Protocol Number: KD025-107

Document Title: A Two-part, Non-randomised, Open-label Study to Evaluate the Effect of Itraconazole, Rifampicin, Rabeprazole, and Omeprazole on the Pharmacokinetics of KD025

Statistical Analysis Plan: Version 2.0

Date of Document: 09 Nov 2018

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REPORTING AND ANALYSIS PLAN

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
Sponsor Study Number: KD025-107

Sponsor: Kadmon Corporation, LLC
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Date of RAP: 09 Nov 2018

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1 Table of Contents

2 List of Abbreviations

ADaM	analysis data model
ADR	adverse drug reaction
AE	adverse event
ATC	anatomical therapeutic chemical
AUC	area under the curve
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
CDISC	Clinical Data Interchange Standards Consortium
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CSR	clinical study report
CV%	coefficient of variation
CVw	intra-subject variability
CYP	cytochrome P450
D	'substantial' decrease from baseline for vital signs parameters
DP	decimal places
ECG	electrocardiogram
Frel	relative bioavailability
GCP	good clinical practice
GMR	geometric mean ratio
h	hour
H	flag used for value that is above normal reference range
I	'substantial' increase from baseline for vital signs parameters

ICH	International Council on Harmonisation
IMP	investigational medicinal product
L	flag used for value that is below normal reference range
LLOQ	lower limit of quantification
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
MPR	molecular weight corrected metabolite to parent ratio
MW	molecular weight
n	number of subjects with an observation
N	number of subjects in the dataset
NA	not applicable
NC	not calculated
NIMP	non-investigational medicinal product
NR	no result
NS	no sample
PI	principal investigator
PK	pharmacokinetic
PPI	proton pump inhibitor
PT	preferred term
Q12h	every 12 hours
QC	quality control
QD	once daily
QTc	corrected QT
QTcB	QT interval corrected using Bazett's correction formula
QTcF	QT interval corrected using Fridericia's correction formula

RAP	Reporting and Analysis Plan
SAE	serious adverse event
SD	standard deviation
SDTM	study data tabulation model
SF	significant figures
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse events
WHO DDE	World Health Organisation Drug Dictionary Enhanced

3 Introduction

This document details the following for Quotient Sciences (Quotient) Study QSC200311 (KD025-107):

- criteria to be used for the definition of the analysis populations relating to safety and pharmacokinetic (PK) data
- handling of missing data
- proposed tables, figures and listings for demographic, dosing, PK and safety data
- methods for PK parameter estimation and the formal statistical analysis

This document has been compiled according to the Quotient standard operating procedure (SOP) "Production of Reporting and Analysis Plans" and has been written based on information contained in the final study protocol, Version 2.0, dated 25 Sep 2018.

3.1 Responsibilities

The Data Sciences Department at Quotient will be responsible for the production of the following items using Quotient SOPs: study data tabulation model (SDTM) and analysis data model (ADaM) datasets, safety output, PK parameter estimation and output, including all summary tables, figures and data listings, and formal statistical analysis; and the clinical study report (CSR).

Quotient will provide two sets of tables, data listings and figures during the study. One set will be provided post-database lock (draft) for Kadmon Corporation, LLC (Kadmon) to review. Quotient will be responsible for the quality control (QC) of all deliverables prior to the client review (Section 13.2). Following review, comments, and all post-review corrections, a final set will be produced for inclusion into the CSR.

3.2 Definitions

3.2.1 Subject Definitions

An evaluable subject is defined as a subject who has sufficient PK data to assess the primary objective of the relevant study part.

An enrolled subject is defined as those subjects who signed the informed consent, qualified per the inclusion/exclusion criteria and were allocated a subject number.

3.2.2 Definition of Treatments

KD025 (investigational medicinal product [IMP]), itraconazole (non-investigational medicinal product [NIMP]), rabeprazole (NIMP), rifampicin (NIMP) and omeprazole (NIMP) are referred to as study drugs in this Reporting and Analysis Plan (RAP).

Throughout the reporting of the study, period, day and treatments will be reported as detailed in Table 1 below.

Table 1 Study Treatments

Part	Period	Treatment Label	Day	IMP/NIMP Dose
1	1	KD025 200 mg QD	Day 1	KD025 200 mg QD
	2	KD025 200 mg QD + itraconazole	Day 3 (Period 1; or Day -7 of Period 2 if washout period is extended) and continuing from Day -6 to Day -1 (Period 2)	itraconazole 200 mg QD for 7 days
			Day 1	KD025 200 mg QD + itraconazole 200 mg QD on 8th day (ie Day 1)
			Day 2	itraconazole 200 mg QD on 9th day (ie Day 2)
	3	KD025 200 mg QD + rabeprazole	Day -3 to Day -1	rabeprazole 20 mg BID for 3 days
			Day 1	KD025 200 mg QD + rabeprazole 20 mg QD on 4th day (ie Day 1)
	4	KD025 200 mg QD + rifampicin	Day -9 to Day -1	rifampicin 600 mg QD for 9 days
			Day 1	KD025 200 mg QD on 10th day (ie Day 1)
2	1	KD025 200 mg BID	Day 1	KD025 200 mg BID (Q12h) on a single day
	2	KD025 200 mg BID + omeprazole	Starting on Day 3 (Period 1, or Day -3 of Period 2 if washout period is extended) and continuing on Day -2 and Day -1 (Period 2)	omeprazole 20 mg QD for 3 days
			Day 1	KD025 200 mg BID (Q12h) on a single day + omeprazole 20 mg QD

QD: once daily; BID: twice daily; Q12h: every 12 hours
KD025 (IMP), itraconazole (NIMP), rabeprazole (NIMP), rifampicin (NIMP) and omeprazole (NIMP) are referred to as study drugs in this RAP

In addition, KD025 alone (Period 1 of each study part) will be described as the reference treatment and KD025 plus NIMP (Periods 2 to 4 of Part 1 and Period 2 of Part 2) will be described as the test treatments.

3.2.3 Definition of Visits

For clinical data, visits will be referred to as Day throughout this document and will be referred to as follows:

Part 1

- Day -28 to Day -2 of Period 1 (Screening)
- Outpatient Visits (Day -3, Period 3; Day -9, Period 4; and Day -5, Period 4)
- Day -1 (Admission) and Day 1 through to Day 3 (Discharge) for each period
- Follow-up (3 to 5 days post-final discharge)

Part 2

- Day -28 to Day -2 of Period 1 (Screening)

- Outpatient Visit (Day -3, Period 2)
- Day -1 (Admission) and Day 1 through to Day 3 (Discharge) for each period
- Follow-up (3 to 5 days post-final discharge)

Time points within these days are detailed in the schedule of assessments in Appendix 1 for Part 1 and in Appendix 2 for Part 2.

Baseline is defined as nominally the last measurement recorded prior to the first dose of investigational medicinal product (IMP) in each study period. These will be defined for each safety endpoint in the relevant reporting sections.

4 Objectives

4.1 Primary Objective

The primary objective of Part 1 of this study is:

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

The primary objective of Part 2 of this 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

4.2 Secondary Objective

The secondary objective of Part 1 of this 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 this 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

4.3 Study Endpoints

4.3.1 Primary Endpoints

The primary endpoints of Part 1 of the study are:

- 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 endpoints of Part 2 of the study are:

- 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)

4.3.2 Secondary Endpoints

The secondary endpoints of Part 1 of the study are:

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

The secondary endpoints of Part 2 of the study are:

- 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

5 Study Design

5.1 Brief Description

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

5.1.1 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 proton pump inhibitor (PPI), rabeprazole, in Period 3; and a strong CYP3A4 inducer, rifampicin, in Period 4.

It is planned to enroll 40 subjects to ensure there are 34 evaluable subjects. A subject will be considered evaluable if they have sufficient data for evaluation of the primary objective of Part 1 of the study ie 34 subjects for each comparison of interest as defined in Section 9.2.4.

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.

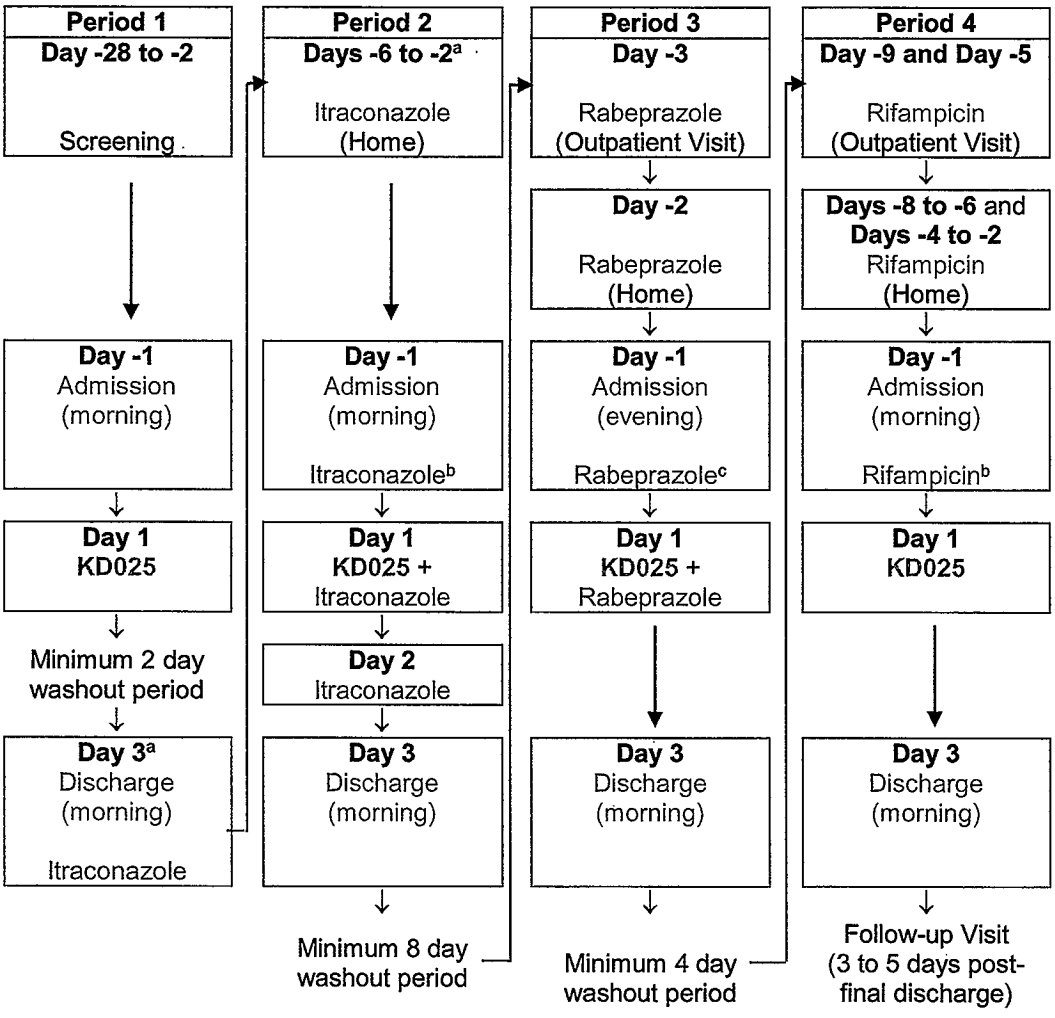
Prior to being admitted to the clinic in Periods 2 to 4, subjects will take multiple doses of the following NIMPs; itraconazole on Day 3 (Period 1; or Day -7 of Period 2 if washout period is extended) and continuing from Day -6 to -1 (Period 2); rabeprazole from Day -3 to -1 (Period 3); rifampicin from 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 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.

The Part 1 study design is presented in Figure 1 below.

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

5.1.2 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.

It is planned to enroll 38 subjects to ensure there are 34 evaluable subjects. A subject will be considered evaluable if they have sufficient data for evaluation of the primary objective of Part 2 of the study.

