Protocol Number: KD025-108

Document Title: An Open-label, Two-part Study Designed to Assess the Absolute Bioavailability of KD025 and to Determine the Mass Balance Recovery, Metabolite Profile and Identification of Metabolite Structures for [^{14}C]-KD025 in Healthy Male Subjects

Statistical Analysis Plan: Version 1.0

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REPORTING AND ANALYSIS PLAN

An open-label, two-part study designed to assess the absolute bioavailability of KD025 and to determine the mass balance recovery, metabolite profile and identification of metabolite structures for [^{14}C]-KD025 in healthy male subjects

Quotient Study Number: QSC200323
Sponsor Study Number: KD025-108

Sponsor:

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1 Table of Contents

2 List of Abbreviations

^{14}C	carbon-14
ADaM	analysis data model
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
ATC	anatomical therapeutic chemical
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
CSR	clinical study report
CV%	coefficient of variation
D	'substantial' decrease from baseline for vital signs parameters
DP	decimal place
ECG	electrocardiogram
F	absolute bioavailability
h	hour
H	flag used for value that is above normal reference range
HR	heart rate
I	'substantial' increase from baseline for vital signs parameters / increase in QTcF interval from baseline
ICH	International Council on Harmonisation
IMP	investigational medicinal product
IV	intravenous
L	flag used for value that is below normal reference range

LLOQ	lower limit of quantification
LOCF	last observation carried forward
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
n	number of subjects with an observation
N	number of subjects in the dataset
NA	not applicable
NC	not calculated
NMT	not more than
NR	no result/not reportable
NS	no sample
PI	principal investigator
PK	pharmacokinetic
PT	preferred term
QC	quality control
QTcF	QT interval corrected for heart rate using Fridericia's correction
RAP	reporting analysis plan
SAE	serious adverse event
SD	standard deviation
SDTM	study data tabulation model
SF	significant figure
SI	substantial increase in QTcF interval from baseline
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse events
TFL	tables, figures and listings

WHO	World Health Organisation

Abbreviations used for pharmacokinetic and mass balance parameters and flags are defined in Section 9.

3 Introduction

This document details the following for Quotient Sciences (Quotient) Study QSC200323 (KD025-108):

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

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 1.0 dated 17 Jan 2019 and non-substantial amendment NSA01 dated 18 Apr 2019.

3.1 Responsibilities

The Data Sciences Department at Quotient will be responsible for the production of the following items using Quotient SOPs: Clinical Data Interchange Standards Consortium (CDISC) study data tabulation model (SDTM) and analysis data model (ADaM) datasets, PK parameter estimation and output, mass balance parameter estimation and output, and safety output; including all summary TFLs; and the clinical study report (CSR).

Quotient will provide two sets of TFLs during the study:

- post database lock TFLs (draft) for Kadmon Corporation LLC (Kadmon) review, and
- post-review TFLs (final) for inclusion into the CSR

Quotient will be responsible for the quality control (QC) of all deliverables prior to the client review (Section 13.2).

Metabolite profiling and structural identification will be the responsibility of Pharmaron, and will be the subject of a separate Analytical Work Plan. These aspects will be reported separately from the CSR as a standalone document.

3.2 Definitions

3.2.1 Subjects Definitions

During the clinical phase of the study, an evaluable subject is defined:

- for Part 1, as a subject who has sufficient data for evaluation of the primary bioavailability objective of the study
- for Part 2, as a subject who has provided biological samples for up to 168 h after drug administration or has demonstrated >90% mass balance recovery, or has <1% of the administered dose eliminated in excreta for two consecutive days, whichever is the sooner

These definitions of an evaluable subject will not be used during the reporting phase including the identification of analysis populations and datasets.

All enrolled subjects are 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

Throughout the reporting of the study, treatments will be reported as detailed in Table 1 below:

Table 1 Study Treatments

Study Part	Treatment	Investigational Medicinal Product	Label used for Reporting Purposes in Tables Figures and Listings
1	A	KD025 Tablet, 200 mg	200 mg KD025 Oral Tablet
1	B	[^{14}C]-KD025 solution for infusion, 20 µg/mL (100 µg in 5 mL)	100 µg [14C]-KD025 IV Infusion
2	C	[^{14}C]-KD025 capsule, 200 mg	200 mg [14C]-KD025 Oral Capsule

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 Screening, and

- for Part 1: Day -1 (Admission) and Day 1 through to Day 3 (Discharge)
- for Part 2: Day -1 (Admission) and Day 1 through to Day 15 with discharge planned to occur on Day 8 and a follow-up phone call 5 to 7 days after discharge or after the end of the last collection period

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. For Part 1, PK data of Treatment B will be reported relative to the start of infusion. For all other PK data, time points will be presented relative to the administration time of Treatment A and C, respectively.

Baseline is defined as nominally the last measurement recorded prior to the first dose of investigational medicinal product (IMP) in each study part.

4 Objectives

4.1 Primary Objective

The primary objectives of this study are:

- to determine the absolute oral bioavailability of KD025 (Part 1)
- to determine the mass balance recovery after a single oral dose of [^{14}C]-KD025 (Part 2)
- to provide plasma, urine and faecal samples for metabolite profiling and structural identification (Part 2)

4.2 Secondary Objectives

The secondary objectives of this study are:

- to obtain information regarding the oral PK of total radioactivity, KD025 and its metabolites KD025m1 and KD025m2, in plasma
- to obtain information regarding the intravenous (IV) PK of [^{14}C]-KD025 in plasma (Part 1)
- to determine the routes and rates of elimination of [^{14}C]-KD025 and associated total radioactivity (Part 2)
- to evaluate the extent of distribution of total radioactivity into blood cells (Part 2)
- to assess the qualitative and quantitative metabolic profile of [^{14}C]-KD025 and carry out the structural elucidation of the main metabolites in plasma (accounting for ≥ 10% of circulating total radioactivity) and in urine and faecal samples (accounting for ≥ 10% of administered dose; Part 2)

- to provide additional safety and tolerability information for KD025

4.3 Study Endpoints

4.3.1 Primary Endpoints

- absolute bioavailability (F) of KD025
- mass balance recovery of total radioactivity in all excreta (urine and faeces): Ae, %Ae, Cum Ae and Cum %Ae
- collection of plasma, urine and faeces for metabolite profiling and structural identification

4.3.2 Secondary Endpoints

- assessment of oral PK of KD025, KD025m1 and KD025m2 and total radioactivity by calculation of: Tlag, Tmax, Cmax, AUC(0-last), AUC(0-inf), AUC%extrap, lambda-z, T1/2, CL/F (KD025 only), Vz/F (KD025 only) and MRT
- assessment of IV PK of [^{14}C]-KD025 by calculation of: Tmax, Cmax, AUC(0-last), AUC(0-inf), AUC%extrap, lambda-z, T1/2, CL, Vz, Vss and MRT
- determination of routes and rates of elimination of ^{14}C- by metabolite profiling and structural identification in plasma, urine and faeces
- evaluation of whole blood:plasma concentration ratios for total radioactivity
- amount and structure of metabolites in plasma (accounting for ≥ 10% of circulating total radioactivity), urine and faeces (accounting for ≥ 10% of administered dose).
- to provide additional safety and tolerability information for KD025 by assessing: adverse events (AEs), vital signs, electrocardiograms (ECGs), physical examinations and laboratory safety tests

5 Study Design

5.1 Brief Description

This is a single centre, non-randomised, open-label, two-part study in 6 healthy male subjects. Subjects must have participated in Part 1 in order to be eligible for Part 2. An overview of the study is presented in Figure 1 and assessment time points are detailed in Appendix 1 for Part 1 and in Appendix 2 for Part 2.

5.1.1 Study Plan Part 1

Part 1 is an open-label, non-randomised single oral dose (tablet) followed by an IV microtracer assessment.

On Day 1, subjects will receive a single dose of KD025 (Treatment A) 30 min after the start of a standard breakfast. Subjects will then receive an IV dose of [^{14}C]-KD025 (100 µg, a 'microdose') containing not more than (NMT) 37 kBq (1000 nCi) [^{14}C], as a 15 min IV infusion (Treatment B), starting 1.75 h after the oral dose administration (Treatment A) ie, starting 15 min before the expected Tmax (2 h) for the oral dose. Subjects will remain resident in the clinic until up to 48 h post-oral dose (ie up to Day 3).

5.1.2 Study Plan Part 2

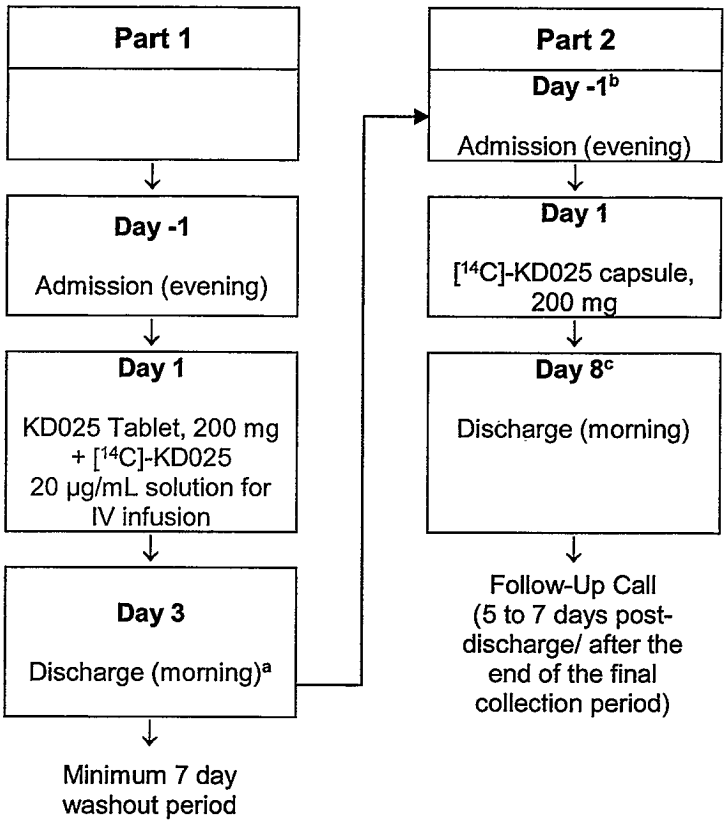
Part 2 is an open-label, non-randomised absorption, distribution, metabolism, excretion (ADME) assessment.

Following a minimum washout period of 7 days, subjects who participated in Part 1 of the study will be admitted to the clinical unit for participation in Part 2 of the study (on Day -1). On the morning of Day 1, each subject will receive a single oral administration of 200 mg [^{14}C]-KD025 capsule containing (NMT 9.8 MBq) (215 µCi) [^{14}C] (Treatment C) 30 min after the start of a standard breakfast.

Subjects will remain resident in the clinic until up to 168 h after dosing (up to Day 8). It is planned that subjects will be released as a group when all subjects have achieved a mass balance cumulative recovery of >90% or if <1% of the dose administered has been collected in urine and faeces within 2 separate, consecutive 24 h periods. This may result in the subjects being discharged as a group prior to completion of the planned residency period. Once the discharge criteria or the planned residency period has been achieved, the subjects will undergo discharge assessments and collection of all samples (blood, urine and faeces) will be stopped.

