects will be admitted to the clinic on the evening of the day prior to IMP administration (Day-1) for confirmation of eligibility and baseline procedures.

Prior to being admitted to the clinic in Period 2, subjects will take single daily doses of the NIMP (omeprazole). At discharge from Period 1, subjects will receive their first dose of omeprazole and will be given sufficient supplies for home dosing on Days -2 and -1, returning to the clinic for admission on the evening of Day -1. If the minimum washout period is extended due to logistics, subjects will receive their first dose of omeprazole during a separate outpatient visit on Day -3 of Period 2.

On the day following admission for each period (Day 1), subjects will receive two doses of IMP (morning and evening, Q12h), either alone (Period 1) or with a NIMP (omeprazole) administered in the fasted state 2 h prior to planned morning IMP dose (Period 2). All IMP dosing will be in the fed state (standard breakfast). All subjects will remain on site until 48 h post-IMP dose for safety and PK assessments. There will be a minimum washout of 2 days between dosing in Period 1 and the start of dosing omeprazole in Period 2. A follow-up visit will take place 3 to 5 days post-final discharge.

The Part 2 study design is presented in Figure 2.

Figure 2 Part 2 Study Sequence



[a] If the minimum washout period is extended, subjects will receive their first dose of omeprazole during a separate outpatient visit on Day -3 of Period 2. Otherwise, subjects will receive the first dose of omeprazole at discharge from Period 1.

8.2 Criteria for In-Study Decisions

Not applicable for this study.

8.3 Subject Withdrawal

If a subject wishes to leave the study at any time, they will be permitted to do so. Every reasonable effort will be made by Quotient Sciences to complete a final assessment/discharge procedures. Quotient Sciences will advise the sponsor of the withdrawal of any subject from the study.

Early withdrawal is defined as the date of the decision to withdraw the subject from the study. Subject completion is defined as the date of the last procedure conducted or last contact (ie, phone call) for that subject.

If a subject requests to leave the clinical unit earlier than the planned discharge time eg due to unforeseen personal circumstances, but aims to return to the unit to complete the study, this will be documented as a subject self-discharge and a protocol deviation. The subject must complete the planned assessments/discharge procedures before discharge from the clinic and will return for the next study period/assessments, as planned.

Subjects will be withdrawn from the study drugs for the following reasons:

- Experiencing a serious or severe AE including but not limited to:
  - corrected QT (QTc) interval of >500 msec or increase in QTc interval of >60 msec from baseline (confirmed following a repeat ECG [mean of triplicate assessments, as applicable])
  - ALT concentration >3 × the upper limit of the reference range
- Termination of the study
- Upon the subject's request (withdrawal of consent)
- Significant deviation from the protocol
- Concurrent illness or requirement for prohibited medication
- At the discretion of the investigator/sponsor

For the purpose of withdrawal criteria in Parts 1 and 2, baseline will be considered as the Period 1 admission/pre-dose measurement; for QTc withdrawal criteria, baseline will be considered as the mean value of the triplicate pre-dose Day 1 (Period 1) ECG measurement.

8.4 Subject Replacement

It is not anticipated that replacement subjects will be used in this study; however, in the event that a replacement will be required, this will be discussed with the investigator and sponsor.

Part 1

If replacement of subjects is invoked, up to 4 additional subjects may be enrolled in Part 1 of the study in order to achieve sufficient evaluable subjects per relevant comparison; the maximum number of subjects that may be dosed is 44. Any subject withdrawn due to an IMP or NIMP-related AE or termination of the study will not be replaced. Subjects withdrawing for other reasons may be replaced at the discretion of the investigator and sponsor to ensure sufficient evaluable subjects. Any replacement subject will be required to complete the reference treatment period (Period 1) in addition to any further test periods (Period 2 to 4) not already completed by the replaced subject.

A subject is considered to be evaluable if they have sufficient PK data to assess the primary objective of Part 1 of the study. It should be noted that 34 subjects are required

for each comparison of interest and therefore replacement subjects may be utilised, eg if only 32 subjects have evaluable data for Periods 1 and 4.

Part 2

If replacement of subjects is invoked, up to 4 additional subjects may be enrolled in Part 2 of the study in order to achieve sufficient evaluable subjects per relevant comparison; the maximum number of subjects that may be dosed is 42. Any subject withdrawn due to an IMP or NIMP-related AE or termination of the study will not be replaced. Subjects withdrawing for other reasons may be replaced at the discretion of the investigator and sponsor to ensure sufficient evaluable subjects. Any replacement subject will be required to complete the reference treatment period (Period 1) in addition to Period 2.

Evaluable subjects are defined as those subjects who have sufficient PK data to assess the primary objective of Part 2 of the study.

8.5 Stopping Criteria

The study will be halted, and the risk to other subjects evaluated, prior to a decision as to whether to terminate the study if any of the following criteria are met:

- The occurrence of an SAE considered at least possibly related to the IMP administration in 1 subject.
- The occurrence of severe, non-serious AEs considered at least possibly related to the IMP administration in 2 subjects in any treatment period.

Relatedness will be determined by the investigator and/ or sponsor. If the study is halted, a temporary halt will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee (EC) in the form of a substantial amendment. The study will not be resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC.

8.6 Study Termination

After the start of protocol activities but prior to the commencement of dosing, the study may be terminated by the sponsor and investigator without consultation with the MHRA and EC. The end of the trial must be notified to the MHRA and EC immediately and at the latest within 15 days after the study is halted, clearly explaining the reasons. A description of follow-up measures taken for safety reasons if applicable, should also be provided.

If the study is abandoned prior to commencement of any protocol activities, the investigator or sponsor must notify the EC and MHRA by letter outlining the reasons for abandonment of the trial.

Once exposure to IMP dosing has begun, the study will be completed as planned unless the following criteria are satisfied that require temporary suspension or early termination of the study:

- The occurrence of SAEs (s), as defined in Section 8.5, if considered to be related to the IMP, as defined in Section 14.2.

- New information regarding the safety of the IMP that indicates a change in the risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

If any of the above occurs, the study may be terminated if careful review of the overall risk/benefit analysis described in Section 6.4 demonstrates that the assumptions have changed and that the overall balance is no longer acceptable. In these circumstances termination can only take place with the agreement of the investigator and sponsor. The MHRA and EC will be informed of study termination.

If it becomes necessary to consider termination of the study after dosing has begun, dosing may be suspended pending discussion between the investigator and sponsor. Dosing will be stopped immediately on safety grounds.

The study may be terminated or suspended at the request of the MHRA or EC.

8.7 Treatment Allocation

This is an open-label, non-randomised study, therefore, a randomisation schedule will not be produced. A treatment allocation list will be produced prior to dosing with IMP, which will dictate the order in which the treatments should be administered to each subject. The treatment allocation list will be retained in the investigator site file.

8.7.1 Subject Numbers

Part 1

Subject numbers will be allocated on the morning of IMP dosing according to the code 001 to 040 using the lowest number available. If required, replacement subjects will be allocated subject numbers 901 to 940, where the last 2 digits are the same as those of the original subject (eg if Subject 005 withdraws, the replacement will have Subject Number 905 and will receive the reference treatment, as well as IMP/NIMP for at least one treatment period not already received by the replaced subject).

Part 2

Subject numbers will be allocated on the morning of IMP dosing according to the code 201 to 238 using the lowest number available. If required, replacement subjects will be allocated subject numbers 801 to 838 where the last 2 digits are the same as those of the original subject (eg if Subject 205 withdraws, the replacement will have Subject Number 805 and will receive the reference treatment (Period 1), as well as the IMP/NIMP for Period 2.

8.7.2 Blinding

This is an open-label, non-randomised study and therefore blinding is not required.

9 Selection of Subjects

Quotient Sciences must have a full medical history from each subject's general practitioner within the last 12 months, prior to enrolment in the study.

Subjects will be recruited from the Quotient Sciences panel or by direct advertising to the public.

Before subjects are admitted to the clinic, The Over Volunteering Prevention System (TOPS) will be checked to ensure that each subject has not participated in a study at another site within at least 3 months of the dosing date.