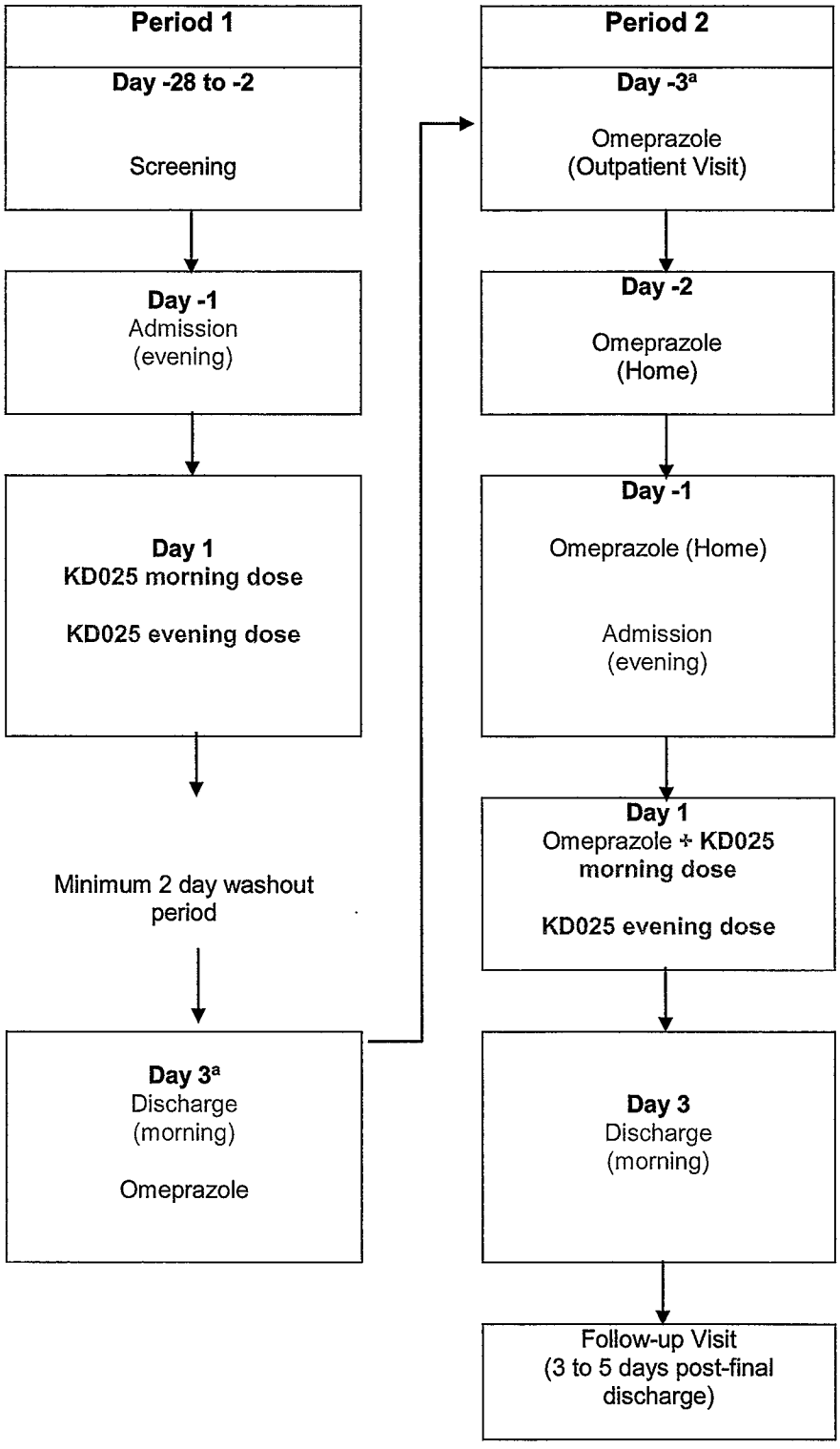
All subjects will undergo preliminary screening procedures to determine their eligibility for the study at the screening visit (Day -28 to Day -2 of Period 1). For each period, subjects will be admitted to the clinic on the evening of the day prior to IMP administration (Day -1) for confirmation of eligibility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

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.

5.2 Study Sample Size

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).

It should be noted that 34 subjects are required for each comparison of interest and therefore replacement subjects may be utilised, see Section 5.3 for further details.

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).

5.3 Randomisation (including Replacement Subjects)

This study is non-randomised.

Part 1

Subject numbers will be allocated on the morning of first dose 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).

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. 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 (Periods 2 to 4) not already completed by the replaced subject.

Part 2

Subject numbers will be allocated on the morning of first dose 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).

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. 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.

5.4 Blinding Issues

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

6 Populations for Analysis

6.1 Safety Population

The safety populations for each of Parts 1 and 2 will include all subjects who have received at least 1 dose of study drug (ie KD025, itraconazole, rabeprazole, rifampicin or omeprazole) in that study part.

The safety populations will be confirmed by Quotient with approval from Kadmon after database lock and will be used for the analysis of demographic and baseline characteristics, and all safety variables.

6.2 Pharmacokinetic Population

The PK population will be defined separately for Part 1 and Part 2 and will include all subjects who have received at least one dose of IMP and who have a minimum of 1 valid post-dose analytical result for PK parameter estimation and who satisfy the following criteria for at least one profile:

- no missing samples at critical time points eg around the Cmax
- no relevant protocol deviations which may impact the study objectives with respect to the PK endpoints and may include any dosing deviations relating to IMP or NIMP
- no relevant AEs such as vomiting which suggest that the dose was not absorbed for a particular subject

The PK populations will be confirmed by Quotient with approval from Kadmon following derivation of all PK parameter estimates.

All subjects will be used for the PK data listings and the PK population will be used for the provision of PK summary statistics, summary tables and figures.

If required, PK analysis datasets will be documented by Quotient with approval from Kadmon at the same time as the PK population. The PK analysis datasets will be a subset of the relevant PK population and will include subjects with sufficient valid PK profiles and who have completed both the test and reference periods for the following pairwise treatment comparisons (test versus reference) to be made ie one PK dataset per comparison):

Part 1

- KD025 200 mg QD + itraconazole (Period 2) vs KD025 200 mg QD alone (Period 1) ie PK Dataset 1
- KD025 200 mg QD + rabeprazole (Period 3) vs KD025 200 mg QD alone (Period 1) ie PK Dataset 2
- KD025 200 mg QD + rifampicin (Period 4) vs KD025 200 mg QD alone (Period 1) ie PK Dataset 3

Part 2

- KD025 200 mg BID + omeprazole (Period 2) vs KD025 200 mg BID alone (Period 1) ie PK Dataset 4

In addition, any dosing deviations relating to any of the NIMPs will be reviewed to assess potential impact on the study objectives ie if a subject has not received all NIMP doses then they may be excluded from the relevant PK analysis dataset.

The PK analysis dataset(s) may be used to generate additional summary tables and figures for the PK concentration and PK parameter data and will be used for the formal statistical analysis of the PK parameter data.

Requirements for additional summary tables and figures will be documented at the same time as the PK population.

7 Subject Disposition, Demographics and Baseline Characteristics

No formal statistical testing will be performed on subject disposition, or on demographic or baseline data. Summaries of subject disposition and analyses populations will be based on all subjects and summaries of all other data described in this section will be based on the safety population, unless otherwise stated.

Separate summary tables and listings will be produced for each study part.

If the PK analysis datasets differ from the safety populations, demographic and baseline data summaries may also be produced for the PK datasets.

7.1 Screening Failures

Data for subjects who have failed screening will not be databased and therefore will not be included in any analyses or any of the tables, figures or data listings.

7.2 Subject Disposition and Withdrawals

The number and percentage of subjects enrolled, dosed (overall and in each period), completed and discontinued will be presented overall. If any subjects discontinued from

the study early then the number of subjects for each reason for discontinuation will be presented overall. However, if none of the subjects discontinued from the study early, then the reasons for discontinuation will not be populated in the summary table.

Subject disposition and withdrawal data will be listed including details of informed consent.

Protocol deviations and any violations of the inclusion/exclusion criteria will also be listed.

7.3 Analysis Populations

A summary table will be produced detailing the number and percentage of subjects in each analysis population presented overall. The reasons for exclusion from each population will also be included in the summary.

Details of subjects included and excluded in the different analysis populations will be listed.

7.4 Analysis Datasets

If applicable, a summary table will be produced detailing the number and percentage of subjects in each PK analysis dataset presented by treatment. The tables will be based on the relevant population the dataset is a subset of (ie the PK population). The reasons for exclusion from each dataset will also be included in the summary.

Details of subjects included and excluded in the different analysis datasets will be listed.

7.5 Demographic Characteristics and Lifestyle Details

Demographic data (date of birth, sex, race, height [cm], weight [kg] and body mass index [BMI; [kg/m^2]) will be recorded at screening.

Age will be calculated using the following formula:

$$\text{Age (years)} = \frac{\text{Date of first dose of IMP} - \text{date of birth}}{365.25}$$

and will be rounded down to the nearest year (using the SAS Software floor function).

Summary statistics (mean, standard deviation [SD], median, minimum, maximum and number of subjects with an observation [n]) will be presented for age, height, weight and BMI at screening by treatment and overall. The number and percentage of subjects will be presented by treatment for race and sex. The denominator for the percentage is all subjects in the safety population for each treatment. If any values are missing, a "missing" row will be presented on the table.

Lifestyle details (ie smoking history [does the subject smoke, use e-cigarettes or use nicotine replacement products?] and alcohol consumption) will be summarised by treatment and overall.

Demographic and lifestyle data for all subjects will be listed.

7.6 Medical/Surgical History

Medical/surgical history will be recorded for each subject at the screening visit and updated at admission. All medical/surgical history data will be listed by subject.

7.7 Prior and Concomitant Medication

Medications (drug name) will be coded using the World Health Organisation Drug Dictionary Enhanced (WHO DDE) Drug Reference List (2017 version or more recent version) using the following Anatomical Therapeutic Chemical (ATC) classification codes:

- drug name
- preferred name (code)
- therapeutic subgroup (ATC 2nd level code)
- chemical subgroup (ATC 4th level code)

Prior medications are defined as medications that start and stop prior to the first dose of IMP. All other medications will be defined as concomitant medications including those that start prior to first dose of IMP and continue thereafter. Any medications with an unknown start or stop date will be assumed to be concomitant medications unless a partial start or stop date indicates otherwise.

All medications, including coded terms, will be listed. One combined data listing of prior and concomitant medications will be provided. All prior medications as defined above will be flagged with a "#" symbol. Within this flagged group medications that started after screening and stopped before dosing of IMP will also be flagged using a "*" symbol.

7.8 Other Baseline Characteristics

All other baseline characteristics, as listed below, at screening and on admission (unless otherwise stated) for each period (as appropriate) will be listed by subject for all subjects:

- alcohol breath test
- carbon monoxide breath test
- urine drug screen
- virology (screening only)
- creatinine clearance (screening only)

8 Efficacy

Not applicable.

9 Pharmacokinetics

9.1 Pharmacokinetic Parameter Estimation

The PK parameters for KD025 and metabolites KD025m1 and KD025m2 in plasma will be estimated where possible and appropriate for each subject and treatment by non-compartmental analysis methods using Phoenix WinNonlin software (v8.0 or a more recent version, Certara USA, Inc., USA).

9.1.1 Definition of Pharmacokinetic Parameters

Plasma PK parameter definitions are provided in Table 2 for Part 1 primary parameters, in Table 3 for Part 1 secondary parameters, in Table 4 for Part 2 primary parameters and in Table 5 for Part 2 secondary parameters.