If mass balance criteria have not been met by all subjects on Day 8, the residency period for the subjects not achieving the release criteria may be extended up to a maximum of 216 h post-dose (Day 10). During the additional residency period only urine and/or faeces will be collected. If the criterion is still not met by Day 10, or if additional residency is not considered appropriate or necessary, then home collections of urine and/or faeces may be requested at the discretion of the investigator for individual subjects. To ensure ongoing wellbeing of the subjects, a follow-up phone call will take place 5 to 7 days post-discharge from the study or after the end of the last collection period.

Figure 1 Study Sequence



[a] Discharge time relative to oral dose, 48 h post-dose.
[b] Subjects who participated in Part 1 will be admitted to the clinical unit on Day -1 of Part 2 after a minimum washout period of 7 days.
[c] If mass balance criteria have not been met by all subjects on Day 8, the residency period for the subjects not achieving the release criteria may be extended up to a maximum of 216 h post-dose (Day 10). During the additional residency period only urine and/or faeces will be collected. If the criterion is still not met by Day 10, or if additional residency is not considered appropriate or necessary, then home collections of urine and/or faeces may be requested at the discretion of the investigator for individual subjects.

5.2 Study Sample Size

No sample size calculation was performed. For a study of this type, a sample size of 6 subjects, to ensure data in 4 evaluable subjects (as defined in Section 3.2.1) is considered appropriate to meet the objectives of the study.

5.3 Subject Numbers (including Replacement Subjects)

This is an open-label, non-randomised study and therefore a randomisation schedule will not be produced.

Subject numbers will be allocated on the morning of dosing in Part 1 according to the code 001 to 006 using the lowest number available.

No replacement subjects are to be used in this study.

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 population will include all subjects who have received at least 1 dose of IMP via either oral administration or IV administration within the study.

The safety population 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 data.

6.2 Pharmacokinetic Population

The PK population will include all subjects who have received at least 1 dose of IMP and who satisfy the following criteria for at least 1 profile in either Part 1 or Part 2:

- no missing samples or invalid post-dose analytical results at critical time points (eg around the Cmax)
- no relevant protocol deviations which may impact the study objectives with respect to the PK endpoints
- no relevant AEs such as vomiting (after oral dosing) or infusion site reaction (after IV dosing) which suggest that the whole dose was not available for absorption/delivery for a particular subject

In the event that quantifiable pre-dose concentrations greater than 5% of Cmax are observed, requirements for further action will be agreed with Kadmon and documented at the same time as the PK population and any corresponding dataset(s).

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

If required, a PK analysis dataset or datasets may also be documented by Quotient with approval from Kadmon at the same time as the PK population. The PK analysis dataset(s) will be a subset of the PK population.

All enrolled subjects will be used for the PK data listings and the PK population will be used for the provision of PK tables and figures. The PK analysis dataset(s) may be used instead of the PK population for generation of PK tables and figures or to generate additional PK tables and figures. Where possible, this decision will be documented at the same time as the PK population and PK analysis dataset(s).

6.3 Mass Balance Population

The mass balance population will be defined for Part 2 and will include all subjects who have received 1 dose of IMP in Part 2 and who have evaluable total radioactivity concentration (urinary and/or faecal) data and who have no protocol deviations that may affect the mass balance analysis. Such protocol deviations would include anything that affects the accurate measurement of the amount of urine/faeces collected or any AEs that may affect the mass balance analysis, for example:

- spillage of urine and/or faeces
- missing collections
- AEs that may affect the mass balance analysis, such as vomiting of the dose

The mass balance population will be confirmed by Quotient with approval from Kadmon once all urinary and faecal data have been received.

If required, a mass balance analysis dataset or datasets may also be documented by Quotient with approval from Kadmon at the same time as the mass balance population. The mass balance analysis dataset(s) will be a subset of the mass balance population.

All enrolled subjects will be used for the mass balance data listings. The mass balance population will be used for the analysis of the mass balance concentration data and the provision of mass balance tables and figures. The mass balance analysis dataset(s) may be used instead of the mass balance population for generation of mass balance tables and figures or to generate additional mass balance tables and figures. Where possible, this decision will be documented at the same time as the mass balance population and mass balance analysis dataset(s).

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 analysis 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.

7.1 Screening Failures

Data for subjects who have failed screening will be databased but will not be subjected to data cleaning and therefore will not be reported, ie will not be included in the STDM or ADaM datasets, or any of the TFLs or the CSR.

7.2 Subject Disposition and Withdrawals

The number and percentage of subjects enrolled, dosed (in Part 1 and Part 2 separately), 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 single summary table will be produced detailing the number and percentage of subjects in each population for each study part (for safety and PK populations) and overall (for safety, PK and mass balance populations). 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 per population will be produced detailing the number and percentage of subjects in each analysis dataset for each study part and overall, as required. The table will be based on the relevant population the dataset is a subset of (ie the PK or mass

balance 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, ethnicity, race, sex, height [cm], weight [kg] and body mass index [BMI; kg/m^2]) will be recorded at screening. Note: Weight is also recorded at admission to Part 2, this data will be listed but not summarised (see Section 10.7). 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). If any subjects are enrolled but not dosed and had other assessments recorded, age will be calculated using the date of informed consent.

Summary statistics (number of subjects with an observation [n], mean, standard deviation [SD], median, minimum and maximum) will be presented overall for age at first dose and for height, weight and BMI at screening. The number and percentage of subjects will be presented overall for race, ethnicity and sex. The denominator for the percentage is all subjects in the safety population. 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 overall as a categorical variable.

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 to each study part. 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 (WHO) Drug Dictionary Global Drug Reference (2019 Q1 version or more recent version) using the following Anatomical Therapeutic Chemical (ATC) classification codes:

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

Prior medications are defined as medications that starts and stop prior to the first dose of IMP. All other medications will be defined as concomitant medications including those that start prior to the 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 part (as appropriate) will be listed by subject for all subjects:

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

8 Efficacy

Not applicable.

9 Pharmacokinetics and Mass Balance

9.1 Pharmacokinetic Parameter Estimation

The PK parameters for [^{14}C]-KD025 (Part 1 IV dose), KD025 (Oral dose in Part 1 and Part 2), KD025m1 (Part 2) and KD025m2 (Part 2) and total radioactivity (Part 2) in plasma will be estimated where possible and appropriate for each subject 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 and reporting specifications are provided in Table 2.

Table 2 Plasma Pharmacokinetic Parameters and Reporting Specifications

Parameter	Definition	Unit	DP or SF	No. of DP/SF	Study Part
Tlag	Time prior to the first measurable (non-zero) concentration (oral administration only)	h	DP	2	1 + 2
Tmax	Time of maximum observed concentration	h	DP	2	1 + 2
Cmax	Maximum observed concentration	mass unit/mL	SF	3	1 + 2
AUC(0-last)	Area under the curve from 0 time to the last measurable concentration	mass unit.h/mL	SF	3	1 + 2
AUC(0-inf)	Area under the curve from dosing extrapolated to infinity	mass unit.h/mL	SF	3	1 + 2
AUCextrap	Percentage of AUC(0–inf) extrapolated beyond the last measurable concentration	%	DP	2	1 + 2
T1/2	Apparent terminal elimination half-life	h	DP	2	1 + 2
lambda-z	The first order rate constant associated with the terminal (log-linear) portion of the curve	1/h	DP	4	1 + 2
CL	Apparent total body clearance after intravenous administration	mL/min	SF	3	1

Parameter	Definition	Unit	DP or SF	No. of DP/SF	Study Part
CL/F	Apparent total body clearance after extravascular administration, where F (fraction of dose bioavailable) is unknown	mL/min	SF	3	1 + 2[a]
Vz	Apparent volume of distribution based on the terminal phase after intravenous administration	L	SF	3	1
Vz/F	Apparent volume of distribution based on the terminal phase after extravascular administration, where F (fraction of dose bioavailable) is unknown	L	SF	3	1 + 2[a]
Vss	Predicted volume of distribution at steady-state after intravenous administration	L	SF	3	1
MRT(0-inf)	Mean residence time extrapolated to infinity (after IV or extravascular administration)	h	DP	2	1 + 2
F Cmax	Absolute bioavailability of the oral formulation compared to IV based on Cmax	%	DP	2	1 + 2
F AUC(0-inf)	Absolute bioavailability of the oral formulation compared to IV based on AUC(0-inf)	%	DP	2	1 + 2
Frel Cmax	Relative bioavailability based on Cmax	%	DP	2	1/2[a]
Frel AUC(0-inf)	Relative bioavailability based on AUC(0-inf)	%	DP	2	1/2[a]
MPR Cmax	Metabolite to parent ratio based on Cmax	NA	DP	2	2
MPR AUC(0-inf)	Metabolite to parent ratio based on AUC(0-inf)	NA	DP	2	2
lambda-z lower[b]	Lower limit on time for values to be included in the calculation of Lambda-z	h	DP	2	1 + 2
lambda-z upper[b]	Upper limit on time for values to be included in the calculation of Lambda-z	h	DP	2	1 + 2

DP = decimal places
SF = significant figures
[a] = only for KD025
[b] = these values should be listed but omitted from the descriptive statistics
NA = not applicable

9.1.2 Rules for Pharmacokinetic Parameter Estimation

For Part 1, PK parameters for Treatment B will be calculated using times relative to the start of infusion. For Treatment A (Part 1) and Treatment C (Part 2), PK parameters will be calculated using times relative to the administration time of Treatment A and C, respectively.

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 rule
Number of points used for lambda-z	At least 3, not including Cmax
Minimum requirements for AUC	At least 3 consecutive quantifiable concentrations
Dose	Oral: Nominal IV: Actual
Rounded dose level	3 Significant Figures

Prior to PK parameter estimation the bioanalytical data may be corrected to account for the proportion of administered [^{14}C] material not measured due to the use of a [^{12}C] LC-MS/MS analysis method. Data correction will only be performed if the [^{14}C]-contribution exceeds 1% of the dose administered. If required, KD025, KD025m1 and KD025m2 bioanalytical data will be multiplied by the determined data correction factor in SAS by the lead statistical programmer (or designee).

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 WinNonLin determined 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.

Absolute Bioavailability of KD025 (F) will be calculated for individual subjects where possible as follows:

$$F = \left\{\frac{\text{AUC or Cmax (KD025 oral)}}{\text{AUC or Cmax ([14C] – KD025 IV)}} \times \frac{\text{Dose(IV)}}{\text{Dose(oral)}}\right\} \times 100$$

F will be calculated using Cmax and AUC(0-inf). If for any reason the AUC(0-inf) is not calculable (NC), then an alternative or additional AUC such as AUC(0-last) or an AUC over a partial area may be used to calculate F.