9.1 Informed Consent

Subjects will be provided with a written explanation of the study at least the day before the screening visit. A physician or nurse will explain to each subject the nature of the study, its purpose, expected duration and the benefits and risks involved in study participation. Subjects will be informed that, for safety reasons, brief details of their involvement in the study may be revealed to other units and companies that carry out clinical studies in the local area. Subjects will then be given the opportunity to ask questions and will be informed of their right to withdraw from the study without prejudice. After this explanation and before entering the study, the subject will voluntarily sign an informed consent form (ICF).

9.2 Inclusion Criteria

1. Healthy males
2. Age 18 to 55 years
3. Good state of health (mentally and physically) as indicated by a comprehensive clinical assessment (detailed medical history and a complete physical examination), ECG and laboratory investigations (haematology, clinical chemistry and urinalysis)
4. Body weight ≥50 kg
5. Body mass index of 18.0 to 32.0 kg/m^2 or, if outside the range, considered not clinically significant by the investigator
6. Must be willing and able to communicate and participate in the whole study
7. Must provide written informed consent
8. Must adhere to the contraception requirements as defined in Section 9.4)

Inclusion criteria 3 from the list above will be re-assessed at the Period 1 admission.

9.3 Exclusion Criteria

1. Subjects who previously participated in any other investigational study drug trial in which receipt of an investigational study drug occurred within 90 days prior to dosing (subjects who have previously received KD025 in Part 1 at least 90 days prior to dosing in Part 2 are eligible to participate).
2. Subjects who are study site employees, or immediate family members of a study site or sponsor employee
3. Subjects with pregnant partners
4. History of any drug or alcohol abuse in the past 2 years
5. Regular alcohol consumption in males >21 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type)
6. Current smokers and those who have smoked within the last 12 months. A breath carbon monoxide reading of greater than 10 ppm at screening and admission
7. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
8. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator at screening

9. Clinically significant abnormal biochemistry, haematology or urinalysis as judged by the investigator (laboratory parameters are listed in Appendix 1)
10. Positive drugs of abuse test result (drugs of abuse tests are listed in Appendix 1) or alcohol breath test at screening and admission
11. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) results
12. Evidence of renal impairment at screening, as indicated by an estimated creatinine clearance (CLcr) of <80 mL/min using the Cockcroft-Gault equation
13. History of clinically significant cardiovascular, renal, hepatic, chronic respiratory or gastrointestinal disease, neurological or psychiatric disorder, as judged by the investigator
14. Subject has a history or presence of any of the following:
    - Active gastrointestinal disease requiring therapy
    - Hepatic disease and/or ALT or AST > ULN
    - Renal disease and/or serum creatinine > ULN
    - Other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs
15. Subjects with a history of cholecystectomy or gall stones
16. Subject has QT interval corrected using Fridericia's formula (QTcF) intervals >450 msec at screening or admission
17. Serious adverse reaction or serious hypersensitivity to any drug or the formulation excipients; including intolerance to itraconazole, rabeprazole, rifampicin and omeprazole.
18. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hayfever is allowed unless it is active
19. Donation or loss of greater than 400 mL of blood within the previous 3 months
20. Subjects who are taking, or have taken, any prescribed or over-the-counter drug (other than 4 g per day paracetamol) or herbal remedies in the 14 days before IMP administration (See Section 11.4). Exceptions may apply on a case by case basis, if considered not to interfere with the objectives of the study, as agreed by the principal investigator (PI) and sponsor's medical monitor.
21. Failure to satisfy the investigator of fitness to participate for any other reason

Exclusion criteria 6, 9, 10, 14, 16, 18, 20 and 21 from the list above will be re-assessed at admission/pre-dose, as applicable.

Healthy subjects who do not meet the inclusion/exclusion criteria for a study should not be enrolled into the study without exception.

9.4 Contraception

The following contraception requirements are aligned with guidance issued by the Heads of Medicines Agency: Clinical Trials Facilitation Group [29].

Male subjects who are sexually active with a partner of child bearing potential must use, with their partner, a condom plus an approved method of effective contraception from the time of informed consent until 90 days after study discharge.

The following methods are acceptable:

- Combined (oestrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - oral

  - intravaginal
  - transdermal

- Progestogen-only hormonal contraception:
  - oral
  - injectable/implantable
  - intrauterine hormone-releasing system

- Implantable intrauterine device

- Surgical sterilisation (for example, vasectomy or bilateral tubal occlusion)

- Male condom with either female cap or diaphragm (double barrier)

Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, they, with their partner, must comply with the contraceptive requirements detailed above.

9.4.1 Exposure to Partners during the Study

There is a significant risk of drug exposure through the ejaculate (which also applies to vasectomised males) that might be harmful to the sexual partners (both male and female), including pregnant partners of male subjects. Therefore, a condom should be used by all male subjects throughout the study and for 90 days after study discharge.

9.4.2 Sperm Donation

Male subjects should not donate sperm for the duration of the study and for at least 90 days after study discharge.

9.5 Pregnancy

Subjects will be instructed that if their partner become pregnant during the study this should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject's partner is subsequently found to be pregnant after the subject is included in the study, then consent will be sought from the partner and, if granted, any pregnancy will be followed and the status of mother and/or child will be reported to the sponsor after delivery.

A pregnancy notification form and follow-up will be completed.

9.6 Additional Study Restrictions

The following additional restrictions will be in place for the duration of the study:

1. Subjects must abstain from alcohol during the 24 h prior to screening and the 24 h prior to admission in Period 1, and 24 h prior to commencing NIMP treatment in Part 1 Periods 2 to 4 and Part 2 Period 2, until discharge for each treatment period
2. Subjects must not drink liquids or eat food containing grapefruit or cranberry from 24 h prior to admission in Period 1, and 24 h prior to commencing NIMP treatment in Part 1 Periods 2 to 4 and Part 2 Period 2, until discharge for each treatment period
3. Subjects must not drink liquids or eat food containing caffeine or other xanthines from 24 h prior to admission until discharge for each treatment period

4. Subjects should refrain from eating food containing poppy seeds for 48 h prior to screening and for 24 h prior to admission until discharge for each treatment period
5. Subjects must not take part in any unaccustomed or strenuous exercise from the 72 h before the screening visit and then from 24 h prior to admission until discharge for each treatment period.

10 Study Procedures

Study procedures will be performed as detailed in the study schedule of assessments in Appendix 2 and Appendix 3, and in accordance with Quotient Sciences standard operating procedures unless otherwise stated in this protocol.

10.1 Screening

Within the 28 days preceding first dose, all subjects will be required to undergo a screening visit. Screening procedures will be carried out in accordance with the study flow chart in Appendix 2 and Appendix 3.

If the start of the study is delayed for any reason so that the interval between screening and first dose exceeds 28 days, all or part of the screening procedures may be repeated at the discretion of the investigator.

Subjects previously screened generically may participate in this study provided they meet the subject selection criteria. Procedures required by this protocol will only be done if they were not performed during generic screening. All screening data must be obtained within 28 days prior to administration of study medication, as stipulated above.

10.1.1 Subject Re-Screening

This study permits the re-screening of a subject who has discontinued the study as a pre-treatment failure (ie subject has not been treated); the reason for failure must be temporary and expected to resolve. If re-screened, the subject must be re-consented.

10.2 Admission and Pre-dose Procedures

The identity of the subjects will be confirmed at admission and pre-dose.

In addition, the ongoing eligibility of subjects will be re-assessed at admission/pre-dose, as described in Sections 9.2 and 9.3.

Reserve subjects for the first dose occasion, in any group, will not require admission procedures to be repeated, if dosing is within 2 days.

Part 1: subjects will be admitted to the clinical unit on the morning before IMP administration (Day -1) for Periods 1, 2 and 4, and on the evening before IMP administration (Day -1) for Period 3.

Part 2: subjects will be admitted to the clinical unit on the evening before IMP administration (Day -1) for both periods.

The admission and pre-dose procedures are presented in Appendix 2 and Appendix 3

10.3 Study Day Procedures

10.3.1 Blood Volume

The total blood volume for each subject will not exceed 550 mL in a 4 week period. The first 0.5 mL of blood withdrawn via cannula will be discarded.

10.3.2 Timing of Procedures

There are times where the protocol requires more than one procedure to be completed at the same time point. In these instances the following will apply to post-dose time points:

Pharmacokinetic samples should take priority over other procedures scheduled at the same time point.