Table 2 Part 1 Primary Plasma Pharmacokinetic Parameters and Rounding Specifications

Parameter	Definition	Unit	DP or SF	No. of DP/SF
Cmax	Maximum observed concentration	mass unit/mL	SF	3
AUC(0-last)	Area under the curve from time zero to the last measurable concentration	mass unit.h/mL	SF	3
AUC(0-inf)	Area under the curve from time zero extrapolated to infinity	mass unit.h/mL	SF	3

SF=significant figures

Table 3 Part 1 Secondary Plasma Pharmacokinetic Parameters and Rounding Specifications

Parameter	Definition	Unit	DP or SF	No. of DP/SF
Tlag	Time prior to the first measurable (non-zero) concentration	h	DP	2
Tmax	Time of maximum observed concentration	h	DP	2
AUC(0-12)	Area under the concentration vs time curve from time zero to 12 h post-dose	mass unit.h/mL	SF	3
AUC(0-24)	Area under the curve from time zero to 24 h post dose	mass unit.h/mL	SF	3
AUC%extrap	Percentage of AUC(0–inf) extrapolated beyond the last measurable concentration	%	DP	2
T1/2	Apparent elimination half-life	h	DP	2
Lambda-z	Slope of the apparent elimination phase	1/h	DP	4
CL/F	Apparent total body clearance calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown	mL/min	SF	3
Vd/F	Apparent volume of distribution based on the terminal phase calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown	L	SF	3
MRT(0-last)	Mean residence time from time zero to the last measurable concentration after extravascular administration	h	DP	2
MRT(0-inf)	Mean residence time extrapolated to infinity after extravascular administration	h	DP	2
Frel Cmax	Relative bioavailability based on Cmax	%	DP	2
Frel AUC(0-last)	Relative bioavailability based on AUC(0-last)	%	DP	2
Frel AUC(0-inf)	Relative bioavailability based on AUC(0-inf)	%	DP	2
MPR Cmax	Metabolite to parent ratio based on Cmax	n/a	DP	2
MPR	Metabolite to parent ratio based on	n/a	DP	2

Parameter	Definition	Unit	DP or SF	No. of DP/SF
AUC(0-last)	AUC(0-last)			
MPR AUC(0-inf)	Metabolite to parent ratio based on AUC(0-inf)	n/a	DP	2
Lambda-z Lower*	Lower limit on time for values to be included in the calculation of Lambda-z	h	DP	2
Lambda-z Upper*	Upper limit on time for values to be included in the calculation of Lambda-z	h	DP	2
R^2*	Coefficient of determination	n/a	DP	4

DP=decimal places
SF=significant figures
*=these values should be listed but omitted from the descriptive statistics
n/a=not applicable

Table 4 Part 2 Primary Plasma Pharmacokinetic Parameters and Rounding Specifications

Parameter	Definition	Unit	DP or SF	No. of DP/SF
Cmax(first dose)	Maximum observed concentration following the first dose	mass unit/mL	SF	3
Cmax(second dose)	Maximum observed concentration following the second dose	mass unit/mL	SF	3
AUC(0-24)	Area under the curve from time zero to 24 h post dose	mass unit.h/mL	SF	3

SF=significant figures

Table 5 Part 2 Secondary Plasma Pharmacokinetic Parameters and Rounding Specifications

Parameter	Definition	Unit	DP or SF	No. of DP/SF
Tlag	Time prior to the first measurable (non-zero) concentration	h	DP	2
Tmax	Time of maximum observed concentration	h	DP	2
AUC(0-12)	Area under the concentration vs time curve from time zero to 12 h post-dose	mass unit.h/mL	SF	3
AUC(12-24)	Area under the concentration vs time curve from 12 h to 24 h	mass unit.h/mL	SF	3
AUC(0-last)*	Area under the curve from time zero (i.e. prior to first dose) to the last measurable concentration	mass unit.h/mL	SF	3
AUC(0-inf)**	Area under the curve from time zero (i.e. prior to first dose) extrapolated to infinity	mass unit.h/mL	SF	3
AUCextrap	Percentage of AUC(0–inf) extrapolated beyond the last measurable concentration	%	DP	2
T1/2	Apparent elimination half-life	h	DP	2
Lambda-z	Slope of the apparent elimination phase	1/h	DP	4
MRT(0-last)	Mean residence time from time zero to the last measurable concentration after extravascular administration	h	DP	2
MRT(0-inf)	Mean residence time extrapolated to infinity after extravascular administration	h	DP	2
Frel Cmax(first dose)	Relative bioavailability based on Cmax(first dose)	%	DP	2

Parameter	Definition	Unit	DP or SF	No. of DP/SF
Frel Cmax(second dose)	Relative bioavailability based on Cmax(second dose)	%	DP	2
Frel AUC(0-24)	Relative bioavailability based on AUC(0-24)	%	DP	2
Frel AUC(0-12)	Relative bioavailability based on AUC(0-12)	%	DP	2
Frel AUC(12-24)	Relative bioavailability based on AUC(12-24)	%	DP	2
Frel AUC(0-last)	Relative bioavailability based on AUC(0-last)	%	DP	2
Frel AUC(0-inf)	Relative bioavailability based on AUC(0-inf)	%	DP	2
MPR Cmax (first dose)	Metabolite to parent ratio based on Cmax(first dose)	n/a	DP	2
MPR Cmax (second dose)	Metabolite to parent ratio based on Cmax(second dose)	n/a	DP	2
MPR AUC(0-last)	Metabolite to parent ratio based on AUC(0-last)	n/a	DP	2
MPR AUC(0-inf)	Metabolite to parent ratio based on AUC(0-inf)	n/a	DP	2
Lambda-z Lower***	Lower limit on time for values to be included in the calculation of Lambda-z	h	DP	2
Lambda-z Upper***	Upper limit on time for values to be included in the calculation of Lambda-z	h	DP	2
R^{2***}	Coefficient of determination	n/a	DP	4

DP=decimal places
SF=significant figures
*=this parameter was referred to as AUC(0-last; first dose) in the protocol
**=this parameter was referred to as AUC(0-inf; first dose) in the protocol
***= these values should be listed but omitted from the descriptive statistics
n/a=not applicable

9.1.2 Rules for Pharmacokinetic Parameter Estimation

The imputation of non-numerical or negative values reported in the input dataset will be performed as follows:

- pre-dose sample times will be entered as zero
- values that are below the limit of quantification (BLQ) obtained prior to the Cmax will be entered as zero
- values that are BLQ after the Cmax will be treated as missing
- should partial AUCs be required then values that are BLQ after Cmax may be imputed as zero for these partial areas if lambda-z cannot be determined
- values that are quantifiable after at least 2 consecutive BLQ values after Cmax will be treated as missing for the calculation of PK parameters
- values that are reported as "No Result" (NR) or "No Sample" (NS) etc. will be treated as missing

PK parameters will be estimated using standard Phoenix WinNonlin methods, details of which may be found in the documentation accompanying the WinNonlin software package. The following constraints will apply:

Parameter Estimation	Constraint
Sampling times	Actual
Trapezoidal method	Linear up/Log down
Number of points used for lambda-z	At least 3, not including Cmax
Minimum requirements for AUC	At least 3 consecutive quantifiable concentrations
Dose	Nominal
Rounded dose level	0 decimal places

Where possible, the terminal elimination rate constant (lambda-z) will be calculated for all subjects. The value of lambda-z will be determined by the slope of the regression line of the natural log transformed concentrations vs time.

The choice of data points for determination of lambda-z will be reviewed by the pharmacokineticist who may adjust the selection in order to provide a more appropriate fit. The choice of data points for determination of lambda-z for each profile will be confirmed following a documented peer review.

Relative Bioavailability (Frel) will be calculated for individual subjects as follows:

$$\text{Frel} = \left\{\frac{\text{AUC or Cmax (test)}}{\text{AUC or Cmax (reference)}}\right\} \times 100$$

Part 1

Frel will be calculated using Cmax, AUC(0-last) and AUC(0-inf). If for any reason the AUC(0-inf) is not calculable then an alternative AUC over a partial area may be used.

The following Frel comparisons will be made:

- KD025 200 mg QD + itraconazole (Period 2) vs KD025 200 mg QD alone (Period 1)
- KD025 200 mg QD + rabeprazole (Period 3) vs KD025 200 mg QD alone (Period 1)
- KD025 200 mg QD + rifampicin (Period 4) vs KD025 200 mg QD alone (Period 1)

Part 2

Frel will be calculated using Cmax(first dose), Cmax(second dose), AUC(0-24), AUC(0-12), AUC(12-24), AUC(0-last) and AUC(0-inf). If for any reason the AUC(0-inf) is not calculable then an alternative AUC over a partial area may be used.

The following Frel comparison will be made:

- KD025 200 mg BID + omeprazole (Period 2) vs KD025 200 mg BID alone (Period 1)

Metabolite to parent ratios (MPR) after a single dose administration will be calculated as follows using Cmax and AUC(0-inf) for Part 1 and Cmax(first dose), Cmax(second dose) and AUC(0-inf) for Part 2. If for any reason the AUC(0-inf) is not calculable then an alternative AUC such as AUC(0-last) or AUC over a partial area may be used:

$$\text{MPR} = \frac{\text{AUC or Cmax (metabolite)}}{\text{AUC or Cmax (parent)}} \times \frac{\text{MW (parent)}}{\text{MW(metabolite)}}$$

Correcting for molecular weight (MW):

- Parent MW = 452.52 g/mole
- KD025m1 MW = 410.44 g/mole
- KD025m2 MW = 411.42 g/mole

9.2 Pharmacokinetic Parameter Reporting Specifications

The following flags/footnotes may be applied to the PK parameters:

Flag	Footnote
a	Rsq of regression was <0.9
b	Period used for regression analysis was less than 2-fold the calculated half-life
c	Extrapolated portion of AUC(0-inf) >20%
d	Insufficient post-Cmax data points for estimation of lambda-z
e	Entire profile BLQ, no pharmacokinetic parameters could be calculated

In the event that a reliable lambda-z cannot be determined or the extrapolated portion of AUC(0-inf) >20%, then the parameter estimates derived using lambda-z and/or AUC(0-inf) may be deemed unreliable and excluded from the summary statistics and formal statistical analysis.

Additional flags may be applied based on emerging data.

Separate summary tables, figures and listings will be produced for each study part.

9.2.1 Bioanalytical and Pharmacokinetic Summary Tables

Summary statistics (ie mean, SD, coefficient of variation [CV%], median, minimum, maximum, n, geometric mean, geometric SD, geometric CV% and geometric n) will be calculated for plasma concentrations by time point for each treatment and analyte. This data will be summarised for the parent KD025 and its metabolites (KD025m1 and KD025m2) on different tables.

Imputation of non-numerical values reported in the plasma concentration data (ie values that are BLQ), will be entered as zero for the determination of summary statistics with the exception of geometric mean parameters where BLQ values will be imputed as half the LLOQ value (except for pre-dose samples on Day 1 which will not be summarised). Data recorded as NR or NS will be handled as missing, ie no assumption will be made about the actual concentration. If applicable, data recorded as not calculated (NC) will be handled as missing.

Concentration data recorded as NR (as by the bioanalytical laboratory) will be queried to ascertain any underlying cause and further imputation may be made if appropriate (eg concentrations above the upper limit of quantification may be set to the upper limit or diluted for reanalysis as appropriate).

Summary statistics (ie mean, SD, CV%, median, minimum, maximum and n) will be presented for all PK parameters for plasma for each treatment and analyte. Also geometric mean, geometric SD, geometric CV% and geometric n will be presented for all PK parameters (except Tlag and Tmax) for each treatment and analyte. This data will be summarised for the parent KD025 and its metabolites (KD025m1 and KD025m2) on different tables.

9.2.2 Bioanalytical and Pharmacokinetic Figures

These data will be plotted separately for the parent KD025 and its metabolites KD025m1 and KD025m2 and will use the PK population throughout unless otherwise stated.

Arithmetic mean plasma concentration vs time curves will be produced on a linear/linear scale and error bars for ± arithmetic SD will be included on the plots.

Geometric mean plasma concentration vs time curves will be produced on a $\log_{10}$/linear scale. Error bars will be included on these plots, where error bars are (geometric mean ×/÷ geometric SD).

Both arithmetic mean and geometric mean plots will be produced for the following:

Part 1

- all four treatments on the same plot, with separate plots for KD025 and its metabolites (3 plots)
  - each plot will represent an analyte: KD025 (parent), KD025m1 (metabolite 1), KD025m2 (metabolite 2)
  - 4 lines on each plot with each line representing a treatment

- both treatments for the relevant treatment comparisons on the same plot, with separate plots for each comparison and for KD025 and its metabolites (9 plots)
  - 3 treatment comparisons (see Section 9.1.2), 3 plots for each treatment comparison
  - each plot representing a study comparison: itraconazole effect (Period 2 vs Period 1), rabeprazole effect (Period 3 vs Period 1) and rifampicin effect (Period 4 vs Period 1) using the appropriate PK analysis dataset
  - 2 lines on each plot with each line representing a treatment

- KD025 and its metabolites on the same plots, with separate plots for each treatment (4 plots)
  - each plot representing a treatment
  - 3 lines on each plot – with each line representing an analyte: KD025 (parent), KD025m1 (metabolite 1), KD025m2 (metabolite 2)

Part 2

- both treatments on the same plot, with separate plots for KD025 and its metabolites (3 plots)
  - each plot will represent an analyte: KD025 (parent), KD025m1 (metabolite 1), KD025m2 (metabolite 2)
  - 2 lines on each plot with each line representing a treatment

- KD025 and its metabolites on the same plots, with separate plots for each treatment (2 plots)
  - each plot representing a treatment
  - 3 lines on each plot – with each line representing an analyte: KD025 (parent), KD025m1 (metabolite 1), KD025m2 (metabolite 2)

Each treatment and analyte will be represented on these plots with a different symbol and a legend will be included on the plots to define the symbols used. If judged to aid interpretation, plots including error bars may also be produced without error bars.