The following comparisons will be made:

- absolute bioavailability tablet (Treatment A vs Treatment B)
- absolute bioavailability capsule (Treatment C vs Treatment B)

Non-dose-corrected relative bioavailability (Frel) will be calculated for individual subjects where possible as follows:

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

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

The following comparisons will be made, where tablet dosing [Treatment A] is considered the reference):

- relative bioavailability capsule versus tablet (Treatment C vs Treatment A)

In Part 2, metabolite to parent ratios (MPR) will be calculated as follows using AUC(0-inf) and Cmax. If for any reason the AUC(0-inf) is not calculable then an alternative or additional AUC such as AUC(0-last) 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):

- KD025 MW = 452.52 g/mole
- KD025m1 MW= 410.44 g/mole
- KD025m2 MW = 411.42 g/mole

In addition, for Part 2, total radioactivity whole blood to plasma ratios will be determined using SAS by the Lead Statistical Programmer (or designee) at the time points defined in the protocol for whole blood total radioactivity sampling. If the blood and/or plasma concentration values are BLQ (ie less than the lower limit of quantification [LLOQ]) at any given time point, then the ratio will not be calculated.

When converting whole blood collection weights to blood volume (if required) for the calculation of the whole blood to plasma ratios, the following conversion factor will be used:

1.06 g of blood = 1 mL of blood

This will be calculated in SAS as follows:

Blood weight (g) / 1.06 = Blood volume (mL)

Alternatively, where total radioactivity concentrations in whole blood have been provided in mass unit/g units the following conversion will be performed using SAS:

*Concentration (mass units/g) * 1.06 = Concentration (mass units/mL)*

9.2 Pharmacokinetic Parameter Reporting Specifications

The following parameters will be reported for each study part and treatment where possible and appropriate, according to the reporting specifications provided in Table 2:

For plasma [^{14}C]-KD025 following IV administration (Part 1)
Tmax, Cmax, AUC(0-last), AUC(0-inf), AUCextrap, T1/2, lambda-z, CL, Vz, Vss, MRT(0-inf)

For plasma KD025 following oral administration (Part 1)
Tlag, Tmax, Cmax, AUC(0-last), AUC(0-inf), AUCextrap, T1/2, lambda-z, CL/F, Vz/F, MRT(0-inf), F Cmax, F AUC(0-inf)

For plasma Total Radioactivity, KD025, KD025m1 and KD025m2 following oral administration (Part 2)
Tlag, Tmax, Cmax, AUC(0-last), AUC(0-inf), AUCextrap, T1/2, lambda-z, CL/F, Vz/F, MRT(0-inf), F Cmax, F AUC(0-inf), MPR Cmax, MPR AUC(0-inf)

Note: CL/F and Vz/F calculated for KD025 only.

For KD025 (Part 1/Part 2)
Frel Cmax, Frel AUC(0-inf)

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
f	Quantifiable pre-dose values were observed, however were considered less than 5 % of Cmax

In the event that the Rsq of regression was <0.9 ('a' flag) or the extrapolated portion of AUC(0-inf) >20% ('c' flag), then lambda-z, AUC(0-inf) and the parameter estimates derived using lambda-z and/or AUC(0-inf), as appropriate, will be deemed unreliable and will be listed but excluded from the summary statistics.

In the event that the period used for regression analysis was less than 2-fold the calculated half-life ('b' flag), parameter estimates derived using lambda-z will be listed, flagged and included in summary statistics.

Additional flags may be applied based on emerging data.

In the event that quantifiable pre-dose values less than 5% of Cmax were observed, all parameter estimates for the profiles affected will be listed, flagged and included in summary statistics.

Note: in the event that quantifiable pre-dose concentrations greater than 5% of Cmax are observed, requirements for further action will be agreed with Kadmon and documented at the same time as the PK population. In this case, an additional flag would be defined.

9.2.1 Bioanalytical and Pharmacokinetic Summary Tables

Summary statistics (ie n, mean, SD, coefficient of variation [CV%], median, minimum, maximum, geometric n, geometric mean, geometric SD and geometric CV%) will be presented for each study part and time point (except pre-dose time points for which geometric summary statistics will not be presented) for the following concentration data where possible:

- Part 1:

- plasma concentrations of KD025 (following Treatment A)
- plasma concentrations of [^{14}C]-KD025 (following Treatment B)

- Part 2 (following Treatment C):
  - plasma concentrations of KD025, KD025m1 and KD025m2
  - plasma concentrations of total radioactivity
  - whole blood concentrations of total radioactivity
  - whole blood:plasma concentration ratios of total radioactivity

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. This also applies to any concentrations that are defined as PK parameters.

Summary statistics (ie n, mean, SD, CV%, median, minimum and maximum) will be calculated for all plasma PK parameters by study part and analyte as follows. Geometric n, geometric mean, geometric SD and geometric CV% will be presented for all PK parameters except Tlag and Tmax.

- Part 1:
  - plasma PK parameters of KD025 (following Treatment A)
  - plasma PK parameters of [^{14}C]-KD025 (following Treatment B)

- Part 2 (following Treatment C):
  - plasma PK parameters of KD025, KD025m1 and KD025m2 and total radioactivity

- Part 1/Part 2:

  - Relative Bioavailability of tablet to capsule formulation

Data recorded as not reportable/no result (NR) or no sample (NS) will be handled as missing, ie no assumption will be made about the actual concentration. If applicable, parameters recorded as not calculated (NC) will be handled as missing.

9.2.2 Bioanalytical and Pharmacokinetic Figures

Arithmetic mean 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 concentration vs time curves will be produced on a log10/linear scale. Error bars will be included on these plots, where the error bars are (geometric mean ×/÷ geometric SD).

Mean concentration vs time plots (using nominal times) will be produced for on the linear/linear and the log 10/linear scale as follows:

<u>Part 1</u>

- KD025 in plasma – 1 profile per plot (Treatment A)
- [^{14}C]-KD025 in plasma – 1 profile per plot (Treatment B)

<u>Part 2</u>

- KD025, KD025m1, KD025m2 and total radioactivity in plasma – 4 profiles on the same plot (Treatment C)
- Total radioactivity in plasma and total radioactivity in whole blood – 2 profiles on the same plot (Treatment C)

Part 1/Part 2
- KD025 in plasma (Treatment A) and KD025 in plasma (Treatment C) – 2 profiles on the same plot

If judged to aid interpretation, the above plots may be produced with or without error bars.

Separate concentration vs time spaghetti plots (using actual sampling time after dosing) will be produced for each study part and analyte (including total radioactivity) for plasma and whole blood with each plot displaying 1 line per profile. These will be produced on the linear/linear and the log 10/linear scale.

Individual concentration vs time plots (using actual sampling times after dosing) will be produced for each individual subject for study part 2 (all analytes, including total radioactivity in plasma and whole blood overlaid).

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, 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).

Where curves from multiple treatments, analytes or subjects are overlaid on the same plot, symbols will be used to identify different subjects/ treatment regimens and a legend will be included on the plots to define the symbols used.

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 including individual ratios (total radioactivity whole blood:plasma) and PK parameters will be listed on a per subject basis. Any flags used will be given with the appropriate definition.

9.2.4 Statistical Analysis of Pharmacokinetic Parameters

No formal statistical analysis will be performed for the PK data in this study. Descriptive statistics are considered adequate for a study of this type.

9.3 Mass Balance Parameter Estimation

For Part 2, Pharmaron will provide the following concentration and weight data on a per subject basis for each collection interval as specified in the clinical protocol:

- total radioactivity concentration (mass unit equivalents/g) for each of urine and faeces
- weight of urine (g)
- faeces weight (g) ie not faecal homogenate weight

Concentration values will be expressed in terms of mass unit equivalents of the free base form. Quotient Data Sciences will be responsible for the calculation of excretion and recovery of total radioactivity in urine, faeces and urine and faeces combined for inclusion into the CSR. For the purposes of this document, "excretion" will be used when describing the amount of total radioactivity excreted and "recovery" will be used when describing the amount of total radioactivity expressed as a percentage of the radioactive dose administered.

9.3.1 Definition of Mass Balance Parameters

A list of mass balance parameter definitions with reporting specifications are provided in Table 3.

Table 3 Mass Balance Parameters and Reporting Specifications

Parameter	Definition	Units	DP or SF	No. of DP/SF
Ae(urine)	amount of total radioactivity excreted in urine	Mass unit equiv	SF	3
%Ae(urine)	amount of total radioactivity excreted in urine expressed as a percentage of the radioactive dose administered	%	DP	2
CumAe(urine)	cumulative amount of total radioactivity excreted in urine	Mass unit equiv	SF	3
Cum%Ae(urine)	cumulative amount of total radioactivity excreted in urine expressed as a percentage of the radioactive dose administered	%	DP	2
Ae(faeces)	amount of total radioactivity excreted in faeces	Mass unit equiv	SF	3
%Ae(faeces)	amount of total radioactivity excreted in faeces expressed as a percentage of the radioactive dose administered	%	DP	2
CumAe(faeces)	cumulative amount of total radioactivity excreted in faeces	Mass unit equiv	SF	3
Cum%Ae(faeces)	cumulative amount of total radioactivity excreted in faeces expressed as a percentage of the radioactive dose administered	%	DP	2
Ae(total)	amount of total radioactivity excreted in urine and faeces combined	Mass unit equiv	SF	3
%Ae(total)	amount of total radioactivity excreted in urine and faeces combined expressed as a percentage of the radioactive dose administered	%	DP	2
CumAe(total)	cumulative amount of total radioactivity excreted in urine and faeces combined	Mass unit equiv	SF	3
Cum%Ae(total)	cumulative amount of total radioactivity excreted in urine and faeces combined expressed as a percentage of the radioactive dose administered	%	DP	2

DP=decimal places
SF=significant figures

Home collections of urine and/or faeces may be requested at the discretion of the investigator for individual subjects. All mass balance parameters will be calculated over all available time points, including home collection, if applicable.

9.3.2 Rules for Mass Balance Parameter Estimation

The following will be calculated for total radioactivity in urine, faeces and urine and faeces combined (ie total) by Quotient Data Sciences (note that the amount excreted in pre-dose samples will not be included in the calculation of the cumulative amount excreted or in the calculation of the cumulative percentage of the radioactive dose excreted):

- the amount excreted in urine, ie Ae(urine), and the amount excreted in faeces, ie Ae(faeces), will be calculated for each collection interval using the following formula (where matrix is either urine or faeces):

$$Ae(<matrix>) = concentration * weight$$

- the total amount excreted in urine and faeces combined, ie Ae(total), will be calculated for each collection interval using the following formula:

$$Ae(total) = Ae(urine) + Ae\ (faeces)$$

- the cumulative amount excreted in urine, ie CumAe(urine), and the cumulative amount excreted in faeces, ie CumAe(faeces), will be calculated by the incremental summation of the Ae(<matrix>) across all collection intervals (where matrix is either urine or faeces). The amount excreted in the pre-dose sample should not be included in the calculation of the cumulative amount excreted.