As guidance, the preferred order of assessments is:

ECGs → **Vitals** → **PK blood sampling** → **Other assessments eg physical exams**

Electrocardiograms should be taken prior to vital signs when both measurements are scheduled at the same time point. Other assessments, eg physical examinations, will be performed within the required time windows.

All safety assessments will be timed and performed relative to the start of IMP dosing.

10.3.3 Discharge from the Clinical Unit

A subject will be allowed to leave the premises following completion of study-specific procedures at 48 h post-IMP dose (Day 3), providing that:

- no AEs have been reported during the study visit
- the subject responds in the affirmative when asked if they are feeling well

If any of these conditions are not met, then the subject will only be allowed to leave the clinical unit with the authorisation of the investigator or appropriately qualified delegate.

10.3.4 Outpatient Visits

Part 1

Subjects will be asked to attend the clinical unit for outpatient visits on Day-3 of Period 3, and Days -9 and -5 of Period 4 for NIMP administration and home supplies, as well as the assessments described in Appendix 2.

Part 2

If the minimum washout period is extended, subjects will be asked to attend the clinical unit for an outpatient visit on Day -3 of Period 2 for NIMP administration and home supplies, as well as the assessments described in Appendix 3. Otherwise, subjects will receive the first dose of omeprazole at discharge from Period 1.

10.3.5 Medical Supervision

A physician will be responsible for the clinical aspects of the study and will be available at all times during the study. In accordance with the current Association of the British Pharmaceutical Industry guidelines, each subject will receive a card stating the telephone number of the investigator.

10.3.6 Follow-up

A follow-up phone visit will take place 3 to 5 days after final discharge to ensure the ongoing wellbeing of the subjects. If a subject reports any AEs which can present a cause for concern, they will be required to attend the clinic for a further follow-up assessment (as an unscheduled visit). Completion of the last follow-up visit (including any unscheduled) will be considered the end of the study.

11 Dosing of Subjects

11.1 Food and Fluid Intake

Water will be allowed ad libitum on the day of dosing. For Part 1 decaffeinated fluids will be allowed ad libitum from lunch time on the day of IMP dosing. For Part 2, decaffeinated fluids will be allowed ad libitum from lunch time on the day of dosing until 1 h before and then from 1 h after the evening dose.

If, for technical reasons, IMP dosing is delayed for more than 2 h beyond the expected dosing time, subjects may receive 200 mL of Lucozade Sport at the originally scheduled dosing time, or earlier if possible.

11.1.1 Investigational Medicinal Product Dosing

Part 1

Breakfast will be controlled by clinical staff members on IMP dosing days for each treatment period (Day 1). The start and stop time of the breakfast must be recorded and where less than 100% of the breakfast has been consumed, the percentage consumed must be recorded.

Subjects will be provided with a light snack on the evening of admission days for each treatment period (Day -1) and will fast from all food and drink (except water) until the following morning, when they will be provided with a standard breakfast. The breakfast should be consumed over a maximum period of 25 min, with dosing occurring 30 min after the start of breakfast. Subjects should be encouraged to eat their meal evenly over the 25 min period. It is acknowledged that some subjects will take less time to eat, but dosing should still occur 30 min after the start of breakfast.

Lunch will be provided at approximately 4 h post-IMP dose, an evening meal at approximately 9 h post-IMP dose and an evening snack at approximately 14 h post-IMP dose. On subsequent days, meals will be provided at appropriate times.

Part 2

In Part 2 the IMP will be administered BID and given in the fed state.

Breakfast will be controlled by clinical staff members on IMP dosing days for each treatment period (Day 1). The start and stop time of the breakfast must be recorded and

where less than 100% of the breakfast has been consumed, the percentage consumed must be recorded.

Subjects will be provided with a light snack on the evening of admission days for each treatment period (Day -1) and will fast from all food and drink (except water) until the following morning, when they will be provided with a standard breakfast. The breakfast should be consumed over a maximum period of 25 min, with dosing occurring 30 min after the start of breakfast. Subjects should be encouraged to eat their meal evenly over the 25 min period. It is acknowledged that some subjects will take less time to eat, but morning dosing should still occur 30 min after the start of breakfast.

Subjects will be dosed in the evening following the evening meal. Evening dosing will occur 30 min after the start of the evening meal (ie, dosing at 12 h post-morning dose; meal to be started 11 h and 30 min post-morning dose). Decaffeinated fluids will be allowed ad libitum from lunch time on the day of dosing until 1 h before and then from 1 h after the evening dose.

Lunch will be provided at approximately 5 h post-morning IMP dose and an evening snack at approximately 14 h post-morning IMP dose. On subsequent days, meals will be provided at appropriate times.

11.1.2 Non-Investigational Medicinal Product Dosing

Part 1

Subjects will take itraconazole for 9 consecutive days; on Day 3 of Period 1 and from Day -6 to Day 2 of Period 2. All doses of itraconazole should be taken with approximately 240 mL water at approximately the same time each morning following breakfast; when co-administered with IMP on Day 1, a total of 240 mL water should be taken.

Subjects will take rabeprazole for 4 consecutive days; from Day -3 to Day 1 of Period 3. All doses of rabeprazole should be taken with approximately 240 mL water. On Days -3 to -1 (BID dosing days) subjects should take rabeprazole at approximately the same time each morning following breakfast, and following an evening meal. On Day 1, rabeprazole will be administered in the fasted state, approximately 2 h prior to IMP administration.

Subjects will take rifampicin for 9 consecutive days; from Day -9 to Day -1 of Period 4. All doses of rifampicin should be taken with approximately 240 mL water at approximately the same time each morning, prior to eating breakfast.

Part 2

Subjects will take omeprazole for 4 consecutive days; from Day -3 to Day 1 of Period 2. All doses of omeprazole should be taken with approximately 240 mL water. On Days -3 to -1 (Period 2 only) subjects should take omeprazole at approximately the same time each morning prior to eating breakfast. On Day 1, omeprazole will be administered in the fasted state, approximately 2 h prior to IMP administration. Decaffeinated fluids will not be allowed from 1 h prior until 1 h post-omeprazole administration (except on Day 1; see Section 11.1.1 Part 2 for details).

11.2 Administration of Test Preparations

Specific details of the IMP and NIMPs, and doses to be administered are provided in Section 5.2 and Section 8.1, respectively.

Part 1

On IMP dosing days (Day 1), subjects will be dosed in the morning and receive KD025 alone (Periods 1 and 4) or in combination with itraconazole (at the same time as IMP; Period 2), or rabeprazole (approximately 2 h prior to IMP; Period 3); a total of 240 mL water will be given immediately following oral administration. The exact time of dosing will be decided based on logistics and will be documented.

On NIMP dosing days, subjects will take treatments at approximately the same time each day with approximately 240 mL water. When NIMP is taken at home, subjects will record the time of administration in a diary card.

Subjects will receive a total of 4 single doses of KD025, each on a separate occasion and multiple doses of itraconazole, rabeprazole and rifampicin, on separate occasions, for 9, 4 and 9 consecutive days, respectively.

The minimum washout period between treatment periods may be changed, if data collected during the study support the change. However, the minimum washout period will not be reduced to less than 5 half-lives of the IMP.

Part 2

On Day 1, Period 1, subjects will be dosed in the morning and will receive KD025 alone with a total of 240 mL water given immediately following oral administration. A second dose of IMP will be administered approximately 12 h after morning dose.

On Day 1, Period 2, subjects will be dosed in the morning with the NIMP approximately 2 h prior to IMP administration. Approximately 240 mL of water will be given immediately following oral administration. A second dose of IMP will be administered approximately 12 h after morning IMP dose. When NIMP is taken at home, subjects will record the time of administration in a diary card.

All IMP doses in Part 2 will be given in the fed state, relative to dosing. See Section 11.1.1 for details.

The exact time of dosing will be decided based on logistics and will be documented.

Subjects will receive a single day BID (Q12h) dose of KD025 on 2 separate occasions, and single doses of omeprazole for 4 consecutive days.

The minimum washout period between treatment periods may be changed, if data collected during the study support the change. However, the minimum washout period will not be reduced to less than 5 half-lives of the IMP.