Spaghetti plots of individual plasma concentrations against actual sampling times after dosing will be produced on both a linear/linear and log10/linear scale for each treatment and analyte separately. These data will be plotted for the parent KD025 and its metabolites KD025m1 and KD025m2 on different plots.

Plots of plasma concentrations against actual sampling times after dosing for each analyte will also be produced separately for each individual subject with each treatment for that subject overlaid on the same plot (parent KD025 and its metabolites KD025m1 and KD025m2 on different plots). Plots of individual plasma concentrations against actual sampling times after dosing for each treatment will also be produced separately for each individual subject with all analytes for that subject overlaid on the same plot. These plots will be produced on both a linear/linear and log10/linear scale.

For all plots on a linear/linear scale, concentration values reported as BLQ will be set to zero. For all plots on a log 10/linear scale then concentration values reported as BLQ will be set to ½ x LLOQ (except for pre-dose samples on Day 1 which will not be plotted).

9.2.3 Bioanalytical and Pharmacokinetic Listings

The sample collection data (eg collection times) for PK samples will be listed. In addition, all concentration data and PK parameters will be listed on a per subject basis. Any flags used will be listed with the appropriate definition. BLQ values will be reported as BLQ in the data listings.

9.2.4 Statistical Analysis of Pharmacokinetic Parameters

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) and AUC(0-inf)

The PK parameters will undergo a natural logarithmic transformation and will be analysed using mixed effect modelling techniques. The model will include terms for treatment fitted as a fixed effect and subject fitted as a random effect.

The following pairwise treatment comparisons *(test versus reference)* are of interest:

Part 1

- KD025 200 mg QD + itraconazole (Period 2) vs KD025 200 mg QD alone (Period 1)

- KD025 200 mg QD + rabeprazole (Period 3) vs KD025 200 mg QD alone (Period 1)
- KD025 200 mg QD + rifampicin (Period 4) vs KD025 200 mg QD alone (Period 1)

Part 2

- KD025 200 mg BID + omeprazole (Period 2) vs KD025 200 mg BID alone (Period 1)

Only subjects who complete both the test and reference treatments within the relevant periods will be included in the statistical analysis. Furthermore for AUC(0-inf) only, a subject must have reliable estimates of AUC(0-inf) for both test and reference treatments within the relative periods to be included in the statistical analysis. If the number of subjects with reliable estimates for both periods is less than 17 (ie less than 50% of planned number of evaluable subjects) then no formal statistical analysis of AUC(0-inf) will be performed ie descriptive summaries only.

The adjusted means including differences from the pairwise comparisons and their associated 90% CIs obtained from the model will be back transformed on the log scale to obtain adjusted geometric mean ratios (GMRs) and 90% confidence intervals (CIs) of the ratios.

In addition, 2 one-sided tests will be performed to obtain the p-value for the test of the null hypothesis of non-equivalence. The one-sided tests will test the following hypotheses against the log transformed lower and upper limits of the equivalence acceptance range.

- Test against the lower limit
  - H_{01}: $\mu_T - \mu_R < \ln(0.7)$
  - H_{11}: $\mu_T - \mu_R \geq \ln(0.7)$

- Test against the upper limit
  - H_{02}: $\mu_T - \mu_R > \ln(1.43)$
  - H_{12}: $\mu_T - \mu_R \leq \ln(1.43)$

where H_{01} and H_{02} are the null hypothesis (ie test and reference not bioequivalent) for the lower and upper limits respectively and H_{11} and H_{12} are the alternative hypothesis (ie test and reference are bioequivalent) for the lower and upper limits respectively. $\mu_T - \mu_R$ is the difference of the log transformed mean values for test and reference. Each one-sided test will be performed at a 5% significance level ie a p-value of less than 5% indicates there is evidence to reject the null hypothesis of non-equivalence.

Adjusted GMRs and 90% CIs for the adjusted GMRs for the pairwise treatment comparisons listed above, where the ratio is defined as test/reference will be presented. In addition, the largest p-value from the 2 one-sided tests and the intra-subject variability values (denoted as CVw in the results table(s)) will also be presented.

The intra-subject variability values will be calculated for all treatments combined and are obtained from the residual term from the SAS Software output. These values are calculated as follows:

$$CVw = 100 \times [exp(Mean\ Square\ Error) - 1]^{1/2}$$

For Part 1, 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 the PK can be concluded for the comparison of interest.

For Part 2, 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 the PK can be concluded for the comparison of interest.

The model will be fitted using the SAS Software procedure PROC MIXED, the method will specified as Restricted Maximum Likelihood and the denominator degrees of freedom for the fixed effects will be calculated using Kenward and Roger's method [1]. The following is an example of the SAS Software code that will be used:

```
PROC MIXED DATA=<input dataset name> METHOD=REML ORDER=INTERNAL;
           CLASS SUBJIDN TRTAN ;
           MODEL LVAR = TRTAN / OUTP=PRED DDFM=KR;
           RANDOM SUBJIDN;
           ESTIMATE <relevant pairwise treatment comparisons> / CL ALPHA=0.10;
           LSMEANS TRTAN / ALPHA=0.10;
           ODS OUTPUT LSMEANS=MEANS ESTIMATES=EST COVPARMS=CVW;
RUN;
```

where

- LVAR is the natural log transformed PK parameter of interest
- SUBJIDN is the numeric subject identifier variable
- TRTAN is the numeric treatment variable for the actual treatment received

Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. If the distributional assumptions for the parametric approach are not satisfied, the removal of outliers or non-parametric methods might be considered. This will be documented in the CSR together with the reasoning supporting the most appropriate action taken, if applicable.

If there are any deviations from the planned treatment, then the analysis model specified or methods of analysis may be re-evaluated, as appropriate. Details of any deviations from the planned analysis will be documented in the CSR.

9.2.5 Statistical Figures for Analysis of Pharmacokinetic Data

For Part 1, plots of GMRs obtained from the statistical model will be produced for each of the PK parameters: Cmax, AUC(0-last) and AUC(0-inf) for KD025 only, with bars representing the 90% CIs. Plots will include horizontal lines to show lower (ie 70.00%) and upper (ie 143.00%) acceptance limits. Separate plots will be produced for each pairwise comparison of interest.

For Part 2, plots of GMRs obtained from the statistical model will be produced for each of the PK parameters: Cmax(first dose), Cmax(second dose) and AUC(0-24) for KD025 only, with bars representing the 90% CIs. Plots will include horizontal lines to show lower (ie 70.00%) and upper (ie 143.00%) acceptance limits.

10 Safety Assessments

Safety data summaries will be presented by actual treatment received in each period and the safety population will be used throughout. Separate summary tables and listings will be produced for each study part.

10.1 Extent of Exposure

The number and percentage of subjects exposed to each study drug on each day (including morning and evening dosing for rabeprazole only in Part 1 and for KD025 only in Part 2) will be summarised by treatment.

10.2 Treatment Compliance

The total number of scheduled doses will be calculated on the basis of the extent of exposure of each subject for each NIMP. The percentage treatment compliance will be summarised (ie mean, SD, median, minimum, maximum and n) for each NIMP. The evaluation of compliance will be based on the following formula and will be calculated by the Lead Statistical Programmer (or designee) as follows:

$$\textit{Percentage treatment compliance} = \frac{\textit{Total number of administered doses}}{\textit{Total number of scheduled doses}} \times 100$$

If a subject withdraws from the study, their percentage treatment compliance will be calculated for the scheduled doses prior to their withdrawal (ie if a subject receives all scheduled doses up until they withdraw from the study, their percentage treatment compliance will be 100%).

Dosing details (including the date and time of all doses administered) will be listed for all subjects. Any recorded deviations from the planned dosing regimen will be listed as protocol deviations.

10.3 Meal Details

Meal details as recorded on the source workbook will be listed. Any recorded deviations from the planned meal times will be listed as protocol deviations.

10.4 Adverse Events

Throughout the study, all AEs will be evaluated by the PI and noted in the AE section of the source workbook.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v21.0 (or most recent version), and reported by system organ class (SOC) and preferred term (PT).

AEs will be classified into the following categories:

- pre-dose AEs: AEs recorded at screening or with a start date and time prior to the first dose of IMP
- treatment-emergent adverse events (TEAEs): AEs that commence during/after the first dose of IMP (ie Period 1) or commence before first dose of IMP (ie a pre-dose AE or existing medical condition) but worsen in intensity during exposure to IMP or NIMP

Where the severity of a pre-dose AE intensifies during/after dosing of either IMP or NIMP this will be defined as a new AE and classified as a TEAE.

TEAEs will be assigned to the period in which the AE first occurred. Where the severity of an AE or symptom changes in a subsequent period, this will be defined as a new AE and included under the treatment associated with the subsequent period. AEs that occur during the washout period will be assigned to the treatment the subject received during the period immediately before the washout period.

AEs will be classified as "unrelated", "possibly related", and "related" when considering their relationship to IMP. TEAEs classified as "possibly related" and "related" will be defined as adverse drug reactions (ADRs). An ADR is any AE where a causal relationship with the IMP is at least a reasonable possibility ie "possibly related" or "related". Pre-dose AEs will always have the classification of "unrelated".

AEs will also be classified as "unrelated", "possibly related", and "related" when considering their relationship to NIMP.AEs will be classified as "mild," "moderate" or "severe" when considering their severity.

If the severity or relationship to IMP/NIMP of a TEAE is missing, the severity/relationship will be tabulated as "missing" in the summary tables.

Where the start date of an AE is missing and the stop date is on or after the day of first dose of IMP or both the start and stop dates are missing then a "worst-case" scenario will be assumed, ie the AE is assumed to have occurred post-dose and is therefore considered treatment-emergent. If a partial start date/time is available then the event will be considered as treatment-emergent unless the partial information suggests otherwise. The period to which the AE will be assigned will be hard coded using SAS Software and documented in a file note.

10.4.1 Summary Tables for Adverse Events

All pre-dose AEs (as defined in Section 10.4) will be excluded from the summary tables but will be listed for all subjects.

Descriptive statistical methods will be used to summarise the TEAE data.

The number and percentage of subjects reporting each TEAE will be summarised for both SOC and PT. For summaries by SOC and PT, with the exception of TEAEs by severity and relationship to IMP, the number of subjects and the number of events will be summarised. For summaries by severity and relationship only the number of subjects will be summarised.

For counts of subjects experiencing events the following will apply:

- a subject experiencing TEAEs in more than one body system, within a study period, will be counted once in the total number of subjects with TEAEs in that study period;
- a subject with more than 1 TEAE in the same SOC, within a study period, counts only once at the SOC level;
- a subject with more than 1 TEAE in the same PT, within a study period, counts only once at the PT level.

For event counts, all events are included.

When it is necessary to calculate percentages, the denominator will be the total number of subjects in the safety dataset for that period (ie number of subjects dosed in each period, shown in TABLE 14.1.1.1

and the numerator will be the total number of subjects reporting a TEAE within the relevant category.

Summaries presented for SOC and PT will be presented in descending order of frequency overall ie most frequently reported SOC in the study and then by most frequently reported PT in the study within each SOC.

10.4.1.1 Overall Summary of Adverse Events

The following will be summarised for the safety population by treatment:

- number and percentage of subjects reporting at least 1 TEAE
- number and percentage of subjects reporting at least 1 ADR
- number and percentage of subjects reporting at least 1 TEAE leading to subject withdrawal
- number and percentage of subjects reporting at least 1 severe TEAE
- number and percentage of subjects reporting at least 1 serious TEAE
- number and percentage of subjects reporting at least 1 TEAE leading to death

- total number of TEAEs
- total number of ADRs
- total number of TEAEs leading to subject withdrawal
- total number of severe TEAEs
- total number of serious TEAEs
- total number of TEAEs leading to death

10.4.1.2 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

All subjects reporting TEAEs will be summarised by treatment. Counts will be given for number of subjects and number of events. Subjects experiencing more than 1 TEAE within a period will be counted only once for number of subjects but will be counted more than once for number of events.