- the cumulative amount excreted in urine and faeces combined, ie CumAe(total), will be calculated across all collection intervals using the following formula:

$$CumAe(total) = CumAe(urine) + CumAe(faeces)$$

- the % recovery of the total radioactive dose in urine, ie %Ae(urine), and the % amount of the total radioactive dose excreted in faeces, ie %Ae(faeces), will be calculated for each collection interval using the following formula (where matrix is either urine or faeces):

$$\%Ae(<matrix>) = 100 * Ae(<matrix>) / Total\ Radioactive\ Dose\ Administered$$

- the % recovery of the total radioactive dose in urine and faeces combined, ie %Ae(total), will be calculated for each collection interval using the following formula:

$$\%Ae(total) = \%Ae(urine) + \%Ae(faeces)$$

- the cumulative % amount of the total radioactive dose excreted in urine, ie Cum%Ae(urine), and the cumulative % amount of the total radioactive dose excreted in faeces, ie Cum%Ae(faeces), will be calculated by the incremental summation of the %Ae(<matrix>) across all collection intervals (where matrix is either urine or faeces). The % amount of the total radioactive dose excreted in the pre-dose sample should not be included in the calculation of the cumulative % of dose excreted.

- the cumulative % amount of the total radioactive dose excreted in urine and faeces combined, ie Cum%Ae(total), will be calculated for each collection interval using the following formula:

$$Cum\%Ae(total) = Cum\%Ae(urine) + Cum\%Ae(faeces)$$

For urine and faeces, where a subject has failed to void over a particular collection interval the amount excreted (Ae) will be set to zero.

If part of a void over a particular collection interval is missing due to spillage or accidental discarding, the Ae will still be calculated providing other samples have been collected within the interval. Where no other samples are collected within the interval, the data will be set to missing for the purposes of the calculation of Ae, %Ae, CumAe and Cum%Ae. In both scenarios the data will be flagged to highlight a missing void.

Imputation of non-numerical values reported in the urine and faecal dataset (ie concentrations that are BLQ) will be entered as zero for calculation of parameters.

When converting urine collection weights to urine volume (if required), the following conversion factor will be used:

1.02 g of urine = 1 mL of urine

This will be calculated in SAS as follows:

Urine weight (g) / 1.02 = Urine volume (mL)

If total radioactivity concentrations in urine have been provided in mass unit/g units, the following conversion (if required) will be performed using SAS:

*Concentration (mass units/g) * 1.02 = Concentration (mass units/mL)*

The radioactivity associated with toilet paper may be determined if considered necessary. The results will be reported for each subject as a single value for the whole collection period and included in the calculation of overall cumulative excretion and recovery parameters.

The following dose levels will be used for mass balance analysis and will be applied with the following constraints:

Radioactive dose level for mass balance analysis	Actual
Rounded dose level	3 significant figures

9.4 Mass Balance Reporting Specifications

9.4.1 Mass Balance Summary Tables

Summary statistics (ie n, mean, SD, CV%, median, minimum and maximum) will be presented for amount excreted (Ae) and recovery (%Ae) by collection period for the following:

- urine, ie Ae(urine) and %Ae(urine), for total radioactivity
- faeces, ie Ae(faeces) and %Ae(faeces), for total radioactivity
- urine and faeces combined, ie Ae(total) and %Ae(total), for total radioactivity

In addition, summary statistics (ie n, mean, SD, CV%, median, minimum and maximum) will be presented for cumulative excretion (CumAe) and cumulative recovery (Cum%Ae) by collection period and for the study as a whole for each of the following:

- urine, ie CumAe(urine) and Cum%Ae(urine), for total radioactivity
- faeces, ie CumAe(faeces) and Cum%Ae(faeces), for total radioactivity

- urine and faeces combined, ie CumAe(total) and Cum%Ae(total), for total radioactivity

If any subject withdraws prior to the end of a study visit or if subjects have differing collection intervals (eg collection to Day 8 for some subjects and Day 10 for others), then a last observation carried forward (LOCF) approach will also be used whilst calculating cumulative parameters (ie CumAe and Cum%Ae), where the last observed value will be carried forward to the subsequent time point. If this is the case, then 2 tables will be presented. The first table will have the observed values without the use of LOCF so the number of subjects may reduce over time and the second table will have the LOCF values included so that the number of subjects will remain constant over time. Table numbering will be revised as applicable.

9.4.2 Mass Balance Figures

Mass balance figures will be presented for the mass balance population.

Arithmetic mean cumulative excretion (ie CumAe) and cumulative recovery (ie Cum%Ae) vs time curves will be produced on a linear/linear scale and will include ± SD bars. This means there will be 2 plots:

- one plot with CumAe(urine), CumAe(faeces) and CumAe(total) for total radioactivity in plasma overlaid
- a separate plot with Cum%Ae(urine), Cum%Ae(faeces) and Cum%Ae(total) for total radioactivity in plasma overlaid

A legend identifying each profile (ie urine, faeces and total) will be displayed on the mean plots. Figures will be produced using the LOCF imputation strategy (see Section 9.4.1) if summary tables are produced for this method.

9.4.3 Mass Balance Listings

The sample collection data (eg collection intervals) for all urine and faecal samples will be listed. In addition, all total radioactivity concentrations, urine and faecal weights and all mass balance parameters will be listed on a per subject basis.

9.4.4 Statistical Analysis of Mass Balance Parameters

No formal statistical analysis is required for the mass balance data in this study. Descriptive statistics are considered adequate for a study of this type.

10 Safety Assessments

The safety population will be used for all safety data summaries.

Separate summary tables and listings will be produced for each study part, unless otherwise specified. Screening data for ECGs and vital signs will be listed only once, under Part 1 listings.

For Part 1, safety data and related summaries will be based on the combination of both regimens associated with the study part, rather than being presented in relation to a specific treatment, unless otherwise specified.

10.1 Extent of Exposure and Treatment Compliance

In Part 1, the dose of Treatment B, including the dose of radioactivity (in kBq), will be summarised (ie, n, mean, SD, median, minimum and maximum). In addition, the number of subjects exposed to Treatment A will also be presented.

In Part 2, the dose of Treatment C, including the dose of radioactivity (in MBq and µCi), will be summarised (ie, n, mean, SD, median, minimum and maximum).

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.

10.2 Meal Details

Meal details as recorded in the database will be listed. Any recorded deviations from the planned meal times will be listed as protocol deviations.

10.3 Adverse Events

Throughout the study, all AEs will be evaluated by the principal investigator (PI) and noted in the AE section of the study database.

For Part 1, AEs will be assigned to the combination of both regimens associated with the study part and not assigned to a specific treatment.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v22.0), and reported by System Organ Class (SOC) and Preferred Term (PT).

Adverse events 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 or commence before first dose of IMP (ie a pre-dose AE or existing medical condition) but worsen in intensity during exposure to IMP.

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

TEAEs will be assigned to the study part in which the AE first occurred. Where the severity of an AE intensifies or symptoms change in a subsequent study part, this will be defined as a new AE and included under the treatment(s) associated with the subsequent study part. Adverse events that occur during the washout period will be assigned to the study part [treatment(s)] the subject received during the period immediately before the washout period.

Adverse events 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 reasonable possibility (ie "possibly related" and "related"). Pre-dose AEs will always have the classification of "unrelated".

Adverse events will be classified as "mild," "moderate" or "severe" when considering their severity.

If the severity or relationship to IMP 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 study part to which the AE will be assigned will be programmatically assigned in SAS.

10.3.1 Summary Tables for Adverse Events

All pre-dose AEs (as defined in Section 10.3) 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 part, will be counted once in the total number of subjects with TEAEs in that study part
- a subject with more than 1 TEAE in the same SOC, within a study part, counts only once at the SOC level;
- a subject with more than 1 TEAE in the same PT, within a study part, 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 population for that study part 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 part and then by most frequently reported PT in the study part within each SOC).

10.3.1.1 Overall Summary of Adverse Events

The following will be summarised for the safety population by study part:

- number and percentage of subjects reporting at least one TEAE
- number and percentage of subjects reporting ADRs
- number and percentage of subjects reporting severe TEAEs
- number and percentage of subjects reporting serious TEAEs
- number and percentage of subjects reporting TEAEs leading to subject withdrawal
- number and percentage of subjects reporting TEAEs leading to death

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

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

All subjects reporting TEAEs will be summarised by study part. Counts will be given for number of subjects and number of events. Subjects experiencing more than 1 TEAE within a study part 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 study part. 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 study part will be counted only once within each SOC and PT using the most severe episode).

10.3.1.3 Summary of Treatment-Emergent Adverse Events by Severity

All subjects reporting TEAEs will be summarised by severity of TEAE (mild, moderate or severe) and study part. 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 study part 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 study part. 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 study part will be counted only once within each SOC and PT using the most severe episode).

10.3.1.4 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 study part. 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 study part 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 study part. 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 study part will be counted only once within each SOC and PT using the most closely related event).

10.3.1.5 Summary of Adverse Drug Reactions

All subjects reporting ADRs will be summarised by study part. Counts will be given for number of subjects and number of events. Subjects experiencing more than 1 ADR within a study part 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 study part. 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 study part will be counted only once within each SOC and PT using the most severe episode).

10.3.1.6 Summary of Serious Adverse Events

All subjects reporting serious adverse events (SAEs) will be summarised by study part. Counts will be given for number of subjects and number of events. Subjects experiencing more than 1 SAE within a study part 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 study part. 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 study part will be counted only once within each SOC and PT using the most severe episode).

10.3.2 Listings for Adverse Events

All pre-dose AEs (as defined in Section 10.3) will be listed including SOC and PT.

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

10.4 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.

10.4.1 Summary Tables for Laboratory Evaluations

Haematology and clinical chemistry data will be summarised (n, mean, SD, median, minimum and maximum) for each laboratory parameter at each time point, including changes from baseline (Day 1, Pre-dose for each study part) to Day 3 in Part 1 and Day 8 in Part 2 by study part.Shift tables from baseline to Day 3 in Part 1 and Day 8 in Part 2 by study part (with respect to the number and percentage of subjects with values below, within or above the reference range) will be presented by study part. Percentages will be based on the number of subjects with measurements at baseline and the relevant post-baseline time point.

Reference ranges for each laboratory parameter will be presented for the relevant parameter in each summary table.

10.4.2 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 database for urinalysis (ie a positive or negative result) with the exception of the following reference ranges for urinalysis:

- pH: 5.0 to 9.0
- Specific gravity: 1.000 to 1.030

10.5 Vital Signs

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

10.5.1 Summary Tables for Vital Signs

Vital signs data (ie systolic and diastolic blood pressure [BP], heart rate and oral body temperature), including change from baseline (Day 1, Pre-dose for each study part), will be summarised (ie n, mean, SD, median, minimum and maximum) at each post-baseline time point by study part.

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.

10.5.2 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 10.5.1) in systolic BP, diastolic BP and heart rate will be flagged with an "I" (increase) or "D" (decrease), 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 Quotient SOP "The Interpretation of the Electrocardiogram, Vital Signs and Clinical Laboratory Data During Phase I / II Clinical Trials") defined in Table 4 will be used.