11.3 Dosing Compliance

During all clinical phases of the study, subjects will be observed by study staff to assure compliance to all study procedures, including dose administration.

Mouth and hand checks will be conducted after dosing to ensure the tablet/capsule has been swallowed.

When NIMP is taken at home, subjects will record the time of administration in a diary card.

The date and time that each subject is dosed will be recorded in the subject's source data. Any violation of compliance will require evaluation by the investigator and sponsor to determine if the subject can continue in the study.

11.4 Prior and Concomitant Medications

No medication will be permitted from 14 days before IMP administration until the follow-up visit except 4 g per day paracetamol and those deemed necessary by the investigator to treat AEs (see also Section 9.3). Any medications used will be recorded.

Emergency equipment and drugs will be available within the clinical unit as per current standard procedures. In the unlikely event that they are required, their use will be documented.

12 Assessment of Efficacy

Not applicable for this Phase I study.

13 Assessment of Pharmacokinetics and Pharmacodynamics

13.1 Assessment of Pharmacokinetics

13.1.1 Pharmacokinetic Blood Sampling

Venous blood samples will be withdrawn via an indwelling cannula or by venepuncture according to the time schedule presented in Appendix 2 and Appendix 3.

The acceptable deviations from the nominal post-dose blood sampling times are as follows:

- The pre-dose blood sample will be taken ≤1 h before dosing.
- 0 to 1 h post-dose samples will be taken within ± 2 min of the nominal post-dose sampling time
- >1 to 12 h post-dose samples will be taken within ± 10 min of the nominal post-dose sampling time
- >12 h post-dose samples will be taken within ± 30 min of the nominal post-dose sampling time

Samples will be collected into appropriate tubes as specified by the bioanalytical laboratory. Details of sample tubes and processing will be contained in the Clinical Sample Processing Manual.

Samples will be shipped to Covance Laboratories Ltd for the analysis of KD025 and metabolites KD025m1 and KD025m2.

13.2 Assessment of Pharmacodynamics

Not applicable for this Phase I study.

14 Assessment of Safety

14.1 Definition and Classification of Adverse Events

An AE is any untoward medical occurrence in a subject that occurs either before dosing (referred to as a pre-dose AE) or once a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

An adverse drug reaction is any AE where a causal relationship with the IMP is at least a reasonable possibility (possibly related or related).

Adverse events will be monitored from the time the subject signs the ICF until after the final follow-up call. The severity of AEs should be assessed as follows:

Mild An AE that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities

Moderate An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed

Severe An AE that prevents normal everyday activities; treatment or other intervention usually needed

14.2 Assessment of Causality

Every effort should be made by the investigator to try to explain each AE and assess its relationship, if any, to the IMP. The temporal relationship of the event to IMP administration should be considered in the causality assessment (ie if the event starts soon after IMP administration and resolves when the IMP is stopped).

Causality should be assessed using the following categories:

Unrelated: Clinical event with an incompatible time relationship to IMP administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the IMP

Possibly related: Clinical event with a reasonable time relationship to IMP administration, and that is unlikely to be attributed to concurrent disease or other drugs or chemicals

Related: Clinical event with plausible time relationship to IMP administration and that cannot be explained by concurrent disease or other drugs or chemicals

The degree of certainty with which an AE is attributed to IMP administration (or alternative causes, eg natural history of the underlying disease, concomitant therapy, etc) will be determined by how well the experience can be understood in terms of one or more of the following:

- known pharmacology of the IMP
- reactions of a similar nature have been previously observed with the IMP or this class of drug
- the experience being related by time to IMP administration, terminating with IMP withdrawal or recurring on re-challenge
- alternative cause

14.3 Recording Adverse Events

Adverse events will be recorded from the time of providing written informed consent until discharge from the study at the follow-up visit. During each study visit the subject will be questioned directly regarding the occurrence of any adverse medical event according to

the schedule in the source data. All AEs, whether ascribed to study procedures or not, will be documented immediately. This will include the date and time of onset, a description of the AE, severity, duration, actions taken, outcome and an investigator's current opinion on the relationship between the study drug and the event. A diagnosis and final opinion on the relationship between the study drug and the event will be provided at the end of the study by the investigator.

Any subject who withdraws from the study due to an AE will be followed up until the outcome is determined and written reports provided by the investigator.

14.4 Serious Adverse Events

14.4.1 Definition of Serious Adverse Events

A serious adverse event is defined as any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- an important medical event as recognised by the PI

SAEs must be immediately reported to the sponsor.

14.4.2 Definition of Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are believed to be related to an IMP and are both unexpected (ie the nature or severity is not expected from the information provided in the Investigator's Brochure) and serious. SUSARs are subject to expedited reporting to the MHRA, EMA and EC (see Section 16.3.2 for details on reporting SUSARs).

14.5 Laboratory Measurements

Blood and urine samples results will be reviewed by a physician and acted upon before the subject is dosed or receives their next dose, or is released from the study, as is appropriate. A list of the laboratory parameters measured is presented in Appendix 1.

14.5.1 Haematology and Clinical Chemistry

Laboratory tests will be performed by The Doctors Laboratory according to the time schedule presented in Appendix 2 and Appendix 3. Blood samples will be collected and processed as detailed in the Clinical Sample Processing Manual. Scheduled blood samples will be taken following an 8 h fast.

The acceptable deviations from the nominal blood sampling time points for laboratory assessments are:

- Post-dose blood samples will be taken ± 1 h from the nominal blood sampling time except when the time point coincides with the PK blood sampling time. In this situation, the time window for the PK sample applies.

Creatinine clearance (CLcr) will be calculated at screening by using the Cockcroft-Gault equation and body weight for eligibility purposes:

$$\text{CLcr (mL/min)} = \frac{(140\text{-age [years]}) \times (\text{body weight [kg]}) \times 1.23}{\text{serum creatinine (µmol/L)}}$$

14.5.2 Urinalysis

Urinalysis will be performed on-site using a dipstick according to the time schedule presented in Appendix 2 and Appendix 3. Urine samples will be collected and processed as detailed in the Clinical Sample Processing Manual. If microscopy is required, a urine sample will be sent to The Doctors Laboratory.

The acceptable deviations from the nominal urine sampling time points for urinalysis are:

- Post-dose urine samples will be taken ± 2 h from the nominal urine sampling time

14.5.3 Drug Screen

A urine drug screen will be performed on-site using a dipstick method according to the time schedule presented in Appendix 2 and Appendix 3. The sample will be collected and processed as detailed in the Clinical Sample Processing Manual. Subjects will be screened for the drugs of abuse listed in Appendix 1.

14.5.4 Alcohol Breath Test

An alcohol breath test will be performed according to the time schedule presented in Appendix 2 and Appendix 3. A positive result will exclude the subject from dosing during that admission.

14.5.5 Carbon Monoxide Breath Test

A carbon monoxide breath test will be performed according to the time schedule presented in Appendix 2 and Appendix 3. A result of greater than 10 ppm will exclude the subject from the study.

14.5.6 Abnormal Laboratory Findings

In cases where laboratory findings are outside the normal range and the investigator believes that the results may be of clinical significance, repeat sampling may be requested as clinically indicated. If the abnormal finding is clinically significant, appropriate actions will be taken eg, the subject will not be entered into the study or the subject may be withdrawn from the study. The subject will be referred to their general practitioner or other appropriate provider for further care. The same will apply if the results of the HBsAg, HCV Ab or HIV test are positive and in addition the investigator will ensure that adequate counselling is available if requested.

Abnormal results at follow-up assessments will also require repeat testing if the investigator believes the results may be of clinical significance.

Any clinically significant abnormality, including changes from baseline, must be reported as an AE.

Additional blood and/or urine samples may be taken for safety tests. Furthermore, additional assays outside those specified in the protocol may be performed for safety reasons as requested by the investigator.

14.6 Vital Signs Measurements

Blood pressure and heart rate will be measured by an automated recorder after the subject has been in a supine position for a minimum of 5 min according to the time schedule presented in Appendix 2 and Appendix 3. Oral temperature will also be measured. The acceptable deviations from the nominal vital signs measurement time points are:

- The pre-dose vital signs measurements will be taken ≤2 h before dosing
- Post-dose vital signs measurements will be taken ± 15 min from the nominal post-dose time points

If a subject shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator.