Additionally, subjects reporting TEAEs will be summarised for SOC and PT by treatment. Counts will be given for number of subjects and number of events. For programming purposes, counts of number of subjects will be by maximum severity ie subjects experiencing more than 1 episode of a TEAE within a period will be counted only once within each SOC and PT using the most severe episode.

10.4.1.3 Summary of Treatment-Emergent Adverse Events by Severity

All subjects reporting TEAEs will be summarised by severity (mild, moderate or severe) and treatment. Counts will be given for number of subjects, not number of events. Counts will be given by maximum severity (ie subjects experiencing more than 1 TEAE within a period will be counted only once using the most severe episode).

Additionally, subjects reporting TEAEs will be summarised for SOC and PT by maximum severity (ie mild, moderate or severe) and treatment. Counts will be given for total number of subjects, not for events. Counts by maximum severity will be given (ie subjects experiencing more than 1 TEAE within a period will be counted only once within each SOC and PT using the most severe episode).

10.4.1.4 Summary of Treatment-Emergent Adverse Events by Relationship to IMP

All subjects reporting TEAEs will be summarised by relationship to IMP (ie unrelated, possibly related and related) and treatment. Counts will be given for number of subjects, not number of events. Counts will be given by the closest relationship to IMP (ie subjects experiencing more than 1 TEAE within a period will be counted only once using the most closely related event).

Additionally, subjects reporting TEAEs will be summarised for SOC and PT by closest relationship to IMP (ie unrelated, possibly related or related) and treatment. Counts will be given for total number of subjects, not for events. Counts by closest relationship will be given (ie subjects experiencing more than 1 TEAE within a period will be counted only once within each SOC and PT using the most closely related event).

10.4.1.5 Summary of Treatment-Emergent Adverse Events by Relationship to NIMP

All subjects reporting TEAEs will be summarised by relationship to NIMP (ie unrelated, possibly related and related) and treatment (Periods 2 to 4 of Part 1 and Period 2 of Part 2 only). Counts will be given for number of subjects, not number of events. Counts will be given by the closest relationship to NIMP (ie subjects experiencing more than 1 TEAE within a period will be counted only once using the most closely related event).

Additionally, subjects reporting TEAEs will be summarised for SOC and PT by closest relationship to NIMP (ie unrelated, possibly related or related) and treatment. Counts will be given for total number of subjects, not for events. Counts by closest relationship will be given (ie subjects experiencing more than 1 TEAE within a period will be counted only once within each SOC and PT using the most closely related event).

10.4.1.6 Summary of Adverse Drug Reactions (ADRs)

All subjects reporting ADRs will be summarised by treatment. Counts will be given for number of subjects and number of events. Subjects experiencing more than 1 ADR within a period will be counted only once for number of subjects but will be counted more than once for number of events.

Additionally, subjects reporting ADRs will be summarised for SOC and PT by treatment. Counts will be given for number of subjects and number of events. For programming purposes counts of number of subjects will be by maximum severity ie subjects experiencing more than 1 episode of a TEAE within a period will be counted only once within each SOC and PT using the most severe episode.

10.4.1.7 Summary of Serious Adverse Events

All subjects reporting serious adverse events (SAEs) will be summarised by treatment. Counts will be given for number of subjects and number of events. Subjects experiencing more than 1 SAE within a period will be counted only once for number of subjects but will be counted more than once for number of events.

Additionally, subjects reporting SAEs will be summarised for SOC and PT by treatment. Counts will be given for number of subjects and number of events. For programming purposes counts of number of subjects will be by maximum severity ie subjects experiencing more than 1 episode of a SAE within a period will be counted only once within each SOC and PT using the most severe episode.

10.4.2 Listings for Adverse Events

All pre-dose AEs (as defined in Section 10.4) will be listed including SOC and PT.

A separate data listing of all TEAEs will be provided including the SOC and PT. In addition, a listing of all SAEs will be provided.

10.5 Laboratory Evaluations

The details of sample collection for laboratory safety analysis are described in the study protocol.

Where a value is provided by the safety laboratory as either above or below the limit of detection this will be set to the limit of detection itself for summary purposes. No imputations will be made in the individual listings.

10.5.1 Summary Tables for Laboratory Evaluations

Haematology and clinical chemistry data will be summarised (mean, SD, median, minimum, maximum and n) for each laboratory parameter at each time point, including changes from baseline at the 48 h (Day 3) post-baseline time point by treatment. For the purposes of laboratory evaluations baseline is defined as follows:

- for Part 1, Periods 1, 2 and 4: Day -1, Admission for each relevant period
- for Part 1, Period 3: Day -3, Outpatient Visit
- for Part 2, Periods 1 and 2: Day 1, pre-dose for each relevant period

Shift tables from baseline to the 48 h post-baseline time point (with respect to the number and percentage of subjects with values below, within or above the reference range) will be presented by treatment. Percentages will be based on the number of subjects with measurements at baseline and the 48 h post-baseline time point.

10.5.2 Listings for Laboratory Evaluations

The sample collection data (eg collection times) for laboratory analysis and urinalysis data will be listed.

All individual subject data, for planned haematology, clinical chemistry, and urinalysis data including derivations such as change from baseline will be listed. If applicable, data from unscheduled laboratory tests will also be listed and flagged with a # to indicate it will not be used in the summary statistics. In these listings, individual data will be flagged

with an "H" or an "L" for values that are higher or lower than their reference ranges, respectively.

Separate listings of all haematology, clinical chemistry and urinalysis values outside their reference ranges by subject will also be provided. References ranges will be supplied by the safety laboratory for haematology and clinical chemistry and per the study workbook for urinalysis (ie a positive or negative result) with the exception of the following reference ranges for urinalysis:

- pH 5.0-9.0 (as per the limits of the current dipstick range)
- Specific gravity 1.000 to 1.030

10.6 Vital Signs

The details of measurement of supine vital signs are described in the study protocol.

10.6.1 Summary Tables for Vital Signs

Vital signs data (ie systolic and diastolic blood pressure [BP], heart rate and oral temperature), including change from baseline (where baseline is defined as pre-dose, Day 1 of the relevant period) will be summarised (ie mean, SD, median, minimum, maximum and n) at each post-baseline time point by treatment.In addition, the number of subjects with 'substantial' increases or decreases or no substantial change from baseline in systolic BP (>±20 mmHg), diastolic BP (>±10 mmHg) and heart rate (>±15 bpm) will be summarised.

10.6.2 Listings for Vital Signs

All individual vital signs data (ie systolic and diastolic BP, heart rate and oral body temperature) including derivations such as change from baseline will be listed.

Individual data will be flagged with an "H" or an "L" for values that are higher or lower than their reference ranges, respectively, and subjects with 'substantial' increases or decreases from baseline (as defined in Section 10.6.1) in systolic BP, diastolic BP and heart rate will be flagged with an 'I' (increase) or 'D' (decrease), respectively. Oral body temperature data will be listed and parameters outside the reference range will be flagged with an "H" or an "L", for values that are higher or lower than their reference ranges, respectively. If applicable, data from unscheduled vital signs assessments will also be listed and flagged with a # to indicate it will not be used in the summary statistics.

In addition, a separate listing of all vital signs data outside their reference ranges by subject will also be provided.

The reference ranges (from the study day workbook) defined in Table 6 will be used.

Table 6 Vital Signs Reference Ranges

Parameter	Split	Lower limit	Upper limit
Systolic BP	18-45 years	90 mmHg	140 mmHg
Systolic BP	>45 years	90 mmHg	160 mmHg
Diastolic BP	NA	40 mmHg	90 mmHg
Heart rate	18-45 years	40 bpm	90 bpm
Heart rate	>45 years	50 bpm	90 bpm
Oral Body Temperature	NA	35.5°C	37.5°C

NA=Not applicable

10.7 ECG Data

The details of measurement of supine ECG parameters are described in the study protocol.

For 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 study period, during which times ECGs will be measured in triplicate.

For 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.

10.7.1 Summary Tables for ECG Data

The arithmetic mean of the triplicate values for each ECG measurement will be computed for each subject at pre-dose and 4 h post-dose on Day 1 of each study period for Part 1 and at pre-morning dose, 4 h post-morning dose, pre-evening dose and 2 h post-evening dose on Day 1 of each study period for Part 2. The arithmetic means will then be used to compute the summary statistics for the observed value and for the change from baseline values. If 1 of the 3 measurements is missing, the mean of the 2 non-missing measurements will be used. If 2 measurements are missing, the remaining non-missing value will be used.

ECG findings, including change from baseline (defined as mean of triplicate Day 1, pre-dose values for each period [ie morning dose for Part 2]), will be summarised (ie mean, SD, median, minimum, maximum and n) at each post-baseline time point by treatment.The number and percentage of subjects with normal and prolonged QT intervals corrected for heart rate using Bazett's correction (ie QTcB) and Fridericia's correction (ie QTcF) and increases in QTcB and QTcF intervals from baseline within the categories defined in Table 7 (based on the International Council on Harmonisation [ICH] E14 guideline [2]) will be summarised by time point and overall. Percentages will be based on the number of subjects with measurements at the relevant time point.

Table 7 ICH E14 Ranges for QTcB and QTcF Intervals

Parameter	ICH E14 Range
QTcB and QTcF intervals	≤450 msec
	451-480 msec
	481-500 msec
	>500 msec
Increase in QTcB and QTcF interval from baseline	<30 msec
	30-60 msec
	>60 msec

10.7.2 Listings for ECG Data

All ECG data (ie single and individual and mean of triplicate readings) including derivations such as change from baseline (mean of triplicate Day 1, pre-dose values for each period [ie morning dose for Part 2]) will be listed.

All ECG data will be flagged with an "H" or an "L" for values that are higher or lower than their reference ranges, respectively. If applicable, data from unscheduled ECG assessments will also be listed and flagged with a # to indicate it will not be used in the summary statistics.

In addition, subjects with increase in QTcF interval from baseline (30-60 msec) and with 'substantial increases' (>60 msec) will be flagged with 'I' and 'SI', respectively.

A separate listing of all ECG parameters outside their reference range by subject will also be provided.

The reference ranges (from the study day workbook for all parameters, except QT Interval, which is from Quotient SOP "The Interpretation of the Electrocardiogram, Vital Signs and Clinical Laboratory Data During Phase I / II Clinical Trials") and defined in Table 8 will be used.

Table 8 ECG Reference Ranges

Parameter	Split	Lower limit	Upper limit
Ventricular Rate (HR)	18-45 years	40 bpm	90 bpm
	>45 years	50 bpm	90 bpm
PR Interval	NA	120 msec	220 msec
QRS Duration	NA	0 msec	120 msec
QT Interval	NA	0 msec	500 msec
QRS Axis	NA	-30°	100°
QTcB/QTcF Interval	NA	0 msec	450 msec
Rhythm	NA	Sinus rhythm, Sinus bradycardia (rate dependent), Sinus arrhythmia	

HR=heart rate
NA=Not applicable

10.8 Body Weight

All body weight data will be listed.

10.9 Physical Examination

All physical examination details and comments on any physical examination findings will be listed by subject for all subjects.

11 Interim Statistical Analyses

No interim statistical analysis is planned for this study.

12 Changes in the Conduct of the Study or Planned Analysis

12.1 Changes in the Conduct of the Study

No changes in the conduct of the study had been reported at the time this document was written.

12.2 Changes to the Planned Analyses

No changes to planned analysis.

12.3 Any Other Relevant Changes

Not applicable.

13 Overall Considerations

13.1 Statistical Programming and Analysis

The Data Sciences Department at Quotient will perform the statistical programming and analysis to produce all analysis datasets, summary tables, figures and data listings using the statistical SAS Software v9.4.

In general terms, categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, SD, median, minimum, maximum and n. For PK data additional statistics including CV%, geometric mean, geometric SD, geometric CV% and geometric n will be presented, as appropriate. The geometric n is the number of subjects included in the calculation of the geometric mean, geometric SD and geometric CV%.

The geometric mean is obtained by applying a natural log transformation to the raw data, calculating the arithmetic mean of the transformed values and then back transforming the arithmetic mean.

The following formula will be used to calculate the geometric SD:

$$geometric\ SD = exp\{SD[log(raw\ data)]\}$$

ie a natural log transformation is applied to the raw data, the arithmetic SD of the transformed values is calculated, and then the arithmetic SD of the transformed values is back transformed.