Table 4 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	NA	40 bpm	100 bpm
Oral Body Temperature	NA	35.5°C	37.5°C

NA=Not applicable

10.6 ECGs

The details of measurement of supine ECG parameters (ie ventricular rate, QT interval, QTcF interval, PR interval, QRS duration, QRS axis and interpretation) are described in the study protocol. ECG parameters will be reported in the order given above in both summary tables and data listings.

10.6.1 Summary Tables for ECGs

ECG data, including change from baseline (Day 1, Pre-dose for each study part), will be summarised (ie n, mean, SD, median, minimum and maximum) at each post-baseline time point by study part.The number and percentage of subjects with normal and prolonged QT intervals corrected for heart rate using Fridericia's correction (ie QTcF) and increases in QTcF intervals from baseline within the categories defined in Table 5 (based on the International Council on Harmonisation [ICH] E14 guideline [1]) will be summarised by time point within each study part. Percentages will be based on the number of subjects with measurements at the relevant time point.

For 'Overall' counts the worst (highest) value for each subject will be used for the counts. For the parameter 'Increase in QTcF interval from baseline', decreases in QTcF value fall into the <30 category (ie every subject should appear once in this summary table and actual change rather than absolute change is used for this parameter).

Table 5 ICH E14 Ranges for QTcF Intervals

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

10.6.2 Listings for ECGs

All ECG measurements (ie single readings), including derivations such as change from baseline, will be listed.

All ECG measurements 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 Quotient SOP "The Interpretation of the Electrocardiogram, Vital Signs and Clinical Laboratory Data During Phase I / II Clinical Trials") and defined in Table 6 will be used.

Table 6 ECG Reference Ranges

Parameter	Split	Lower limit	Upper limit
Ventricular Rate (HR)	NA	40 bpm	100 bpm
QT Interval	NA	NA	500 msec
QTcF Interval	Male	NA	450 msec
PR Interval	NA	120 msec	220 msec
QRS Duration	NA	NA	120 msec
QRS Axis	NA	-30°	100°

HR=heart rate
NA=Not applicable

10.7 Body Weight

All body weight data will be listed. Body weight data from screening will be captured with demographic and baseline characteristics. Body weight data from admission to Part 2 will be listed separately.

10.8 Physical Examination

All physical examination details and comments on any physical examination findings will be listed by subject for all subjects. Subjects who have no clinically significant findings at post treatment time points will be reported as 'No Clinically Significant Abnormal Findings' for the purposes of the listing.

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

For consistency across study parts, the definition of Tlag in part 2 was updated to match that of Tlag in Part 1. In addition, the definition of AUCextrap has been clarified.

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 and TFLs 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 n, mean, SD, median, minimum and maximum. For PK data, additional statistics including CV%, geometric n, geometric mean, geometric SD and geometric CV% 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 will be presented as detailed in Table 7 below, unless otherwise stated:

Table 7 Reporting Conventions for Summary Statistics

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

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

Note: The above table relates to rounding of summary stats from data received to certain number of decimal places. Summary stats on data received to a certain number of significant figures will be presented to the same number of significant figures as the 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 enrolled subjects (as defined in Section 3.2.1). Details of age and sex will be included on all data listings.

If any nominal 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 assessment 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 for mass balance parameter estimation using SAS Software is described in Section 9.3.2. Imputations for reporting PK are described in Section 9.2.1.

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

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.

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 summary tables. All summary tables will be QC'd as follows:

- for tables presented by study part only (ie no time points), all summary statistics will be QC'd
- for tables presented by study part and time point, at least one time point in each table will be QC'd – different combinations of time point will be selected across tables
- where tables are produced using a macro for multiple parameters, a minimum of 3 tables, using study part and time point as appropriate, will be QC'd
- for AEs, the study part/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:

- all data points for 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

13.2.3 Quality Control - Data Listings

All data listings will be subjected to a 100% manual QC check against the study database or other appropriate source data for a minimum of 2 subjects. If appropriate, the subjects checked will include at least one subject who withdrew early from the study.

14 SAS Data Transfer

All SAS datasets used for analysis and reporting will be transferred to Kadmon on issue of the final CSR. This will be performed in compliance with CDISC ADaM (IG v1.1), data will be transferred as SAS Software transport files and will include define.xml (v2.0) output as well as a Data Reviewers Guide in pdf, which will be linked to the ADaM define.xml.

In addition, KD025m1 and KD025m2 Part 1 data provided by Covance will not be reported or analysed but will be transferred to Kadmon as raw data and will be included in the SDTM datasets

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 2016 documents and figures will be produced as PDF files. Listings will be sorted by subject ID number and treatment (where applicable).

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 TFLs 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] International Council for Harmonisation (ICH) Topic E 14, The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Guidelines approved by the Committee for Medicinal Products for Human Use (CHMP) in May 2005 which came into force November 2005.

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Table Number	Table Title
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14.1.2.1	Analysis Populations Summary Statistics: All Enrolled Subjects Part 1 & Part 2
14.1.2.2	Analysis Datasets Summary Statistics: PK Population Part 1 & Part 2 *(Programming note: Only produce table if there is a PK analysis dataset. If no PK or mass balance analysis dataset defined then do not produce table 14.1.2.2 or 14.1.2.3, and re-number table 14.1.2.1 as 14.1.2)*
14.1.2.3	Analysis Datasets Summary Statistics: Mass Balance Population Part 1 & Part 2 *(Programming note: Only produce table if there is a mass balance analysis dataset defined. If no PK or mass balance dataset defined then do not produce table 14.1.2.2 or 14.1.2.3, and re-number table 14.1.2.1 as 14.1.2. If there is a mass balance dataset but no PK dataset, then do not produce table 14.1.2.2 and re-number table 14.1.2.3 as 14.1.2.2)*
	Demographic and Baseline Characteristics
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14.2.1.2.1	Plasma Pharmacokinetic Concentrations Summary Statistics: *<PK Population/PK Analysis Dataset>* Part 2: [14C]-KD025 Oral Capsule *<KD025 / KD025m1 / KD025m2 (units)>*
14.2.1.2.2	Plasma Pharmacokinetic Concentrations: Total Radioactivity Summary Statistics: *<PK Population/PK Analysis Dataset>* Part 2: [14C]-KD025 Oral Capsule
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	Plasma and Whole Blood Pharmacokinetic Parameters
14.2.2.1	Plasma Pharmacokinetic Parameters Summary Statistics: *<PK Population/PK Analysis Dataset>* Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion *< KD025 / [14C]-KD025 >*
14.2.2.2.1	Plasma Pharmacokinetic Parameters Summary Statistics: *<PK Population/PK Analysis Dataset>* Part 2: [14C]-KD025 Oral Capsule *< KD025 / KD025m1 / KD025m2 >*
14.2.2.2.2	Plasma Pharmacokinetic Parameters: Total Radioactivity Summary Statistics: *<PK Population/PK Analysis Dataset>* Part 2: [14C]-KD025 Oral Capsule
14.2.2.2.3	Whole Blood Pharmacokinetic Parameters: Total Radioactivity Summary Statistics: *<PK Population/PK Analysis Dataset>* Part 2: [14C]-KD025 Oral Capsule
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14.2.3.1.2	Excretion: Total Radioactivity Cumulative Ae(Urine) <*Units*> Summary Statistics: <Mass Balance Population/Mass Balance Analysis Dataset> Part 2: [14C]-KD025 Oral Capsule
14.2.3.1.3	Recovery: Total Radioactivity %Ae(Urine) by Collection Period Summary Statistics: <Mass Balance Population/Mass Balance Analysis Dataset> Part 2: [14C]-KD025 Oral Capsule
14.2.3.1.4	Recovery: Total Radioactivity Cumulative %Ae(Urine) Summary Statistics: <Mass Balance Population/Mass Balance Analysis Dataset> Part 2: [14C]-KD025 Oral Capsule
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14.2.3.2.2	Excretion: Total Radioactivity Cumulative Ae(Faeces) <*Units*> Summary Statistics: <Mass Balance Population/Mass Balance Analysis Dataset> Part 2: [14C]-KD025 Oral Capsule
14.2.3.2.3	Recovery: Total Radioactivity %Ae(Faeces) by Collection Period Summary Statistics: <Mass Balance Population/Mass Balance Analysis Dataset> Part 2: [14C]-KD025 Oral Capsule
14.2.3.2.4	Recovery: Total Radioactivity Cumulative %Ae(Faeces) Summary Statistics: <Mass Balance Population/Mass Balance Analysis Dataset> Part 2: [14C]-KD025 Oral Capsule
	Excretion and Recovery – Urine and Faeces Combined
14.2.3.3.1	Excretion: Total Radioactivity Ae(Total) by Collection Period <*Units*> Summary Statistics: <Mass Balance Population/Mass Balance Analysis Dataset> Part 2: [14C]-KD025 Oral Capsule

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14.2.3.3.2	Excretion: Total Radioactivity Cumulative Ae(Total) <*Units*> Summary Statistics: <Mass Balance Population/Mass Balance Analysis Dataset> Part 2: [14C]-KD025 Oral Capsule
14.2.3.3.3	Recovery: Total Radioactivity %Ae(Total) by Collection Period Summary Statistics: <Mass Balance Population/Mass Balance Analysis Dataset> Part 2: [14C]-KD025 Oral Capsule
14.2.3.3.4	Recovery: Total Radioactivity Cumulative %Ae(Total) Summary Statistics: <Mass Balance Population/Mass Balance Analysis Dataset> Part 2: [14C]-KD025 Oral Capsule
	Cumulative Excretion and Recovery Parameters
14.2.3.4	Excretion and Recovery: Total Radioactivity Overall Cumulative Excretion and Recovery Parameters Summary Statistics: <Mass Balance Population/Mass Balance Analysis Dataset> Part 2: [14C]-KD025 Oral Capsule
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14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events Summary Statistics: Safety Population Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
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 Oral Tablet & [14C]-KD025 IV Infusion
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 Oral Tablet & [14C]-KD025 IV Infusion
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 Oral Tablet & [14C]-KD025 IV Infusion
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14.4.1.2	Haematology Shift Table: Safety Population Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
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14.2.2.1.2	Plasma Pharmacokinetic Concentrations Log10/Linear Scale Geometric Mean (×/÷ Geometric SD) Values: *<PK Population/PK Analysis Dataset>* Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion *< KD025 / [14C]-KD025 >*
14.2.2.1.3	Plasma Pharmacokinetic Concentrations Linear/Linear Scale Spaghetti Plots of All Individual Values: *<PK Population/PK Analysis Dataset>* Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion *< KD025 / [14C]-KD025 >*
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14.2.2.2.2	Plasma Pharmacokinetic Concentrations Log10/Linear Scale Geometric Mean (×/÷ Geometric SD) Values: *<PK Population/PK Analysis Dataset>* Part 2: [14C]-KD025 Oral Capsule *(Programming note: KD025. KD025m1, KD025m2 and total radioactivity will be overlaid on the same plot)*