Any clinically significant abnormality, including changes from baseline, must be reported as an AE.

14.7 ECG Measurements

Twelve-lead ECGs will be measured after the subject has been in the supine position for a minimum of 5 min according to the time schedule presented in Appendix 2 and Appendix 3.

In Part 1, single ECGs will be measured at all time points with the exception of pre-dose and 4 h post-dose on Day 1 of each period, during which times ECGs will be measured in triplicate, a minimum of 2 min apart.

In Part 2, single ECGs will be measured at all time points with the exception of pre-morning dose, 4 h post-morning dose, pre-evening dose and 2 h post-evening dose on Day 1 of each period, during which times ECGs will be measured in triplicate, a minimum of 2 min apart.

The acceptable deviations from the nominal ECG measurement time points are:

- The pre-dose ECG measurements will be taken ≤2 h before dosing
- Post-dose ECG measurements will be taken ± 15 min from the nominal post-dose time point

If a subject shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator.

Any clinically significant abnormality, including changes from baseline, will be reported as an AE.

14.8 Body Weight

The subject's body weight will be measured as detailed in Appendix 2 and Appendix 3.

14.9 Physical Examination

Subjects will undergo a physical examination as detailed in Appendix 2 and Appendix 3.

14.10 Additional Safety Procedures

Additional non-invasive procedures that are already specified in the protocol may be performed, if it is believed that an important effect of the IMP/NIMPs is occurring or may occur at a time when no measurements are scheduled, or if extra procedures are needed in the interests of safety.

Additional blood samples for safety assessments may be taken if required by the investigator at any point.

15 Statistics and Data Analysis

15.1 Sample Size Justification

For the purposes of sample size calculation the following assumptions have been made:

- Estimates of intra-subject variability (CVw) of 50% and 40% for Cmax and AUC(0-last), respectively. Data obtained from previous food effect study (QCL117415, data on file)
- Two one-sided tests with a probability of type 1 error of 0.05 for PK endpoints Cmax and AUC(0-last), ie 90% CI to be calculated
- Acceptance interval of 70.00% to 143.00%
- 80% power assuming the true ratio is between 95.00% and 105.00%

Part 1

Based on the above assumptions, 40 subjects are to be dosed to achieve 34 evaluable subjects for Cmax (PK parameter with highest CVw value). Evaluable subjects are defined as those subjects who have sufficient PK data to assess the primary objective of Part 1 of the study.

Part 2

Based on the above assumptions, 38 subjects are to be dosed to achieve 34 evaluable subjects for Cmax (PK parameter with highest CVw value). Evaluable subjects are defined as those subjects who have sufficient PK data to assess the primary objective of Part 2 of the study.

15.2 Data Management

Data management will be performed by Quotient Sciences.

All study data recorded in the source will be transcribed into a validated study database which has an audit trail to log all subsequent changes to the data. All queries will be resolved within the study database with the assistance of clinical staff and reference to the source data.

Adverse events and medications will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (v21.0) and the World Health Organisation Drug Dictionary Enhanced (WHO DDE) Drug Reference List (2017 or a more recent version), respectively. An independent coding review will also be performed within the Data Sciences department.

Clinical chemistry and haematology data (and other safety laboratory data) will be collected by a central laboratory (The Doctors Laboratory) and stored electronically in their clinical pathology system. The data will be transferred electronically to Quotient Sciences and all demographic details and sample dates will be cross-referenced with the corresponding data on the study database. All queries will be resolved with the assistance of laboratory staff, or if necessary, clinical staff.

The database will be closed after all queries have been resolved. The database will be locked when all criteria listed in the Data Management Plan are met.

Further details are addressed in the Data Management Plan.

15.3 Pharmacokinetic Data Analysis

The plasma concentration data for KD025 and metabolites KD025m1 and KD025m2, provided by Covance Laboratories Ltd, will be analysed by Quotient Sciences using Phoenix WinNonlin v8.0 or a more recent version (Certara USA, Inc., USA).

Plasma concentration data will be tabulated and plotted for each subject for whom concentrations are quantifiable. PK analysis of the concentration time data obtained will be performed using appropriate non-compartmental techniques to obtain estimates of the following PK parameters, where possible and appropriate:

Part 1

Primary Parameters

Cmax	Maximum observed drug concentration
AUC(0-last)	Area under the concentration vs time curve from time zero to the last sampling time with quantifiable drug
AUC(0-inf)	Area under the concentration vs time curve from time zero extrapolated to infinity

Secondary Parameters

Tlag	Elapsed time from dosing at which the drug was first quantifiable in a concentration vs time profile following oral dosing
Tmax	Elapsed time from dosing at which Cmax (the maximum drug concentration) was apparent
AUC(0-12)	Area under the concentration vs time curve from time zero to 12 h post-dose
AUC(0-24)	Area under the concentration vs time curve from time zero to 24 h post-dose
AUC%extrap	Percentage of AUC(0-inf) accounted for by extrapolation
Frel	Relative bioavailability of (test) to (reference) for Cmax, AUC(0-last) and AUC(0-inf), where test is the exposure in the presence of itraconazole (Period 2), rabeprazole (Period 3), rifampicin (Period 4) and reference is the exposure of KD025 administered alone (Period 1).
Lambda-z	Slope of the regression line passing through the apparent elimination phase in a concentration vs time plot
T1/2	Apparent elimination half-life
MRT	Mean residence time

CL/F	Apparent plasma clearance
Vd/F	Apparent volume of distribution based on the terminal phase
MPR	Molecular weight corrected metabolite to parent ratio

Part 2

Primary Parameters

Cmax (first dose)	Maximum observed drug concentration following the first dose
Cmax (second dose)	Maximum observed drug concentration following the second dose
AUC(0-24)	Area under the concentration vs time curve from time zero to 24 h post-dose

Secondary Parameters

Tlag	Elapsed time from dosing at which the drug was first quantifiable in a concentration vs time profile following oral dosing
Tmax	Elapsed time from dosing at which Cmax (the maximum drug concentration) was apparent
AUC(0-12)	Area under the concentration vs time curve from time zero to 12 h post-dose
AUC(12-24)	Area under the concentration vs time curve from 12 h to 24 h post-dose
AUC(0-last; first dose)	Area under the concentration vs time curve from time zero to the last sampling time with quantifiable drug from first dose
AUC(0-inf; first dose)	Area under the concentration vs time curve from time zero extrapolated to infinity from first dose
AUC%extrap	Percentage of AUC(0-inf) accounted for by extrapolation
Frel	Relative bioavailability of (test) to (reference) for Cmax (first dose and last dose), AUC(0-24), AUC(0-12), AUC(12-24), AUC(0-last) and AUC(0-inf), where test is the exposure in the presence of omeprazole (Period 2) and reference is the exposure of KD025 administered alone (Period 1).
Lambda-z	Slope of the regression line passing through the apparent elimination phase in a concentration vs time plot
T1/2	Apparent elimination half-life
MRT	Mean residence time
MPR	Molecular weight corrected metabolite to parent ratio

Further details of the PK data analysis will be included in the reporting and analysis plan (RAP).

15.4 Statistical Data Analysis

Statistical analysis and production of summary tables, figures and listings for this study will be performed by Quotient Sciences using the statistical package SAS (v9.4 or more recent version).

In general terms, categorical data (including treatment-emergent AEs) will be presented using counts and percentages, while continuous variables will be presented using the mean, median, standard deviation, minimum and maximum. Additional statistics will be

provided for PK-related data including coefficient of variation (CV%), geometric mean, geometric CV% and geometric n (ie the number of subjects with an observation that were included in the natural logarithmic transformation).

Descriptive summaries for all safety data (AEs, vital signs, ECGs and safety laboratory assessments) by regimen will be provided (including changes from baseline as required).

Descriptive summaries for all PK data by regimen will be provided.