The following formula will be used to calculate the geometric CV%:

$$geometric\ CV\% = 100 \times \left(exp\{SD[log(raw\ data)]\}^2 - 1\right)^{1/2}$$

ie a natural log transformation is applied to the raw data, the arithmetic SD of the transformed values is calculated. This value is then squared. The square value is back transformed and a value of 1 is subtracted from the back transformed value. A square root is then applied and the resulting value is multiplied by 100.

In general summary statistics and statistical analysis results will be presented as detailed in Table 9 below, unless otherwise stated:

Table 9 Reporting Conventions for Summary Statistics and Statistical Analysis

Data Type	Statistic	Number of decimal places for reporting (i)
Frequency	Counts (n)	None
	Percentages (%)	1 decimal place
Summary statistic	n	None
	Mean	i + 1 decimal places
	Median	i + 1 decimal places
	SD	i + 1 decimal places
	Min	i decimal places
	Max	i decimal places
	CV%	1 decimal place
	Geometric n	None
	Geometric Mean	i + 1 decimal places
	Geometric SD	i + 1 decimal places
	Geometric CV%	1 decimal place
Statistical analysis	Ratios	2 decimal places
	Confidence intervals	2 decimal places
	p-values	if <0.001: presented as <0.001
		if ≥0.001 and <0.099: presented to 3 decimal places
		all other p-values will be presented to 2 decimal places

i refers to the number of decimal places reported in the source workbook or other appropriate source data for the original data

Details of how the PK parameters will be presented are detailed in Section 9.1.1. Where data requires rounding, values ending with 1 to 4 will be rounded down and values ending with 5 to 9 will be rounded up.

All data listings will be based on all subjects ie subjects who signed informed consent and have met the inclusion/exclusion criteria and whose data are subsequently entered into the database. Details of age and sex will be included on all data listings.

All statistical tests relating to PK parameters will be two one-sided tests each at a 5% significance level, leading to 90% (2-sided) CIs.

If any baseline measurements are found to be missing then consideration will be given to imputation using the preceding time point (eg Screening, Admission, if applicable). Unscheduled assessments may be used if appropriate. Details of any such imputations will be documented as part of the safety population.

There will be no other imputations for the safety data with regard to missing values or study discontinuation (ie subjects who do not complete the study).

Imputation for PK parameter estimation using WinNonlin is described in Section 9.1.2 and imputations for reporting PK data are described in Section 9.2.

If partial dates are available for smoking history, prior medications or medical/surgical history, there will be no date imputations. The data listings will only show the date information for the date part that is available eg if only the year part of the date is available then YYYY will be presented in the listing. If the full date information is missing, then this will be presented as missing on the data listing.

13.2 Quality Control of Summary Tables, Figures and Listings and Statistical Analysis

Isolated data errors detected as a result of the QC checks that are deemed significant (ie errors that would impact the interpretation of the results in relation to the study objectives) will be corrected as per the data management plan. Systematic data errors will be investigated further. The data will be corrected if necessary, and the appropriate table, figure, and/or listing re-generated and then re-checked. A summary of QC findings will be provided to Kadmon.

In addition to QC checks, a documented peer review will be performed of all SAS Software-generated report standard summary tables, figures and data listings, including a review of SAS Software code and program log files.

13.2.1 Quality Control - Summary Tables

Manual QC methods (ie comparison of results in the table to results calculated by a calculator or spreadsheet) will be used for all analyses and summary tables. All summary tables will be QC'd as follows:

- where tables are presented by treatment (ie no time points), all summary statistics for 1 treatment will be QC'd; QC will alternate between treatment to avoid the same treatment being QC'd every timewhere tables are presented by treatment and time point, a single treatment at 1 time point in each table will be QC'd; QC will alternate between treatment and time point to avoid the same treatment and time point being QC'd every time
- where tables are produced using a macro for multiple parameters, a minimum of 3 tables, using different treatments or combinations of treatments and time point as appropriate, will be QC'd
- for AEs, the treatment details will be 100% QC'd against the treatment allocation list for all subjects
- AE summary tables will be 100% checked using the relevant data listing

13.2.2 Quality Control - Figures

All figures will be QC'd manually using the corresponding/appropriate summary table or data listing, as follows:

- across all figures, QC will alternate between treatments to avoid the same treatment being QC'd every time
- where a figure presents data from more than 1 treatment, only 1 treatment will be QC'd. However, all data points for that treatment will be checked
- where figures are produced using a macro for individual subjects and/or multiple parameters, a minimum of 3 figures will be QC'd
- mean figures will be QC'd using the corresponding summary table
- figures showing individual data will be QC'd using the corresponding data listing

13.2.3 Quality Control - Data Listings

All data listings will be subjected to a 100% manual QC check against the source workbook or other appropriate source data for a minimum of 4 subjects for each study part. If appropriate, the subjects checked will include at least one subject who withdrew early from the study.

13.2.4 Quality Control - Statistical Analysis

QC of statistical analyses will be performed by peer review of program code, log and output. This will be performed by a statistician at Quotient who is not responsible for performing the statistical analysis.

14 SAS Data Transfer

All SAS study data used for analysis and reporting, including safety and PK data will be transferred to Kadmon on issue of the final CSR. These will be performed in compliance with CDISC (SDTM IG v3.2, ADaM IG v1.1). Quotient will provide metadata files and data will be transferred as SAS Software transport files.

15 Programming Conventions

Quotient standards for layout of tables, figures and data listings and programming conventions will be used as follows:

- courier new, font size 8
- landscape
- US Letter size (8.5 x 11 inches)

Tables and listings will be produced as MS Word 2013 documents and figures will be produced as PDF files. Listings will be sorted by subject ID number and period.

The mock tables (Section 20) presented are a representation of Quotient reporting standards. However these are provided for illustrative purposes only. The numbering and titles of all tables, figures and listings and the formatting, labelling, footnotes and cosmetic appearance of tables may be modified or additional labelling/footnotes may need to be added during analysis and reporting, for clarification purposes. Any such changes will not be regarded as changes to planned analyses.

16 Reference List

[1] Applied Mixed Models in Medicine, Brown and Prescott, 242-243, 3rd edition 2015
[2] 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.

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16.2.7.1.3	Serious Adverse Events Individual Values: All Subjects Part 1: KD025 QD dosing
16.2.7.2.1	Pre-dose Adverse Events Individual Values: All Subjects Part 2: KD025 BID dosing
16.2.7.2.2	All Treatment-Emergent Adverse Events Individual Values: All Subjects Part 2: KD025 BID dosing
16.2.7.2.3	Serious Adverse Events Individual Values: All Subjects Part 2: KD025 BID dosing
	Laboratory Data

Listing Number	Listing Title
16.2.8.1.1.1	Blood Sample Collection Details for Laboratory Analysis Individual Values: All Subjects Part 1: KD025 QD dosing
16.2.8.1.1.2	Blood Sample Collection Comments Individual Values: All Subjects Part 1: KD025 QD dosing
16.2.8.1.2	Haematology Individual Values: All Subjects Part 1: KD025 QD dosing
16.2.8.1.3	Haematology Individual Values Outside the Reference Range: All Subjects Part 1: KD025 QD dosing
16.2.8.1.4	Clinical Chemistry Individual Values: All Subjects Part 1: KD025 QD dosing
16.2.8.1.5	Clinical Chemistry Individual Values Outside the Reference Range: All Subjects Part 1: KD025 QD dosing
16.2.8.1.6	Urinalysis Sample Collection Individual Values: All Subjects Part 1: KD025 QD dosing
16.2.8.1.7	Urinalysis Individual Values: All Subjects Part 1: KD025 QD dosing
16.2.8.1.8	Urinalysis Individual Values Outside the Reference Range: All Subjects Part 1: KD025 QD dosing
16.2.8.2.1.1	Blood Sample Collection Details for Laboratory Analysis Individual Values: All Subjects Part 2: KD025 BID dosing
16.2.8.2.1.2	Blood Sample Collection Comments Individual Values: All Subjects Part 2: KD025 BID dosing
16.2.8.2.2	Haematology Individual Values: All Subjects Part 2: KD025 BID dosing
16.2.8.2.3	Haematology Individual Values Outside the Reference Range: All Subjects Part 2: KD025 BID dosing
16.2.8.2.4	Clinical Chemistry Individual Values: All Subjects Part 2: KD025 BID dosing

Listing Number	Listing Title
16.2.8.2.5	Clinical Chemistry Individual Values Outside the Reference Range: All Subjects Part 2: KD025 BID dosing
16.2.8.2.6	Urinalysis Sample Collection Individual Values: All Subjects Part 2: KD025 BID dosing
16.2.8.2.7	Urinalysis Individual Values: All Subjects Part 2: KD025 BID dosing
16.2.8.2.8	Urinalysis Individual Values Outside the Reference Range: All Subjects Part 2: KD025 BID dosing
16.2.8.3.1	Haematology: Reference Ranges
16.2.8.3.2	Clinical Chemistry: Reference Ranges
16.2.8.3.3	Urinalysis: Reference Ranges
	Vital Signs, ECGs and Other Data
16.2.9.1.1.1	Vital Signs Individual Values: All Subjects Part 1: KD025 QD dosing
16.2.9.1.1.2	Vital Signs Individual Values Outside the Reference Range: All Subjects Part 1: KD025 QD dosing
16.2.9.1.2.1.1	ECG Data Individual Values: All Subjects Part 1: KD025 QD dosing
16.2.9.1.2.1.2	ECG Data Mean Values: All Subjects Part 1: KD025 QD dosing
16.2.9.1.2.2	ECG Data Individual Values Outside the Reference Range: All Subjects Part 1: KD025 QD dosing
16.2.9.1.3	Physical Examination Data Individual Values: All Subjects Part 1: KD025 QD dosing
16.2.9.1.4	Body Weight Data Individual Values: All Subjects Part 1: KD025 QD dosing
16.2.9.2.1.1	Vital Signs Individual Values: All Subjects Part 2: KD025 BID dosing

Listing Number	Listing Title
16.2.9.2.1.2	Vital Signs Individual Values Outside the Reference Range: All Subjects Part 2: KD025 BID dosing
16.2.9.2.2.1.1	ECG Data Individual Values: All Subjects Part 2: KD025 BID dosing
16.2.9.2.2.1.2	ECG Data Mean Values: All Subjects Part 2: KD025 BID dosing
16.2.9.2.2.2	ECG Data Individual Values Outside the Reference Range: All Subjects Part 2: KD025 BID dosing
16.2.9.2.3	Physical Examination Data Individual Values: All Subjects Part 2: KD025 BID dosing
16.2.9.2.4	Body Weight Data Individual Values: All Subjects Part 2: KD025 BID dosing

20 Mock Tables

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.1.1.1
Subject Disposition by Reason
Summary Statistics: All Subjects
Part 1: KD025 QD dosing

	TREATMENT	OVERALL (N=XX) n (%)
Subjects enrolled		xx (xx.x)
Subjects dosed		xx (xx.x)
in Period 1	KD025 200 mg QD	xx (xx.x)
in Period 2	KD025 200 mg QD + itraconazole	xx (xx.x)
in Period 3	KD025 200 mg QD + rabeprazole	xx (xx.x)
in Period 4	KD025 200 mg QD + rifampicin	xx (xx.x)
Subjects completed		xx (xx.x)
Subjects discontinued		xx (xx.x)
Reason for discontinuation		
REASON 1		xx (xx.x)
REASON 2		xx (xx.x)
REASON 3		xx (xx.x)
...		...
<All categories on source workbook>		xx (xx.x)

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day
Percentages for the reasons for discontinuation are based on the number of subjects who discontinued
All other percentages are based on the number of subjects enrolled
A subject may be discontinued for one reason only

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(Programming note: Continue this table for all reasons for discontinuation as recorded on the source workbook. If none of the subjects were discontinued then the reasons for discontinuation will not be populated. A similar table will be produced for Part 2 [Table 14.1.2.1])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.1.1.2.1
Analysis Populations
Summary Statistics: All Subjects
Part 1: KD025 QD dosing

	OVERALL (N=XX) n (%)
Number (%) of subjects in Safety Population	xx (xx.x)
Reasons for exclusion from Safety Population *<All categories on source listing>*	xx (xx.x)
Number (%) of subjects in PK Population	xx (xx.x)
Reasons for exclusion from PK Population *<All categories on source listing>*	xx (xx.x)