Figure Number	Figure Title
14.2.2.2.3	Plasma and Whole Blood Pharmacokinetic Concentrations: Total Radioactivity Linear/Linear Scale Arithmetic Mean (± Arithmetic SD) Values: *<PK Population/PK Analysis Dataset>* Part 2: [14C]-KD025 Oral Capsule *(Programming note: Plasma and whole blood total radioactivity concentrations will be overlaid on the same plot)*
14.2.2.2.4	Plasma and Whole Blood Pharmacokinetic Concentrations: Total Radioactivity Log10/Linear Scale Geometric Mean (×/÷ Geometric SD) Values: *<PK Population/PK Analysis Dataset>* Part 2: [14C]-KD025 Oral Capsule *(Programming note: Plasma and whole blood total radioactivity concentrations will be overlaid on the same plot)*
14.2.2.2.5	Plasma Pharmacokinetic Concentrations Linear/Linear Scale Spaghetti Plots of All Individual Values: *<PK Population/PK Analysis Dataset>* Part 2: [14C]-KD025 Oral Capsule *<Analyte>* *(Programming note: KD025, KD025m1 and KD025m2 will be displayed on separate pages)*
14.2.2.2.6	Plasma Pharmacokinetic Concentrations Log10/Linear Scale Spaghetti Plots of All Individual Values: *<PK Population/PK Analysis Dataset>* Part 2: [14C]-KD025 Oral Capsule *<Analyte>* *(Programming note:KD025, KD025m1 and KD025m2 will be displayed on separate pages)*

Figure Number	Figure Title
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14.2.2.2.9	Plasma and Whole Blood Pharmacokinetic Concentrations Linear/Linear Scale Individual Values for Subject *<xxx>*: *<PK Population/PK Analysis Dataset>* Part 2: [14C]-KD025 Oral Capsule *<Subject>* *(Programming note: KD025, KD025m1, KD025m2 and total radioactivity [plasma and whole blood] will be overlaid on the same plot)*
14.2.2.2.10	Plasma and Whole Blood Pharmacokinetic Concentrations Log10/Linear Scale Individual Values for Subject *<xxx>*: *<PK Population/PK Analysis Dataset>* Part 2: [14C]-KD025 Oral Capsule *<Subject>* *(Programming note: KD025, KD025m1, KD025m2 and total radioactivity [plasma and whole blood] will be overlaid on the same plot)*

Figure Number	Figure Title
14.2.2.3.1	Plasma Pharmacokinetic Concentrations: Oral Formulations, KD025 Linear/Linear Scale Arithmetic Mean (± Arithmetic SD) Values: <*PK Population/PK Analysis Dataset*> Part 1 and 2 *(Programming note: Treatments A and C will be overlaid on the same plot)*
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16.2.5.3.2.3	Plasma and Whole Blood Pharmacokinetic Concentrations: Total Radioactivity Individual Values: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule *(Programming note: This listing will include whole blood:plasma concentration ratios)*
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16.2.7.1.1	Pre-dose Adverse Events Individual Values: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
16.2.7.1.2	All Treatment-Emergent Adverse Events Individual Values: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
16.2.7.1.3	Serious Adverse Events Individual Values: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
16.2.7.2.1	Pre-dose Adverse Events Individual Values: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule
16.2.7.2.2	All Treatment-Emergent Adverse Events Individual Values: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule
16.2.7.2.3	Serious Adverse Events Individual Values: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule
	Laboratory Data
16.2.8.1.1.1	Blood Sample Collection Details for Laboratory Analysis Individual Values: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
16.2.8.1.1.2	Blood Sample Collection Comments Individual Values: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
16.2.8.1.2.1	Haematology Individual Values: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
16.2.8.1.2.2	Haematology Individual Values Outside the Reference Range: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
16.2.8.1.3.1	Clinical Chemistry Individual Values: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion

Listing Number	Listing Title
16.2.8.1.3.2	Clinical Chemistry Individual Values Outside the Reference Range: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
16.2.8.1.4.1	Urinalysis Sample Collection Individual Values: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
16.2.8.1.4.2	Urinalysis Individual Values: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
16.2.8.1.4.3	Urinalysis Individual Values Outside the Reference Range: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
16.2.8.2.1.1	Blood Sample Collection Details for Laboratory Analysis Individual Values: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule
16.2.8.2.1.2	Blood Sample Collection Comments Individual Values: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule
16.2.8.2.2.1	Haematology Individual Values: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule
16.2.8.2.2.2	Haematology Individual Values Outside the Reference Range: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule
16.2.8.2.3.1	Clinical Chemistry Individual Values: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule
16.2.8.2.3.2	Clinical Chemistry Individual Values Outside the Reference Range: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule
16.2.8.2.4.1	Urinalysis Sample Collection Individual Values: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule
16.2.8.2.4.2	Urinalysis Individual Values: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule
16.2.8.2.4.3	Urinalysis Individual Values Outside the Reference Range: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule

Listing Number	Listing Title
	Vital Signs and ECGs
16.2.9.1.1.1	Vital Signs Individual Values: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
16.2.9.1.1.2	Vital Signs Individual Values Outside the Reference Range: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
16.2.9.1.2.1	ECGs Individual Values: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion *(Programming note: The order of ECG parameters is to be as per* Section 10.6*)*
16.2.9.1.2.2	ECGs Individual Values Outside the Reference Range: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
16.2.9.2.1.1	Vital Signs Individual Values: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule
16.2.9.2.1.2	Vital Signs Individual Values Outside the Reference Range: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule
16.2.9.2.2.1	ECGs Individual Values: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule *(Programming note: The order of ECG parameters is to be as per* Section 10.6*)*
16.2.9.2.2.2	ECGs Individual Values Outside the Reference Range: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule
	Other Data
16.2.9.3.1	Physical Examination Data Individual Values: All Enrolled Subjects Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion
16.2.9.3.2.1	Physical Examination Data Individual Values: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule
16.2.9.3.2.2	Body Weight Data Individual Values: All Enrolled Subjects Part 2: [14C]-KD025 Oral Capsule

20 Mock Tables

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Protocol: KD025-108

TABLE 14.1.1
Subject Disposition by Reason
Summary Statistics: All Enrolled Subjects
Part 1 & Part 2

	OVERALL (N=X) n (%)
Subjects enrolled (1)	xx (xx.x)
Subjects dosed	
in Part 1	xx (xx.x)
in Part 2	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>	xx (xx.x)

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1 and a 200 mg KD025 oral capsule in Part 2
A subject may be discontinued for one reason only. (1) An enrolled subject signed the informed consent, qualified per the inclusion/exclusion criteria and was allocated a subject number

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Programming note: This table will be continued for all reasons for discontinuation as recorded on the source. If none of the subjects discontinued from the study early then reasons for discontinuation will not be populated in the summary table
Programming note: Percentages are based on the number of subjects enrolled

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Protocol: KD025-108

TABLE 14.1.2.1
Analysis Populations
Summary Statistics: All Enrolled Subjects
Part 1 & Part 2

	Part 1 (N=X) n (%)	Part 2 (N=X) n (%)	OVERALL (N=X) n (%)
Number (%) of subjects in safety population	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reasons for exclusion from safety population			
<All categories from source>	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number (%) of subjects in PK population	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reasons for exclusion from PK population			
<All categories from source>	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number (%) of subjects in mass balance population		xx (xx.x)	xx (xx.x)
Reasons for exclusion from mass balance population			
<All categories from source>		xx (xx.x)	xx (xx.x)

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1 and a 200 mg KD025 oral capsule in Part 2
A subject may be excluded for more than one reason

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Programming note: This table will be continued for all reasons for exclusion as recorded on the source. If none of the subjects were excluded from a population then reasons for exclusion will not be populated in the summary table.
Programming note: Percentages are based on the number of subjects enrolled

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Protocol: KD025-108

TABLE 14.1.2.2
Analysis Datasets
Summary Statistics: PK Population
Part 1 & Part 2

	Part 1 (N=X) n (%)	Part 2 (N=X) n (%)	OVERALL (N=X) n (%)
Number (%) of subjects in PK analysis set	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reasons for exclusion from PK analysis set			
<All categories from source>	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1 and a 200 mg KD025 oral capsule in Part 2
A subject may be excluded for more than one reason

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Programming note: This table will be continued for all reasons for exclusion as recorded on the source. If none of the subjects were excluded from an analysis set then reasons for exclusion will not be populated in the summary table.
Programming note: Repeat for mass balance population on separate page (with sub-heading 'Summary Statistics: Mass Balance Population') if required
Programming note: Produce similar table for mass balance population (if mass balance dataset defined) as table 14.1.2.3 if a PK dataset is also defined or 14.1.2.2 if not.
Programming note: Percentages are based on the number of subjects in the relevant population

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TABLE 14.1.3
Demographic and Baseline Characteristics
Summary Statistics: Safety Population
Part 1 & Part 2

		OVERALL (N=X)
Age (years)	n	xx
	Mean	xx.x
	SD	xx.x
	Median	xx.x
	Min	xx
	Max	xx
Ethnicity n(%)	<All categories on source>	xx (xx.x)
Race n(%)	<All categories on source>	xx (xx.x)
Sex n(%)	Male	xx (xx.x)
Height (cm)	…	…
Weight (kg)	…	…
BMI (kg/m^2)	…	…

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1 and a 200 mg KD025 oral capsule in Part 2

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Programming note: This table will continue for all categories of ethnicity and race.
Height, Weight and BMI will be assessed using the same descriptive statistics as Age.
If any values are missing, then a "missing" row will be included in the table, as applicable

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TABLE 14.1.4
Lifestyle Details: Smoking History and Alcohol Consumption at Baseline
Summary Statistics: Safety Population
Part 1 & Part 2

		OVERALL (N=X) n (%)
Does subject smoke (1)	NO	xx (xx.x)
	PREVIOUSLY	xx (xx.x)
Alcohol Consumption (2)	NONE	xx (xx.x)
	YES: NOT REGULAR (2)	xx (xx.x)

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1 and a 200 mg KD025 oral capsule in Part 2
Baseline is defined as at Screening
(1) Anyone who smoked or used e-cigarettes or nicotine replacement products in the last 12 months is excluded from the study. (2) Anyone who regularly consumes alcohol (>21 units/week in males) is excluded from the study. 1 unit = 1/2 pint beer, 25 mL of 40% spirit, 1.5 to 2 units = 125 mL glass of wine depending on type

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Protocol: KD025-108

TABLE 14.1.5.1
Extent of Exposure
Summary Statistics: Safety Population
Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion

Statistic	200 mg KD025 Oral Tablet (N=X)	100 µg [14C]-KD025 IV Infusion (N=X) (µg)	100 µg [14C]-KD025 IV Infusion (N=X) (kBq)
n	xx	xx	xx
Mean		xx.xx	xx.xx
SD		xx.xx	xx.xx
Median		xx.xx	xx.xx
Min		xx.x	xx.x
Max		xx.x	xx.x

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1

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TABLE 14.1.5.2
Extent of Exposure
Summary Statistics: Safety Population
Part 2: [14C]-KD025 Oral Capsule

	200 mg [14C]-KD025 Oral Capsule (N=X)		
Statistic	(mg)	(MBq)	(µCi)
n	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx
SD	xx.xx	xx.xx	xx.xx
Median	xx.xx	xx.xx	xx.xx
Min	xx.x	xx.x	xx.x
Max	xx.x	xx.x	xx.x

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg [14C]-KD025 oral capsule in Part 2

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Protocol: KD025-108

TABLE 14.2.1.1
Plasma Pharmacokinetic Concentrations
Summary Statistics: <PK Population/PK Analysis Dataset>
Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion

KD025 <units> (N=X)

	Arithmetic (1)							Geometric (2)			
Time Point	n	Mean	SD	CV%	Median	Min	Max	n	Mean	SD	CV%
PRE-DOSE	xx	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx				
TIME POINT 1	xx	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x
TIME POINT 2	xx	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x
TIME POINT 3	xx	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x
…	…	…	…	…	…	…	…	…	…	…	…
<All other time points>	xx	xx.xxx	xx.xxx	xx.x	xx.xxx	xx.xx	xx.xx	xx	xx.xxx	xx.xxx	xx.x

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1
No imputation was carried out for concentration values reported as NR (not reportable/no result) or NS (no sample)
The LLOQ value was <value, units>
(1) For arithmetic summary statistics, concentration values reported as BLQ are set to zero.
(2) Geometric summary statistics are not calculated for the pre-dose time-point. For calculation of geometric summary statistics, values reported as BLQ are set to ½ × LLOQ.