Formal statistical analysis will be performed for KD025 and metabolites KD025m1 and KD025m2 PK parameters as follows:

- **Part 1:**Cmax, AUC(0-last) and AUC(0-inf)
- **Part 2:**
  - Primary: Cmax(first dose), Cmax(second dose) and AUC(0-24)
  - Secondary: AUC(0-12), AUC(12-24), AUC(0-last; first dose) and AUC(0-inf; first dose)

The PK parameters will undergo a natural logarithmic transformation and will be analysed using mixed effect modelling techniques. The mixed effects model will include terms for treatment as a fixed effect and subject as a random effect. Adjusted geometric mean ratios (GMRs) and 90% confidence intervals (CIs) for the adjusted GMRs will be provided for the comparisons of interest, where the ratios are defined as test/reference. A separate model will be fitted for each comparison of interest and will only include subjects who complete both periods for the relevant comparison of interest.

Part 1

- Period 2 (KD025 + itraconazole) vs Period 1 (KD025 alone)
- Period 3 (KD025 + rabeprazole) vs Period 1 (KD025 alone)
- Period 4 (KD025 + rifampicin) vs Period 1 (KD025 alone)

If the 90% CIs for each of KD025 (parent only) Cmax, AUC(0-last) and AUC(0-inf) lie within the acceptance interval of 70.00% to 143.00%, then the absence of an effect on PK can be concluded for the comparison of interest.

Part 2

- Period 2 (KD025 + omeprazole) vs Period 1 (KD025 alone)

If the 90% CIs for each of KD025 (parent only) Cmax(first dose), Cmax(second dose), and AUC(0-24) lie within the acceptance interval of 70.00% to 143.00%, then the absence of an effect on PK can be concluded for the comparison of interest.

Populations for analysis will be determined for safety and PK data after database lock when the relevant data are available using the criteria defined in the RAP; the RAP will be signed off prior to database lock.

Further details relating to the statistical analysis will be included in the study-specific RAP including the following:

- Criteria to be used to define each of the analysis populations

- Additional detail covering the analyses and/or description of primary and secondary analyses and safety data
- Handling of missing data, unused or spurious data
- Handling of data from withdrawn subjects

All safety and PK data will be listed.

15.5 Interim Analysis

No formal interim analyses are planned for this study.

16 Safety Reporting to Ethics Committees and Regulatory Authorities

16.1 Events Requiring Expedited Reporting

SUSARs (Section 14.4.2) are subject to expedited reporting to the MHRA, EMA and EC.

In addition to SUSARs, other safety issues may qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an IMP or that would be sufficient to consider changes in the IMPs administration or in the overall conduct of the study, for instance:

- an increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important
- SAEs that occur after the subject has completed the clinical study where the sponsor considers them to be a SUSAR
- new events related to the conduct of the study or the development of the IMPs and likely to affect the safety of the subjects, such as:
    - an SAE which could be associated with the study procedures and which could modify the conduct of the study
    - a major safety finding from a newly completed animal study (such as carcinogenicity)
    - any anticipated end or temporary halt of a study for safety reasons and conducted with the same IMPs in another country by the same sponsor

16.2 Urgent Safety Measures

If Quotient Sciences or any of its staff or contractors becomes aware of an actual or potential urgent safety issue, then the sponsor must be immediately contacted so that appropriate urgent safety measures can be agreed. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of subjects participating in a clinical study
- A serious risk to human health or potentially a serious risk to human health

An urgent safety issue may include issues with an investigational drug or comparators, study procedures, inter-current illness (including pandemic infections), concomitant medications, concurrent medical conditions or any other issues related to the safe conduct of the study or that pose a risk to study subjects.

In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, Quotient Sciences may take urgent safety measures before informing the sponsor, but the sponsor must be informed immediately after the hazard has resolved.

Quotient Sciences will take responsibility for informing appropriate competent authorities, and the EC.

16.3 Reporting

16.3.1 Reporting Serious Adverse Events

The investigator is required to notify the study sponsor within 24 h of becoming aware of the occurrence of an SAE or serious adverse reaction. A copy of the written report of the event should promptly be sent to the study sponsor for information purposes, in accordance with ICH guidelines for GCP.

Contact information for **SAE/SUSAR** reporting:

APCER Life Sciences, LLC
Fax: +44-3308084297
In the event of an issue with the fax line, forward SAE/SUSAR via email to:
ClinicalSAEReporting@kadmon.com

Additionally, the investigator will be able to contact the **medical monitor** at all times:

Sanjay Aggarwal, M.D.
Kadmon Corporation, LLC
55 Cambridge Parkway, Suite 300E
Cambridge, MA 02142
Telephone: Direct: 724-778-6129
Mobile: 857-253-8642
E-mail: Sanjay.Aggarwal@kadmon.com

16.3.2 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

It is the responsibility of the sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify the investigator of their decision as soon as possible.

16.3.3 Expedited Reporting of Events

It is the responsibility of the sponsor to determine whether an event requires expedited reporting and to notify the investigator of their decision as soon as possible.

Where expedited reporting is required, the following procedures should be followed.

Fatal or life-threatening SUSARs

It is the responsibility of the sponsor to report fatal or life-threatening SUSARs to the MHRA and EMA as soon as possible, but no later than 7 calendar days after they first became aware of the reaction.

The investigator is required to notify the EC of any SUSAR as soon as possible, but no later than 7 calendar days after they first became aware of the reaction. Any additional relevant information should be sent within 8 days of the report.

Other SUSARs

It is the responsibility of the sponsor to report other SUSARs to the MHRA and EMA as soon as possible, but no later than 15 calendar days after they first became aware of the reaction.

The investigator is required to notify the EC of any other SUSAR as soon as possible, but no later than 15 calendar days after they first became aware of the reaction.

16.3.4 Reporting of Urgent Safety Issues

Quotient Sciences is required to inform the appropriate competent authorities and the EC within 3 calendar days of the urgent safety issue.

16.4 Serious Breaches

It is the responsibility of the sponsor to notify the licensing authority of any serious breach, which is likely to affect, to a significant degree, the safety or mental integrity of the subjects of the study or the scientific value of the study.

All serious breaches will be notified to the MHRA within 7 days. The reporting will be performed by the party who suspects the serious breach.

17 Protocol Amendments and Deviations

17.1 Amendments

After the protocol has been submitted to the MHRA and/or EC, any amendment must be agreed by the investigator after discussion with the sponsor and will be formally documented.

All substantial amendments will be submitted to the MHRA and/or EC for an opinion as required by current regulations.

If the participant information sheet and ICF are updated as a result of the substantial amendment, the new approved versions will be used to re-consent currently enrolled subjects and must be provided to additional subjects prior to their entry into the study.

17.2 Protocol Deviations

The study must be conducted in accordance with the Clinical Protocol. Should a protocol deviation occur, it must be promptly assessed in order to decide whether any of these non-compliances should be reported to the MHRA as a serious breach of GCP and the Clinical Protocol.

Protocol waivers are not acceptable.

Deviations from the protocol will be recorded as noted by the clinical staff. If necessary, the sponsor will be informed of the deviation.

Any protocol deviations assessed as major will be discussed with the sponsor in order to determine if the withdrawal criteria stated in Section 8.3 have been met.

18 Regulatory

18.1 Compliance

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

- International Council for Harmonisation GCP Guidelines approved by the Committee for Medicinal Products for Human Use (CHMP) on 17 Jul 1996, which came into force on 17 Jan 1997, updated Jul 2002, integrated addendum E6(R2) dated 09 Nov 2016 [30]
- The Medicines for Human Use (Clinical Trials) Regulations. Statutory Instruments 2004 No. 1031 [31]
- The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2006 No. 1928 [32]
- The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations. Statutory Instruments 2006 No. 2984 [33]
- The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2008 No. 941 [34]

In addition, the study will be performed according to the ethical principles outlined in the World Medical Association Declaration of Helsinki and its amendments [35].

18.2 Ethics Approval

Prior to the initiation of the study, the protocol and associated documentation must be given a favourable opinion by an EC. A copy of this written approval and any correspondence with the EC will be provided to the sponsor.

18.3 MHRA Approval

Prior to the initiation of the study, the Clinical Trial Authorisation application must be approved by the MHRA. A copy of this approval and any correspondence with the MHRA will be available at the clinical and sponsor sites. A copy of the MHRA approval will be provided to the EC.

18.4 Source Data

A study-specific source document identification list will be finalised with the sponsor prior to the start of the clinical phase of the study. The document will identify what data should be considered source data for this study.