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state

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(Programming note: A similar table will be produced for Part 2 [Table 14.1.2.2.1])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.1.1.2.2
Analysis Datasets
Summary Statistics: PK Population
Part 1: KD025 QD dosing

	KD025 200 mg QD (N=XX) n (%)	KD025 200 mg QD + itraconazole (N=XX) n (%)	KD025 200 mg QD + rabeprazole (N=XX) n (%)	KD025 200 mg QD + rifampicin (N=XX) n (%)
Number (%) of subjects in PK Analysis Dataset 1	xx (xx.x)	xx (xx.x)		
Reasons for exclusion from PK Analysis Dataset 1				
<Reason 1>	…	…		
<Reason 2>	…	…		
…	…	…		
Number (%) of subjects in PK Analysis Dataset 2	xx (xx.x)		xx (xx.x)	
Reasons for exclusion from PK Analysis Dataset 2				
<Reason 1>	…		…	
<Reason 2>	…		…	
…	…		…	

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day

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(Programming note: This table will be continued for all PK Datasets (1-3 expected) and for all reasons for exclusion. Footnotes will include a definition of each PK dataset. A similar table will be produced for Part 2 [Table 14.1.2.2.2])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.1.1.3
Demographic and Baseline Characteristics
Summary Statistics: Safety Population
Part 1: KD025 QD dosing

		KD025 200 mg QD (N=XX) n (%)	KD025 200 mg QD + itraconazole (N=XX) n (%)	KD025 200 mg QD + rabeprazole (N=XX) n (%)	KD025 200 mg QD + rifampicin (N=XX) n (%)	Overall (N=XX) n (%)
Age (years)	Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	SD	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x
	Min	xx	xx	xx	xx	xx
	Max	xx	xx	xx	xx	xx
	n	xx	xx	xx	xx	xx
Sex n (%)	Male	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race n (%)	<All categories on source workbook>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Height (cm)	…	…	…	…	…	…
Weight (kg)	…	…	…	…	…	…
BMI (kg/m2)	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day

Data summarised are taken at Screening visit

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(Programming note: Continue this table for all categories of race as recorded on the source workbook and for height [cm], weight [kg] and BMI [kg/m^2]. If any values are missing, these will be represented by row labelled as "Missing". A similar table will be produced for Part 2 [Table 14.1.2.3])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.1.1.4
Lifestyle Details: Smoking History and Alcohol Consumption at Baseline
Summary Statistics: Safety Population
Part 1: KD025 QD dosing

		KD025 200 mg QD (N=XX) n (%)	KD025 200 mg QD + itraconazole (N=XX) n (%)	KD025 200 mg QD + rabeprazole (N=XX) n (%)	KD025 200 mg QD + rifampicin (N=XX) n (%)	Overall (N=XX) n (%)
Does subject smoke or use e-cigarettes and/or nicotine replacement products?	YES	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	NO	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PREVIOUSLY	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Alcohol Consumption	NONE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	1-14 UNITS/WEEK	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	15-20 UNITS/WEEK	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day

1 unit = 1/2 pint beer, 25 mL of 40% spirit or a 125 mL glass of wine

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(Programming note: A similar table will be produced for Part 2 [Table 14.1.2.4])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.1.1.5
Extent of Exposure
Summary Statistics: Safety Population
Part 1: KD025 QD dosing

TREATMENT	Day	Dose of KD025 200 mg QD n (%)	Dose of itraconazole n (%)	Dose of rabeprazole n (%)	Dose of rifampicin n (%)
KD025 200 mg QD (N=XX)	Day 1	xx (xx.x)			
KD025 200 mg QD + itraconazole (N=XX)	Day 3, Period 1		xx (xx.x)		
	Day -6		xx (xx.x)		
	…		…		
	Day -1		xx (xx.x)		
	Day 1	xx (xx.x)	xx (xx.x)		
	Day 2		xx (xx.x)		
KD025 200 mg QD + rabeprazole (N=XX)	Day -3, Morning			xx (xx.x)	
	Day -3, Evening			xx (xx.x)	
	…			…	
	Day -1, Morning			xx (xx.x)	
	Day -1, Evening			xx (xx.x)	
	Day 1	xx (xx.x)		xx (xx.x)	
KD025 200 mg QD + rifampicin (N=XX)	Day -9				xx (xx.x)
	…				…
	Day -1				xx (xx.x)
	Day 1	xx (xx.x)			

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day

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(Programming note: Continue this table for all periods and all days. If the minimum washout period is extended between Period 1 and Period 2, the first time-point for the second treatment may be changed from Day 3, Period 1 to Day -7, Period 2. A similar table will be produced for Part 2 [Table 14.1.2.5])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.1.1.6
Treatment Compliance for each NIMP
Summary Statistics: Safety Population
Part 1: KD025 QD dosing

Percentage of Compliance (%)	Itraconazole (N=XX)	Rabeprazole (N=XX)	Rifampicin (N=XX)
Mean	xx.xx	xx.xx	xx.xx
SD	xx.xx	xx.xx	xx.xx
Median	xx.xx	xx.xx	xx.xx
Min	xx.xx	xx.xx	xx.xx
Max	xx.xx	xx.xx	xx.xx
n	xx	xx	xx

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day

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(Programming note: A similar table will be produced for Part 2 [Table 14.1.2.6])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.2.1.1.1
Plasma Pharmacokinetic Concentrations: KD025 (units)
Summary Statistics: *<PK Population/PK Analysis Dataset>*
Part 1: KD025 QD dosing

									Geometric			
TREATMENT	Time point	Mean	SD	CV%	Median	Min	Max	n	Mean	SD	CV%	n
KD025 200 mg QD (N=XX)	PRE-DOSE	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x	xx
	TIME POINT 1	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x	xx
	TIME POINT 2	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x	xx
	…	…	…	…	…	…	…	…	…	…	…	…
	<All other time points>	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x	xx
…	…	…	…	…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…	…	…	…	…
KD025 200 mg QD + rifampicin (N=XX)	PRE-DOSE	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x	xx
	TIME POINT 1	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x	xx
	TIME POINT 2	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x	xx
	…	…	…	…	…	…	…	…	…	…	…	…
	<All other time points>	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x	xx

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day
For the arithmetic summary statistics concentration values reported as BLQ have been set to zero
For the geometric summary statistics concentrations values reported as BLQ have been set to ½ LLOQ (x.xx (ng/mL))

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(Programming note: Continue this table for all time points. A similar table will be produced for Part 2 [Table 14.2.2.1.1] and for each metabolite [KD025m1 Tables 14.2.1.1.2 (Part 1) and 14.2.2.1.2 (Part 2) and KD025m2 Tables 14.2.1.1.3 (Part 1) and 14.2.2.1.3 (Part 2)])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.2.1.2.1
Plasma Pharmacokinetic Parameters: KD025
Summary Statistics: *<PK Population/PK Analysis Dataset>*
Part 1: KD025 QD dosing

		PK Parameters				
TREATMENT	Statistic	Parameter 1 (ng/mL)	Parameter 2 (ng/mL)	Parameter 3 (ng/mL)	…	< All PK parameters (ng/mL)>
KD025 200 mg QD (N=XX)	Mean	xx.x	xx.xx	xx.xx	…	xx.xxxx
	SD	xx.x	xx.xx	xx.xx	…	xx.xxxx
	CV%	xx.x	xx.x	xx.x	…	xx.x
	Median	xx.x	xx.xx	xx.xx	…	xx.xxxx
	Min	xx	xx.x	xx.x	…	xx.xxx
	Max	xx	xx.x	xx.x	…	xx.xxx
	n	xx	xx	xx	…	xx
	Geometric Mean	xx.x	xx.xx	xx.xx		xx.xx
	Geometric SD	xx.x	xx.xx	xx.xx		xx.xx
	Geometric CV%	xx.x	xx.x	xx.x		xx.x
	Geometric n	xx	xx	xx		xx
…	…	…	…	…	…	…
KD025 200 mg QD + rifampicin (N=XX)	Mean	xx.x	xx.xx	xx.xx	…	xx.xxxx
	SD	xx.x	xx.xx	xx.xx	…	xx.xxxx
	CV%	xx.x	xx.x	xx.x	…	xx.x
	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day

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(Programming note: Continue this table for all PK parameters. A similar table will be produced for Part 2 [Table 14.2.2.2.1] and for each metabolite [*KD025m1* Tables 14.2.1.2.2 (Part 1) and 14.2.2.2.2 (Part 2) and *KD025m2 Tables* 14.2.1.2.3 (Part 1) and 14.2.2.2.3 (Part 2), Geometric statistics will not be presented for Tlag and Tmax])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.2.1.2.4
Plasma Pharmacokinetic Parameters: KD025
Statistical Analysis Results - Assessment of Relative Bioavailability: *<PK Population/PK Analysis Dataset>*
Part 1: KD025 QD dosing

Parameter	Test/Reference	Test n	Test Adj Geo Mean (1)	Reference n	Reference Adj Geo Mean (1)	Ratio (%) (2)	90% CI (3)	P-value (4)	CVw (%) (5)
Cmax (units)	KD025 200 mg QD + itraconazole / KD025 200 mg QD alone	xx	xxx.xx	xx	xxx.xx	xx.xx	(xx.xx, xx.xx)	xx.xx	xx.xx
	KD025 200 mg QD + rabeprazole / KD025 200 mg QD alone	xx	xxx.xx	xx	xxx.xx	xx.xx	(xx.xx, xx.xx)	xx.xx	xx.xx
	KD025 200 mg QD + rifampicin / KD025 200 mg QD alone	xx	xxx.xx	xx	xxx.xx	xx.xx	(xx.xx, xx.xx)	xx.xx	xx.xx
AUC(0-last) (units)	…	…	…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day; Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day
Results obtained from mixed effect model including terms for treatment (ie period) fitted as a fixed effect and subject fitted as a random effect after natural log transformation of PK parameters
(1) Adj Geo Mean = Adjusted geometric mean from mixed effect model, (2) Ratio of adj geo means, (3) CI = Confidence Interval for ratio of adj geo means (ie test/reference), the absence of an effect on the PK can be concluded for the comparison of interest if PK parameters lie entirely within the interval 70.00% to 143.00%, (4) P-value from two on-sided tests (null hypothesis of non-equivalence), (5) CVw = Intra-subject variability

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(Programming note: A similar table will be produced for Part 2 [Table 14.2.2.2.4] and for each metabolite [KD025m1 Tables 14.2.1.2.5 (Part 1) and 14.2.2.2.5 (Part 2) and KD025m2 Tables 14.2.1.2.6 (Part 1) and 14.2.2.2.6 (Part 2)])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.3.1.1
Overall Summary of Treatment-Emergent Adverse Events
Summary Statistics: Safety Population
Part 1: KD025 QD dosing

		KD025 200 mg QD (N=XX) n (%)	KD025 200 mg QD + itraconazole (N=XX) n (%)	KD025 200 mg QD + rabeprazole (N=XX) n (%)	KD025 200 mg QD + rifampicin (N=XX) n (%)
Number (%) of subjects	reporting at least 1 TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	reporting at least 1 ADR	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	reporting at least 1 TEAE leading to subject withdrawal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	reporting at least 1 severe TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	reporting at least 1 serious TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	reporting at least 1 TEAE leading to death	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total Number of	TEAEs	xx	xx	xx	xx
	ADRs	xx	xx	xx	xx
	TEAEs leading to subject withdrawal	xx	xx	xx	xx
	severe TEAEs	xx	xx	xx	xx
	serious TEAEs	xx	xx	xx	xx
	TEAEs leading to death	xx	xx	xx	xx

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day
Adverse events are coded using MedDRA vXX.X
n = the number of subjects reporting event. Events = the number of events reported.
The incidence of subjects reporting adverse events is calculated counting multiple occurrences once per subject
An adverse drug reaction (ADR) is any AE where a causal relationship with the IMP is at least reasonable possibility ie "possibly related" or "related"

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(Programming note: A similar table will be produced for Part 2 [Table 14.3.2.1])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.3.1.2
Subjects Reporting Treatment-Emergent Adverse Events
By MedDRA System Organ Class and Preferred Term
Summary Statistics: Safety Population
Part 1: KD025 QD dosing

System Organ Class Preferred Term	KD025 200 mg QD (N=XX) n (%)	Event	KD025 200 mg QD + itraconazole (N=XX) n (%)	Event	KD025 200 mg QD + rabeprazole (N=XX) n (%)	Event	KD025 200 mg QD + rifampicin (N=XX) n (%)	Event
Subjects reporting TEAEs	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
etc	…	…	…	…	…	…	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
etc	…	…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency
n = the number of subjects reporting event. Events = the number of events reported.
The incidence of subjects reporting adverse events overall, by system organ class or by preferred term is calculated counting multiple occurrences once per subject

PROGRAM PATH: X:\~\QSC200311\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: A similar table will be produced for Part 2 [Table 14.3.2.2])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.3.1.3
Subjects Reporting Treatment-Emergent Adverse Events
By MedDRA System Organ Class, Preferred Term and Severity
Summary Statistics: Safety Population
Part 1: KD025 QD dosing

	KD025 200 mg QD (N=XX)			….	KD025 200 mg QD + rifampicin (N=XX)		
System Organ Class Preferred Term	Mild n (%)	Moderate n (%)	Severe n (%)	…	Mild n (%)	Moderate n (%)	Severe n (%)
Subjects reporting TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…		…	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency
The incidence of subjects reporting adverse events overall, by system organ class or by preferred term is calculated counting multiple occurrences once per subject for the maximum severity reported.