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Programming note: This table will be continued for all time points for each analyte on a new page
Programming note: Similar tables will be produced for Part 2 (update heading and footnote accordingly) for:
- Table 14.2.1.2.1 ie Plasma Pharmacokinetic Concentrations
- Table 14.2.1.2.2 ie Plasma Pharmacokinetic Concentrations: Total Radioactivity
- Table 14.2.1.2.3 ie Whole Blood Pharmacokinetic Concentrations: Total Radioactivity

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Protocol: KD025-108

TABLE 14.2.2.1
Plasma Pharmacokinetic Parameters
Summary Statistics: <PK Population/PK Analysis Dataset>
Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion

KD025 (N=X)

	PK Parameter				
Statistic	Parameter 1 (units)	Parameter 2 (units)	Parameter 3 (units)	.....	All Other PK Parameters (units)
n	xx	xx	xx	...	xx
Mean	xx.xxx	xx.xxx	xx.xxx	...	xx.xxx
SD	xx.xxx	xx.xxx	xx.xxx	...	xx.xxx
CV%	xx.x	xx.x	xx.x	...	xx.x
Median	xx.xxx	xx.xxx	xx.xxx	...	xx.xxx
Min	xx.xx	xx.xx	xx.xx	...	xx.xx
Max	xx.xx	xx.xx	xx.xx	...	xx.xx
Geometric n	xx	xx	xx	...	xx
Geometric Mean	xx.xxx	xx.xxx	xx.xxx	...	xx.xxx
Geometric SD	xx.xxx	xx.xxx	xx.xxx	...	xx.xxx
Geometric CV%	xx.x	xx.x	xx.x	...	xx.x

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1
The LLOQ value was <value, units>

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Programming note: This table will be continued for all parameters for each analyte on a new page
Programming note: Similar tables will be produced for Part 2 (update heading and footnote accordingly) for:
- Table 14.2.2.2.1 ie Plasma Pharmacokinetic Parameters
- Table 14.2.2.2.2 ie Plasma Pharmacokinetic Parameters: Total Radioactivity
- Table 14.2.2.2.3 ie Whole Blood Pharmacokinetic Parameters: Total Radioactivity
- Table 14.2.2.2.4 ie Whole Blood:Plasma Concentration Ratios: Total Radioactivity

Programming note: Similar tables will be produced without part and analyte headings (update footnote accordingly) for:
- Table 14.2.2.3 ie Relative Bioavailability of Oral Formulations: KD025

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TABLE 14.2.3.1.1
Excretion: Total Radioactivity
Ae(Urine) by Collection Period <(units)>
Summary Statistics: <Mass Balance Population/Mass Balance Analysis Dataset>
Part 2: [14C]-KD025 Oral Capsule

[14C]-KD025 (N=X)

Collection Period	n	Mean	SD	CV%	Median	Min	Max
TIME0-TIME1	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x
TIME1-TIME2	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x
TIME2-TIME3	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x
…	…	…	…	…	…	…	…
<All other time intervals>	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg [14C]-KD025 oral capsule in Part 2
Where a subject has failed to void or has a BLQ concentration over a particular collection interval, the amount excreted (Ae) has been set to zero

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Programming Note: similar tables will be produced for:
- Table 14.2.3.1.3 ie %Ae(Urine) (Recovery)
- Table 14.2.3.2.1 ie Ae(Faeces)
- Table 14.2.3.2.3 ie %Ae(Faeces) (Recovery)
- Table 14.2.3.3.1 ie Ae[total]
- Table 14.2.3.3.3 ie %Ae[total] (Recovery)

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TABLE 14.2.3.1.2
Excretion: Total Radioactivity
Cumulative Ae(Urine) <(units)>
Summary Statistics: <Mass Balance Population/Mass Balance Analysis Dataset>
Part 2: [14C]-KD025 Oral Capsule

[14C]-KD025 (N=X)

Collection Period	n	Mean	SD	CV%	Median	Min	Max
TIME0-TIME1	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x
TIME0-TIME2	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x
TIME0-TIME3	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x
…	…	…	…	…	…	…	…
<All other time intervals>	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg [14C]-KD025 oral capsule in Part 2

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Programming note: If required as a result of early withdrawal or varying follow-up periods, a further set of tables will be produced for LOCF values. Table numbers will be incremented by .1 for observed values and .2 for LOCF.
Programming note: Similar tables will be produced for:
- Table 14.2.3.1.4 ie Cumulative %Ae(Urine) (Recovery)
- Table 14.2.3.2.2 ie Cumulative Ae(Faeces)
- Table 14.2.3.2.4 ie Cumulative %Ae(Faeces) (Recovery)
- Table 14.2.3.3.2 ie Cumulative Ae[total]
- Table 14.2.3.3.4 ie Cumulative %Ae[total] (Recovery)

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TABLE 14.2.3.4
Excretion and Recovery: Total Radioactivity
Overall Cumulative Excretion and Recovery Parameters
Summary Statistics: <Mass Balance Population/Mass Balance Analysis Dataset>
Part 2: [14C]-KD025 Oral Capsule

[14C]-KD025 (N=X)

	Urine		Faeces		Total	
	CumAe (units)	Cum%Ae (%)	CumAe (units)	Cum%Ae (%)	CumAe (units)	Cum%Ae (%)
n	xx	xx	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
SD	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
CV%	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Median	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Min	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Max	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg [14C]-KD025 oral capsule in Part 2
CumAe represent cumulative excretion. Cum%Ae represents cumulative recovery as a percentage of the radioactive dose administered

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Protocol: KD025-108

TABLE 14.3.1.1
Overall Summary of Treatment-Emergent Adverse Events
Summary Statistics: Safety Population
Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion

Event	200 mg KD025 Oral Tablet & 100 µg [14C]-KD025 IV infusion (N=X) n(%)	Total Number of Events
TEAE	xx (xx.x)	xx
ADR (1)	xx (xx.x)	xx
Severe TEAE	xx (xx.x)	xx
Serious TEAE	xx (xx.x)	xx
TEAE leading to subject withdrawal	xx (xx.x)	xx
TEAE leading to death	xx (xx.x)	xx

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1
TEAEs are coded using MedDRA v22.0
(1) An ADR is any AE that the investigator considers possibly related or related to the IMP
n is the number of subjects reporting at least one event

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Programming note: Similar table will be produced for Part 2 (ie Table 14.3.2.1)

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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 Oral Tablet & [14C]-KD025 IV Infusion

	200 mg KD025 Oral Tablet & 100 µg [14C]-KD025 IV infusion (N=X)	
	n(%)	Events n
Subjects Reporting TEAEs	xx (xx.x)	xx
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx
PREFFERED TERM 1	xx (xx.x)	xx
PREFFERED TERM 2	xx (xx.x)	xx
etc	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx
PREFFERED TERM 1	xx (xx.x)	xx
PREFFERED TERM 2	xx (xx.x)	xx
etc	…	…
…	…	…

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1
TEAEs are coded using MedDRA v22.0 and are presented in descending order of frequency
Subjects experiencing more than 1 episode of a TEAE are counted only once within each SOC and PT
Event is the total number of TEAEs within the relevant SOC and PT

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Programming note: Counts of number of subjects are by maximum severity (ie using the most severe episode)
Programming note: Similar table will be produced for Part 2 (ie Table 14.3.2.2)

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Protocol: KD025-108

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 Oral Tablet & [14C]-KD025 IV Infusion

	200 mg KD025 Oral Tablet & 100 µg [14C]-KD025 IV infusion (N=X)		
	Mild n(%)	Moderate n(%)	Severe n(%)
Subjects Reporting TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFFERED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFFERED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFFERED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFFERED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…
…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1
TEAEs are coded using MedDRA v22.0 and are presented in descending order of frequency
Counts are given for total number of subjects, not for events
Counts of number of subjects are by maximum severity (ie subjects experiencing more than 1 episode of a TEAE are counted only once within each SOC and PT using the most severe episode)

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Programming note: Similar table will be produced for Part 2 (ie Table 14.3.2.3)

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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 Oral Tablet & [14C]-KD025 IV Infusion

	200 mg KD025 Oral Tablet & 100 µg [14C]-KD025 IV infusion (N=X)		
	Unrelated n(%)	Possibly Related n(%)	Related n(%)
Subjects Reporting TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFFERED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFFERED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFFERED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFFERED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…
…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1
TEAEs are coded using MedDRA v22.0 and are presented in descending order of frequency
Counts are given for total number of subjects, not for events
Counts are given by closest relationship (ie subjects experiencing more than 1
TEAE are counted only once within each SOC and PT using the most closely related event)

PROGRAM PATH: X:\~\QSC200323\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

Programming note: Similar table will be produced for Part 2 (ie Table 14.3.2.4)

Kadmon Corporation LLC
Protocol: KD025-108

TABLE 14.3.1.5
Subjects Reporting Adverse Drug Reactions
By MedDRA System Organ Class and Preferred Term
Summary Statistics: Safety Population
Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion

	200 mg KD025 Oral Tablet & 100 µg [14C]-KD025 IV infusion (N=X)	
	n(%)	Events n
Subjects Reporting ADRs (1)	xx (xx.x)	xx
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx
PREFFERED TERM 1	xx (xx.x)	xx
PREFFERED TERM 2	xx (xx.x)	xx
etc	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx
PREFFERED TERM 1	xx (xx.x)	xx
PREFFERED TERM 2	xx (xx.x)	xx
etc	…	…
…	…	…