18.5 Declaration of the End of the Study

The definition of the end of the study is defined as the last visit of the last subject (eg follow-up assessment). Any changes to this definition will be notified as a substantial amendment (see Section 17.1).

The EC and MHRA should be notified in writing of the conclusion of the study within 90 days of the end of the study, or within 15 days if the study is terminated early, clearly explaining the reasons for the termination.

18.6 Document Storage and Archiving

All documentation and correspondence pertaining to the study (source data, raw data, letters etc) will be kept in accordance with the ICH guidelines for Good Clinical Practice 1996, updated 2002 (ICH GCP Section 4.9.5) [30], The Medicines for Human Use (Clinical Trials) Regulations 2004 [31] and The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 [32][33].

All study related documents will be retained for a minimum period of 5 years. After this time, the sponsor will be contacted to ascertain whether continued storage or destruction is required in accordance with current regulations.

19 Quality Control and Quality Assurance

Quality control of all data collected from this study will be performed in accordance with Quotient standard operating procedures. This study (or elements thereof) may be subject to Quotient quality assurance audit, in line with current internal auditing procedures. Similarly, the study (or elements thereof) may be subject to sponsor quality assurance audit.

19.1 Monitoring

GCP requires that studies are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. A study monitor, independent of Quotient Sciences, will be appointed to verify that the study is conducted in accordance with current GCP, regulatory requirements, the protocol and that the data are authentic, accurate and complete.

The investigator agrees to receive visits from a study monitor and provide assistance to verify protocol implementation, source data completion and transcription of data into the electronic case report form, document storage and AE reporting.

Quotient Sciences will extend the professional privilege of access to the subjects' clinical source documents to the study monitor, EC, regulatory bodies or other authorised personnel (eg auditor) for the purposes of source data verification.

Following completion of the study both study related documents and subject data may be sent to the sponsor at a location outside of the UK where data protection laws differ. In the interests of confidentiality, subjects will not be identified on any such documents or data, and specific subject consent for such a disposition will be obtained.

20 Finance and Insurance

The sponsor (Kadmon Corporation, LLC) has funded this study. A no-fault clinical trials insurance has been obtained by the sponsor. The sponsor insurance will compensate subjects in accordance with the Association of the British Pharmaceutical Industry Guidelines for Phase I Clinical Trials 2012 edition [36].

21 Publication

Please refer to the Master Services Agreement for information on publication.

Quotient Sciences shall have the right to publish the results of the research, subject to the sponsor's prior written consent, which shall not be unreasonably withheld or delayed. Following the receipt of such consent, Quotient Sciences shall submit a copy

of the proposed publication to the sponsor who shall have 30 days in which to request amendments thereto which, to the extent that such proposed amendments are reasonable, Quotient shall be obliged to incorporate prior to such publication.

The sponsor undertakes that, prior to publication of any information, article, paper, report or other material concerning the research, it will submit a copy of such publication to Quotient Sciences who shall have 30 days in which to request amendments thereto which, to the extent that such proposed amendment are reasonable, the sponsor shall be obliged to incorporate prior to such publication.

22 References

[1] Cohen IR. Discrimination and dialogue in the immune system. *Semin Immunol.* 2000; 12(3):215-9; discussion 57-344.

[2] Steinman L, Merrill JT, McInnes IB et al. Optimization of current and future therapy for autoimmune diseases. *Nat Med.* 2012; 18(1):59-65.

[3] Korn T, Bettelli E, Oukka M, et al. IL-17 and Th17 Cells. *Annu Rev Immunol.* 2009; 27:485-517.

[4] Sakaguchi S, Yamaguchi T, Nomura T, et al. Regulatory T cells and immune tolerance. *Cell.* 2008; 133(5):775-787.

[5] Leung T, Manser E, Tan L, et al. A novel serine/threonine kinase binding the Ras-related RhoA GTPase which translocates the kinase to peripheral membranes. *J Biol Chem.* 1995;270(49):29051-29054

[6] Nakagawa O, Fujisawa K, Ishizaki T, et al. ROCK-I and ROCK-II, two isoforms of Rho-associated coiled-coil forming protein serine/threonine kinase in mice. *FEBS Lett.* 1996; 392(2):189-193.

[7] Zanin-Zhorov A, Weiss JM, Nyuydzefe MS, et al. Selective oral ROCK2 inhibitor down-regulates IL-21 and IL-17 secretion in human T cells via STAT3-dependent mechanism. *Proc Natl Acad Sci U S A.* 2014; 111(47):16814-16819.

[8] Zhou Y, Huang X, Hecker L, et al. Inhibition of mechanosensitive signaling in myofibroblasts ameliorates experimental pulmonary fibrosis. *J Clin Invest.* 2013; 123(3):1096-1108.

[9] Herskowitz JH, Feng Y, Mattheyses AL, et al. Pharmacologic inhibition of ROCK2 suppresses amyloid-beta production in an Alzheimer's disease mouse model. *J Neurosci.* 2013; 33(49):19086-19098.

[10] Tybulewicz VL, Henderson RB. Rho family GTPases and their regulators in lymphocytes. *Nat Rev Immunol.* 2009; 9(9):630-644.

[11] Biswas PS, Gupta S, Chang E, et al. Phosphorylation of IRF4 by ROCK2 regulates IL-17 and IL-21 production and the development of autoimmunity in mice. *J Clin Invest.* 2010; 120(9):3280-3295.

[12] Isgro J, Gupta S, Jacek E, et al. Enhanced rho-associated protein kinase activation in patients with systemic lupus erythematosus. *Arthritis Rheum.* 2013; 65(6):1592-1602.

[13] Investigator's Brochure for KD025. Edition 7.0; 14 Apr 2017.

[14] Williams MP, Sercombe J, Hamilton MI, Pounder RE. A placebo-controlled trial to assess the effects of 8 days of dosing with rabeprazole versus omeprazole on 24-h intragastric acidity and plasma gastrin concentrations in young healthy male subjects. *Aliment Pharmacol Ther.* 1998.12(11):1079-1089.

[15] FDA Center for Drug Evaluation and Research: Draft Guidance: Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications Guidance for Industry. October 2017.

[16] Kantola T, Kivistö KT, Neuvonen PJ. Effect of itraconazole on the pharmacokinetics of atorvastatin. *Clin Pharmacol Ther.* 1998 Jul; 64(1):58-65.

[17] Lebrun-Vignes B, Archer VC, Diquet B, Let al. Effect of itraconazole on the pharmacokinetics of prednisolone and methylprednisolone and cortisol secretion in healthy subjects. *Br J Clin Pharmacol.* 2001; 51(5):443-450.

[18] Jalava KM, Olkkola KT, Neuvonen PJ Effect of itraconazole on the pharmacokinetics and pharmacodynamics of zopiclone. *Eur J Clin Pharmacol.* 1996;51(3-4):331-334

[19] Summary of Product Characteristics: Itraconazole 100 mg Capsules, hard. Actavis UK Ltd. Updated 24 Aug 2017. Accessed at https://www.medicines.org.uk/emc/medicine/24176.

[20] Hardin TC et al; PK of Itraconazole following oral administration to normal volunteers. *Antimicrobial Agents and Chemotherapy*. 1988; 32(9) 1310–1313.

[21] Baldwin CM and Keam SJ. Rabeprazole: A review of its use in the management of gastric acid-related diseases in adults. *Drugs* 2009; 69:1373-1401.

[22] Summary of Product Characteristics: Rabeprazole 20 mg Gastro-resistant Tablets. Actavis UK Ltd. Updated 05 May 2017. Accessed at https://www.medicines.org.uk/emc/medicine/27143/SPC/Rabeprazole+20mg+Gastro-resistant+Tablets/.

[23] Yamashita F et al. Modelling of Rifampicin-Induced CYP3A4 activation dynamics for the prediction of clinical drug-drug interactions from In vitro data; PLOS ONE 2013; 8(9) e70330.

[24] Summary of Product Characteristics: Rifadin 300 mg Capsules. Sanofi. Updated 22 Mar 2017. Accessed at: https://www.medicines.org.uk/emc/medicine/3960/PIL/Rifadin+300mg+Capsules.