PROGRAM PATH: X:\~\QSC200311\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: Continue this table for all treatments. A similar table will be produced for Part 2 [Table 14.3.2.3])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.3.1.4
Subjects Reporting Treatment-Emergent Adverse Events
By MedDRA System Organ Class, Preferred Term and Relationship to IMP
Summary Statistics: Safety Population
Part 1: KD025 QD dosing

	KD025 200 mg QD (N=XX)			…	KD025 200 mg QD + rifampicin (N=XX)		
System Organ Class Preferred Term	Unrelated n (%)	Possibly related n (%)	Related n (%)	…	Unrelated n (%)	Possibly related n (%)	Related n (%)
Subjects reporting TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…		…	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency
The incidence of subjects reporting adverse events overall, by system organ class or by preferred term is calculated counting multiple occurrences once per subject for the most closely related event.

PROGRAM PATH: X:\~\QSC200311\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: Continue this table for all treatments. A similar table will be produced for Part 2 [Table 14.3.2.4])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.3.1.5
Subjects Reporting Treatment-Emergent Adverse Events
By MedDRA System Organ Class, Preferred Term and Relationship to NIMP
Summary Statistics: Safety Population
Part 1: KD025 QD dosing

	KD025 200 mg QD + itraconazole (N=XX)			…	KD025 200 mg QD + rifampicin (N=XX)		
System Organ Class Preferred Term	Unrelated n (%)	Possibly related n (%)	Related n (%)	…	Unrelated n (%)	Possibly related n (%)	Related n (%)
Subjects reporting TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…		…	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	…	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency
The incidence of subjects reporting adverse events overall, by system organ class or by preferred term is calculated counting multiple occurrences once per subject for the most closely related event.

PROGRAM PATH: X:\~\QSC200311\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: Continue this table for all treatments. A similar table will be produced for Part 2 [Table 14.3.2.5])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.3.1.6
Subjects Reporting Adverse Drug Reactions
By MedDRA System Organ Class and Preferred Term
Summary Statistics: Safety Population
Part 1: KD025 QD dosing

System Organ Class Preferred Term	KD025 200 mg QD (N=XX)		KD025 200 mg QD + itraconazole (N=XX)		KD025 200 mg QD + rabeprazole (N=XX)		KD025 200 mg QD + rifampicin (N=XX)	
	n (%)	Event	n (%)	Event	n (%)	Event	n (%)	Event
Subjects reporting ADRs	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
etc	…	…	…	…	…	…	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
etc	…	…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day
TEAEs related to treatment are coded using MedDRA vXX.X and are presented in descending order of frequency
n = the number of subjects reporting event. Events = the number of events reported
The incidence of subjects reporting adverse events overall, by system organ class or by preferred term is calculated counting multiple occurrences once per subject
An adverse drug reaction (ADR) is any AE where a causal relationship with the IMP is at least reasonable possibility ie "possibly related" or "related"

PROGRAM PATH: X:\~\QSC200311\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: A similar table will be produced for Part 2 [Table 14.3.2.6])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.3.1.7
Subjects Reporting Serious Adverse Events
By MedDRA System Organ Class and Preferred Term
Summary Statistics: Safety Population
Part 1: KD025 QD dosing

System Organ Class Preferred Term	KD025 200 mg QD (N=XX)		KD025 200 mg QD + itraconazole (N=XX)		KD025 200 mg QD + rabeprazole (N=XX)		KD025 200 mg QD + rifampicin (N=XX)	
	n (%)	Event	n (%)	Event	n (%)	Event	n (%)	Event
Subjects reporting Serious Adverse Events	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
etc	…	…	…	…	…	…	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
etc	…	…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day
Serious adverse events are coded using MedDRA vXX.X and are presented in descending order of frequency
n = the number of subjects reporting event. Events = the number of events reported
The incidence of subjects reporting adverse events overall, by system organ class or by preferred term is calculated counting multiple occurrences once per subject

PROGRAM PATH: X:\~\QSC200311\~\TFLS\PRODUCTION\TAB_XX

DDMMMYYYY HH:MM

(Programming note: A similar table will be produced for Part 2 [Table 14.3.2.7])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.4.1.1
Haematology
Summary Statistics including Change from Baseline: Safety Population
Part 1: KD025 QD dosing

<Parameter> (units)

		Result						Change from Baseline					
TREATMENT	DAY	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max	n
KD025 200 mg QD	BASELINE	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx						
(N=XX)	TIME POINT 1	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
KD025 200 mg QD	BASELINE	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx						
+ itraconazole (N=XX)	TIME POINT 1	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
KD025 200 mg QD	BASELINE	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx						
+ rabeprazole (N=XX)	TIME POINT 1	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
KD025 200 mg QD	BASELINE	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx						
+ rifampicin (N=XX)	TIME POINT 1	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx

Note: The data in this table are presented in listings x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day
Baseline is defined as Day -1, Admission for Periods 1, 2 and 4. Baseline is defined as Day -3, Admission for Period 3.

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(Programming note: Continue this table for all haematology parameters changing the subtitle as appropriate. Repeat this table for Clinical Chemistry for Part 1 [Table 14.4.1.3] and Part 2 [Table 14.4.2.3]. A similar table will be produced for Part 2 [Table 14.4.2.1])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.4.1.2
Haematology
Shift Table from Baseline to Post-Baseline Assessments: Safety Population
Part 1: KD025 QD dosing

<Parameter> (units)

			Below at Baseline			Within at Baseline	Above at Baseline		
TREATMENT	DAY	N#	Below n (%)	Within n (%)	Above n (%)	...	Below n (%)	Within n (%)	Above n (%)
KD025 200 mg QD (N=XX)	TIME POINT 1	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	...	xx (xx.x)	xx (xx.x)	xx (xx.x)
KD025 200 mg QD + itraconazole (N=XX)	TIME POINT 1	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	...	xx (xx.x)	xx (xx.x)	xx (xx.x)
KD025 200 mg QD + rabeprazole (N=XX)	TIME POINT 1	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	...	xx (xx.x)	xx (xx.x)	xx (xx.x)
KD025 200 mg QD + rifampicin (N=XX)	TIME POINT 1	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	...	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day
Baseline is defined as Day -1, Admission for Periods 1, 2 and 4. Baseline is defined as Day -3, Admission for Period 3.
N# is the total number of subjects in the relevant treatment and is used in the denominator for calculating the percentages of subjects. n indicates the number of subjects with a baseline and a post baseline assessment at the time point indicated
Below/within/above indicate the number (%) of subjects with assessments below/within/above the normal reference range

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DDMMMYYYY HH:MM

(Programming note: Continue this table for all haematology parameters changing the subtitle as appropriate. Repeat this table for Clinical Chemistry for Part 1 [Table 14.4.1.4] and Part 2 [Table 14.4.2.4]. A similar table will be produced for Part 2 [Table 14.4.2.2])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.5.1.1
Vital Signs
Summary Statistics, Changes from Baseline and Substantial Changes from Baseline: Safety Population
Part 1: KD025 QD dosing

<Parameter> (units)

			Result						Change from Baseline						Substantial Change		
TREATMENT	DAY	Time point	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max	n	DEC	NONE	INC
KD025 200 mg QD	DAY 1	PRE-DOSE	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx									
(N=XX)		TIME POINT 1	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx	xx
		TIME POINT 2	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx	xx
		…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…
	…	<All other time points>	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx	xx
KD025 200 mg QD	DAY 1	PRE-DOSE	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx									
+ itraconazole		TIME POINT 1	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx	xx
(N=XX)		TIME POINT 2	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx	xx
		…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…
	…	<All other time points>	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx	xx
…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day
Baseline is defined as DAY 1, PRE-DOSE of the relevant study period
Substantial change is defined as: increase/decrease > ± 20 mmHg Systolic BP, > ± 10 mmHg Diastolic BP and > ± 15 bpm HR
DEC: number of subjects with substantial decrease from baseline; NONE: number of subjects with no substantial change from baseline,
INC: number of subjects with substantial increase from baseline

PROGRAM PATH: X:\~\QSC200311\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: Continue this table for all treatments, time points and all vital sign parameters changing the subtitle as appropriate. A similar table will be produced for Part 2 [Table 14.5.2.1])

Kadmon Corporation, LLC
Protocol: KD025-107 Page x of y

TABLE 14.5.1.2.1
ECG Data
Summary Statistics including Change from Baseline: Safety Population
Part 1: KD025 QD dosing

<Parameter> (units)

			Result						Change from Baseline					
TREATMENT	DAY	Time point	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max	n
KD025 200 mg QD	DAY 1	PRE-DOSE	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx						
(N=XX)		TIME POINT 1	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
		TIME POINT 2	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
		…	…	…	…	…	…	…	…	…	…	…	…	…
	…	<All other time points>	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
KD025 200 mg QD	DAY 1	PRE-DOSE	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx						
+ itraconazole		TIME POINT 1	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
(N=XX)		TIME POINT 2	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
		…	…	…	…	…	…	…	…	…	…	…	…	…
	…	<All other time points>	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx
…	…	…	…	…	…	…	…	…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day
Baseline is defined as the mean of the triplicate values on DAY 1, PRE-DOSE of the relevant study period

PROGRAM PATH: X:\~\QSC200311\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

(Programming note: Continue this table for all treatments, time points and all ECG sign parameters changing the subtitle as appropriate. A similar table will be produced for Part 2 [Table 14.5.2.2.1])

Kadmon Corporation, LLC
Protocol: KD025-107

TABLE 14.5.1.2.2
ECG Data
QTcB and QTcF Categorical Data
Summary Statistics: Safety Population
Part 1: KD025 QD dosing

				QTcB Interval					QTcB Interval Increase	
TREATMENT	DAY	Time point	N#	≤450 msec n (%)	451-480 msec n (%)	481-500 msec n (%)	>500 msec n (%)	<30 msec n (%)	30-60 msec n (%)	>60 msec n (%)
KD025 200 mg QD (N=XX)	DAY 1	PRE-DOSE	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)			
		TIME POINT 1	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		TIME POINT 2	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		…	…	…	…	…	…	…	…	…
	…	<All other time points>	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
KD025 200 mg QD + itraconazole (N=XX)	DAY 1	PRE-DOSE	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)			
		TIME POINT 1	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		TIME POINT 2	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		…	…	…	…	…	…	…	…	…
	…	<All other time points>	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	…	…	…	…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects are planned to receive KD025 200mg QD (IMP), all doses administered in the fed state
Period 1: IMP; Period 2: 7 days itraconazole 200mg QD, IMP+itraconazole 200mg QD on 8th day, itraconazole 200mg QD on 9th day;
Period 3: 3 days rabeprazole 20mg BID, IMP+rabeprazole 20mg QD on 4th day; Period 4: 9 days rifampicin 600mg QD, IMP on 10th day
Baseline is defined as the mean of the triplicate values on DAY 1, PRE-DOSE of the relevant study period
Categories for QTcB interval and QTcB interval increases are based on ICH E14 guidelines
N# is the total number of subjects in the relevant treatment group and is used in the denominator for calculating the percentages of subjects, n indicates the number of subjects with observations at the given time point

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((Programming note: Continue this table for all treatments and time points. QTcF interval and QTcF interval increases will be continued onto a separate page. A similar table will be produced for Part 2 [Table 14.5.2.2.2])

Appendix 1 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 study 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 2 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