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1
(1) An ADR is any AE that the investigator considers possibly related or related to the IMP
ADRs are coded using MedDRA v22.0 and are presented in descending order of frequency
Subjects experiencing more than 1 episode of an ADR are counted only once within each SOC and PT
Event is the total number of ADRs within the relevant SOC and PT

PROGRAM PATH: X:\~\QSC200323\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

Programming note: Counts of number of subjects are by maximum severity (ie using the most severe episode)
Programming note: Similar table will be produced for serious AEs and Part 2 (ie Table 14.3.1.6, 14.3.2.5 and 14.3.2.6)

Kadmon Corporation LLC
Protocol: KD025-108

TABLE 14.4.1.1
Haematology
Summary Statistics: Safety Population
Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion

200 mg KD025 Oral Tablet & 100 µg [14C]-KD025 IV Infusion (N=X)
<Parameter> (<units>) [ref range xxx - xxx (male)]

	Result						Change from Baseline					
Time Point	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x						
Day 3	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1
BASELINE is defined as Day 1, Pre-dose

PROGRAM PATH: X:\~\QSC200323\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

Programming note: This table will be continued for all haematology parameters and all time points.
Programming note: A similar table will be produced for Clinical Chemistry and Part 2 (ie Table 14.4.1.3, 14.4.2.1 and 14.4.2.3 - note that the post-baseline time point is different for Part 2, update table accordingly)

Kadmon Corporation LLC
Protocol: KD025-108

TABLE 14.4.1.2
Haematology
Shift Table: Safety Population
Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion

200 mg KD025 Oral Tablet & 100 µg [14C]-KD025 IV Infusion (N=X)
<Parameter> (<units>) [ref range xxx - xxx (male)]

		Baseline		
Time Point Assessment	N#	Below n(%)	Within n(%)	Above n(%)
Day 3	xx			
Below		xx (xx.x)	xx (xx.x)	xx (xx.x)
Within		xx (xx.x)	xx (xx.x)	xx (xx.x)
Above		xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1
BASELINE is defined as Day 1, Pre-dose
N# is the total number of subjects that have a value at baseline and each given time-point 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

PROGRAM PATH: X:\~\QSC200323\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

Programming note: This table will be continued for all haematology parameters and all time points.
Programming note: A similar table will be produced for Clinical Chemistry and Part 2 (ie Table 14.4.1.4, 14.4.2.2 and 14.4.2.4 - note that the post-baseline time point is different for Part 2, update table accordingly)

Kadmon Corporation LLC
Protocol: KD025-108

TABLE 14.5.1.1
Vital Signs
Summary Statistics: Safety Population
Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion

200 mg KD025 Oral Tablet & 100 µg [14C]-KD025 IV Infusion (N=X)
<Parameter> (<units>) [ref range xxx - xxx (male)]

	Result						Change from Baseline						Substantial Change (1)		
Time Point	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max	DEC	NONE	INC
BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x									
TIME POINT 1	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx
TIME POINT 2	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx
TIME POINT 3	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx
…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…
<All other time points>	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1
BASELINE is defined as Day 1, Pre-dose
(1) 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:\~\QSC200323\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

Programming note: This table will be continued for all vital signs parameters and may be continued over more than one page
Programming note: A similar table will be produced for Part 2 (ie Table 14.5.2.1)

Kadmon Corporation LLC
Protocol: KD025-108

TABLE 14.5.1.2.1
ECGs
Summary Statistics: Safety Population
Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion

200 mg KD025 Oral Tablet & 100 µg [14C]-KD025 IV Infusion (N=X)
<Parameter> (<units>) [ref range xxx - xxx (male)]

	Result						Change from Baseline					
Time Point	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x						
TIME POINT 1	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x
TIME POINT 2	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x
TIME POINT 3	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x
…	…	…	…	…	…	…	…	…	…	…	…	…
<All other time points>	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x

Note: The data in this table are presented in listing x.x
All subjects received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1
BASELINE is defined as Day 1, Pre-dose

PROGRAM PATH: X:\~\QSC200323\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

Programming note: This table will be continued for all ECG parameters and may be continued over more than one page
Programming note: Parameter may be added as the first column in this table.
Programming note: A similar table will be produced for Part 2 (ie Table 14.5.2.2.1)

Kadmon Corporation LLC
Protocol: KD025-108

TABLE 14.5.1.2.2
ECGs
QTcF Categorical Data
Part 1: KD025 Oral Tablet & [14C]-KD025 IV Infusion

200 mg KD025 Oral Tablet & 100 µg [14C]-KD025 IV Infusion (N=X)
<Parameter> (<units>) [ref range xxx - xxx (male)]

		QTcF Intervals (msec)				QTcF Interval Increase (msec)		
Time Point	N#	<=450 n(%)	451-480 n(%)	481-500 n(%)	>500 n(%)	<30 n(%)	30-60 n(%)	>60 n(%)
BASELINE	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)
TIME POINT 3	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 received a 200 mg KD025 oral tablet followed by 100 µg [14C]-KD025 IV infusion in Part 1
BASELINE is defined as Day 1, Pre-dose
Categories for QTcF interval and QTcF interval increases are based on ICH E14 guidelines
N# is the total number of subjects at the relevant time point 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

PROGRAM PATH: X:\~\QSC200323\~\TFLS\PRODUCTION\TAB_XX DDMMMYYYY HH:MM

Programming note: A similar table will be produced for Part 2 (ie Table 14.5.2.2.1)

Appendix 1: Part 1 Study Flow Chart

Study Day	S	A	Resident in Clinic														
	-28 to -2	-1	1														
Timepoint relative Oral Dosing (h)			P	0	0.5	0.75	1	1.5	1.75	1.83	1.92	2	2.08	2.16	2.25	2.5	2.75
Timepoint relative to end of IV infusion (h)									-0.25	-0.16	-0.08	0	0.08	0.16	0.25	0.5	0.75
General Assessments																	
Informed Consent	X																
Medical History	X	X															
Weight and Height (including BMI)	X																
Vein Assessment	X																
CO Breath Test	X	X															
Drug Screen	X	X															
Alcohol Breath Test	X	X															
KD025 Oral Administration				X													
[^{14}C]-KD025 IV Administration									X[a]								
Safety Assessments																	
Physical Examination	X																
Safety Labs[b]	X		X														
Urinalysis	X		X														
ECG	X	X	X														
Vital Signs[c]	X	X	X														
Adverse Events	←																→
Prior and Concomitant Medication	←																→
PK and Total Radioactivity Assessments																	
Plasma Samples for KD025[d]			X		X		X	X				X					
Plasma samples for [^{14}C]-KD025[e]									X	X	X	X	X	X	X	X	X

Appendix 1 Part 1 Study Flow Chart (Continued)

Study Day	Resident in Clinic														D
	1												2		3
Timepoint relative Oral Dosing (h)	3	3.5	3.75	4	5	5.75	6	7	8	10	12	14	24	36	48[g]
Timepoint relative to end of IV infusion (h)	1	1.5	1.75	2	3	3.75	4	5	6	8	10	12	22	34	46[g]
Safety Assessments															
Physical Examination															X[f]
Safety Labs[b]															X
Urinalysis															X
ECG			X			X							X		X
Vital Signs[c]			X			X							X		X
Adverse Events	←														→
Prior and Concomitant Medication	←														→
PK and Total Radioactivity Assessments															
Plasma Samples for KD025[d]	X			X	X		X		X	X	X		X	X	X
Plasma samples for [^{14}C]-KD025[e]	X	X		X	X		X	X	X	X	X	X	X	X	X

^{14}C: carbon-14, A: Admission, BMI: Body mass index, CO: carbon monoxide, D: Discharge, ECG: Electrocardiogram; IV: intravenous, P: pre-dose, S: Screening, 0.08 h: 5 min, 0.16 h: 10 min. Footnotes on next page

[a] 15 min IV infusion of [^{14}C]-KD025 solution to be given 1.75 h post oral dose.
[b] Haematology and clinical chemistry at each time point including virology at screening. Creatinine clearance will be estimated at screening from serum creatinine using the Cockcroft-Gault equation.
[c] Blood pressure, heart rate and oral temperature will be measured at the time points indicated above relative to the start of the infusion.
[d] All post-dose time points are relative to the oral KD025 dose
[e] All post-dose time points are relative to the end of the [^{14}C]-KD025 infusion.
[f] Targeted (symptom driven) physical examination
[g] Discharge from clinical unit

Appendix 2: Part 2 Study Flow Chart

Study Day	A[a]	Resident in Clinic																			D[b]	FUP[c]
	-1	1												2	3	4	5	6	7		8	13-15
		P	Time Relative to KD025 Dosing (h)																			
			0	0.5	1	1.5	2	3	4	5	6	8	10	12	24	36	48	72	96	120	144	168	
General Assessments																						
Medical History	X																					
Body Weight	X																					
CO Breath Test	X																					
Drug Screen	X																					
Alcohol Breath Test	X																					
[^{14}C]-KD025 Administration			X																			
Safety Assessments																						
Physical Examination[d]																					X	
Safety Labs[e]		X																			X	
Urinalysis		X																			X	
ECG	X	X					X		X						X						X	
Vital Signs[f]	X	X					X		X						X						X	
Adverse Events	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→	
Prior and Concomitant Medication	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→	
Mass Balance and PK Assessments																						
Plasma Samples for KD025, KD025m1, KD025m2 and TR		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Whole blood samples for TR		X			X				X			X		X	X		X	X	X	X	X	X
Plasma Samples for Metabolite Profiling and ID		X			X				X			X		X	X		X	X	X	X	X	X
Urine Samples for TR[g]	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←		
Faecal Samples for TR[h]	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←		

^{14}C: carbon-14, A: Admission, CO: carbon monoxide, D: Discharge, ECG: Electrocardiogram, FUP: Follow-up visit/call, ID: Identification, P: Pre-dose, TR: total radioactivity. Footnotes on next page

[a] Subjects who participated in Part 1 will be admitted to the clinical unit after a minimum washout period of 7 days.
[b] Discharge from clinical unit. Subjects may be discharged as a group earlier if a cumulative mass balance recovery of >90% has been achieved or if <1% of the dose administered has been collected in urine and faeces within 2 separate, consecutive 24 h periods. If the mass balance criteria have not been met by all subjects on Day 8, the residency period for the subjects not achieving the release criteria may be extended by up to a maximum of 2 additional 24 h periods (up to 216 h post-dose, Day 10) for further collection of urine and faeces. If the criteria are not met by Day 10, or if any additional residency is not considered appropriate or necessary, then home collections of urine and/or faeces may be requested at the discretion of the investigator for individual subjects.
[c] A follow-up phone call will take place 5 to 7 days after discharge or after the end of the last collection period.
[d] Targeted (symptom driven) physical examination
[e] Haematology and clinical chemistry at each time point.
[f] Blood pressure, heart rate and oral temperature will be measured at each time point
[g] A single urine sample will be collected at pre-dose (the first void of the day) and then during the following collection periods 0-6, 6-12, 12-24 h post-dose and then daily (24 h collections) until Day 8/Discharge.
[h] Faeces will be collected from admission until pre-dose and then daily (24 h collections) until Day 8/Discharge.