[25] Highlights of prescribing information, PRILOSEC. AstraZeneca Pharmaceuticals LP. Last updated September 2012. Accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019810s096lbl.pdf

[26] Summary of. Product Characteristics: Omeprazole 20 mg Gastro-resistant tablets. DEXCEL-PHARMA Ltd. Last Updated 20 Feb 2017. Accessed at https://www.medicines.org.uk/emc/product/663/smpc

[27] FDA Guidance: Food effect, bioavailability and fed bioequivalence studies. 2002.

[28] EMA – Guidance on the investigation of bioequivalence. 20 January 2010.

[29] Heads of Medicines Agency: Clinical Trials Facilitation Group guidance. Accessed at: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

[30] International Council for Harmonisation Good Clinical Practice (GCP) Guidelines approved by the Committee for Medicinal Products for Human Use (CHMP) on 17 Jul 1996, which came into force on 17 Jan 1997, updated Jul 2002, integrated addendum E6(R2) dated 09 Nov 2016.

[31] The Medicines for Human Use (Clinical Trials) Regulations. Statutory Instruments 2004 No. 1031.

[32] The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2006 No. 1928.

[33] The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations. Statutory Instruments 2006 No. 2984.

[34] The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2008 No. 941.

[35] World Medical Association, Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects (and all subsequent amendments).

[36] Guidelines for Phase I Clinical Trials. Association of the British Pharmaceutical Industry Guidelines. London, UK; 2012 Edition (as amended 12/11/2014).

Appendix 1 Clinical Laboratory Parameters

Haematology	Clinical Chemistry	Virology	Urinalysis	Drugs of Abuse
Basophils	Alanine Aminotransferase (ALT)	Hepatitis B Surface Antigen	Bilirubin	Amphetamines
Eosinophils	Albumin	Hepatitis C Antibody	Blood	Barbiturates
Haematocrit	Alkaline Phosphatase	HIV Antibody	Glucose	Benzodiazepines
(Packed Cell Volume- PCV)	Aspartate Aminotransferase (AST)		Ketones	Cocaine
Haemoglobin	Bicarbonate		Leukocytes	Marijuana/Cannabis.
Lymphocytes	Bilirubin (Total)		Nitrites	Methadone
Mean Cell Haemoglobin (MCH)	Bilirubin (Direct) (only if Total is elevated)		pH	Methamphetamine/ Ecstasy
Mean Cell Haemoglobin Concentration (MCHC)	Calcium		Protein	Morphine/Opiates
Mean Cell Volume (MCV)	Chloride		Specific gravity	Phencyclidine
Monocytes	Creatine Kinase (CK)		Urobilinogen	Tricyclic Antidepressants
Neutrophils	Creatinine[a]		**At discretion of investigator based on urinalysis results**	
Platelet Count	Gamma Glutamyl Transferase (GGT)		Microbiology	
Red Blood Cell (RBC) Count	Glucose		Urine Microscopy	
White Blood Cell (WBC) Count	Glucose (Fasting)			
	Potassium			
	Phosphate (Inorganic)			
	Protein (Total)			
	Sodium			
	Urea			

[a] Creatinine clearance will be calculated at screening using the Cockcroft-Gault equation for eligibility purposes

Appendix 2 Part 1 Study Flow Chart

	Screening	Outpatient Visit	Periods 1 to 4																
			Admission[a]	Resident in Clinic														Discharge	Follow-up Visit[b]
Study Day	-28 to -2	-3 (Period 3) -9 (Period 4) -5 (Period 4)	-1	1												2		3	
				Pre-dose	Time Relative to KD025 Dosing (h)														
					0	0.5	1	1.5	2	3	4	5	6	8	10	12	24	36	48	
General Assessments																				
Informed Consent	X																		
Medical History	X		X																
Weight and Height	X		X[c]																
Vein Assessment	X																		
Carbon Monoxide Breath Test	X		X																
Drug Screen	X		X																
Alcohol Breath Test	X		X																
Non-IMP Administration[d]		X[d]	X[d]	X[d]	X[d]												X[d]		X[d]	
IMP Administration[e]					X															
Safety Assessments																				
Physical Examination	X																			X
Safety Labs[f]	X	X[g]	X[h]																X	X
Urinalysis	X	X[g]	X[h]																X	X
ECG[i]	X		X	X[i]					X		X[i]					X				X
Vital Signs[j]	X		X	X					X		X					X				X
Concomitant Medication	◄																			►
Adverse Events	◄																			►
PK Assessments																				
Plasma Samples for KD025 and metabolites KD025m1 and KD025m2				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Footnotes on next page

[a] Morning of Periods 1, 2 and 4, evening of Period 3
[b] A follow-up visit will take place 3 to 5 days post-final discharge
[c] Weight only at admission
[d] Itraconazole on Day 3 (of Period 1; or Day -7 of Period 2 if washout period is extended) and continuing from Day -6 to -1 (Period 2); rabeprazole from Day -3 to -1 (Period 3); rifampicin from Day -9 to -1 (Period 4). On Day -1, subjects will take itraconazole (Period 2) and rifampicin (Period 4) in the clinic after admission, and rabeprazole (Period 3) at home prior to admission.
[e] IMP will be administered in the fed state. Co-administration with NIMP in Periods 2 and 3; itraconazole will be administered at the same time as IMP in Period 2 (fed state) and rabeprazole will be administered approximately 2 h prior to IMP in Period 3 (fasted state)
[f] Haematology and clinical chemistry; virology and creatinine clearance at screening only
[g] Day -3 (Period 3) and Day -5 (Period 4) only
[h] Periods 1, 2 and 4 only
[i] Twelve-lead ECGs will be measured after the subject has been in the supine position for a minimum of 5 min. Single ECGs will be measured at all time points with the exception of pre-dose and 4 h post-dose on Day 1 of each period, during which times ECGs will be measured in triplicate, a minimum of 2 min apart
[j] Blood pressure, heart rate and oral temperature

Appendix 3 Part 2 Study Flow Chart

	S	O	Periods 1 and 2																										
			A[a]	Resident in Clinic																								D	FUP[b]
Study Day	-28 to -2	-3 (Period 2)	-1	1																							2	3	6-8
				Pre-dose	Time Relative to KD025 Dosing (h)																										
					0	0.5	1	1.5	2	3	4	5	6	8	10	12	12.5	13	13.5	14	15	16	17	18	20	22	24	36	48	
General Assessments																													
Informed Consent	X																												
Medical History	X		X																										
Weight and Height	X		X[c]																										
Vein Assessment	X																												
CO Breath Test	X		X																										
Drug Screen	X		X																										
Alcohol Breath Test	X		X																										
Non-IMP Administration[d]		X[d]	X[d]	X[d]																									
IMP Administration[e]					X											X													
Safety Assessments																													
Physical Examination	X																											X	
Safety Labs[f]	X	X[g]		X[h]																								X	X
Urinalysis	X	X[g]	X[h]																									X	X
ECG[i]	X		X	X[i]					X		X[i]					X[i]				X[i]									X
Vital Signs[j]	X		X	X					X		X					X				X									X
Concomitant Medication	←																											→	
Adverse Events	←																											→	
PK Assessments																													
Plasma Samples for KD025, KD025m1 and KD025m2				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

S: Screening, O: Outpatient visit, A: Admission, D: Discharge, FUP: Follow-up visit. Footnotes on next page

[a] Evening admission
[b] A follow-up visit will take place 3 to 5 days post-final discharge
[c] Weight only at admission
[d] Subjects will take omeprazole either at discharge from Period 1 or at a separate outpatient visit (Period 2, Day -3), then at home, once daily until Day -1 prior to admission.
[e] Subject will receive IMP BID (Q12h). IMP will be administered in the fed state. For Period 2 only, an NIMP (omeprazole) will be administered in the fasted state 2 h prior to planned morning IMP dose
[f] Haematology and clinical chemistry; virology and creatinine clearance at screening only
[g] Day -3 Period 2 only
[h] Periods 1 and 2
[i] Twelve-lead ECGs will be measured after the subject has been in the supine position for a minimum of 5 min. Single ECGs will be measured at all time points with the exception of pre-morning dose, 4 h post-morning dose, pre-evening dose and 2 h post-evening dose on Day 1 of each period, during which times ECGs will be measured in triplicate, a minimum of 2 min apart
[j] Blood pressure, heart rate and oral temperature