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

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Quotient Sciences

CLINICAL STUDY PROTOCOL

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
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CONFIDENTIALITY AND GCP COMPLIANCE STATEMENT

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

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

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

Nand Singh BSc, MD, DPM, MFPM
Principal Investigator
Senior Clinical Research Physician

Signature

21 JAN 2019
Date

Signatures for Sponsor

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MRCP (UK)
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Signature

18-JAN-2019

Date

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3 Synopsis

Sponsor:	Drug Substance:	EudraCT No.:
Kadmon Corporation LLC	KD025 and [^{14}C]-KD025	2018-004773-28

Title of Study:
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

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

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

Objectives:
Primary Objectives:

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

Secondary Objectives:

- To obtain information regarding the oral pharmacokinetics (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

Methodology:
This is a single centre, non-randomised, open-label, two-part study in healthy male subjects.

Part 1 Methodology:
Part 1 is an open-label, non-randomised single oral dose followed by an IV microtracer assessment in 6 healthy male subjects. On Day 1 subjects will receive a single dose of KD025 (Treatment A), in the fed state. 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), 1.75 h after the oral dose administration (Treatment A) ie, 15 min before the expected Tmax (2 h) for the oral dose.

Treatment	Investigational Medicinal Product (IMP)
A	KD025 Tablet, 200 mg
B	[^{14}C]-KD025 solution for infusion, 20 µg/mL (100 µg in 5mL), containing NMT 37 kBq (1000 nCi) [^{14}C], as a 15 min IV infusion, 100 µg

^{14}C: carbon-14, kBq: Kilobecquerel, IV: Intravenous, µCi: Microcurie, nCi: Nanocurie, NMT: Not more than. All IMPs are described as free base equivalent.

Part 1 Study Design

All subjects will undergo preliminary screening procedures to determine their eligibility for Parts 1 and 2 of the study at the screening visit (Day -28 to Day -2 of Part 1). Subjects will be admitted to the clinical unit on the evening prior to investigational medicinal products (IMPs) administration (Day -1) for confirmation of eligibility and baseline procedures. Subjects will be dosed on the morning following admission (Day 1). Following an overnight fast (approximately 10 h), subjects will consume a standard breakfast and will receive a single dose of KD025 (Treatment A) 30 min after the start of breakfast. One hour and 45 min post Treatment A administration, subjects will receive an IV infusion of [^{14}C]-KD025 solution (Treatment B). Subjects will remain resident in the clinic until up to 48 h post-oral dose (up to Day 3). The minimum washout period between dose administrations in Part 1 and 2 will be 7 days.

Part 2 Methodology:

Part 2 is an open-label, non-randomised absorption, distribution, metabolism, excretion (ADME) assessment in 6 healthy male subjects. 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 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) on the morning of Day 1 after a standard breakfast.

Treatment	IMP Dose
C	[^{14}C]-KD025 capsule, containing NMT 9.8 MBq (215 µCi) ^{14}C, 200 mg

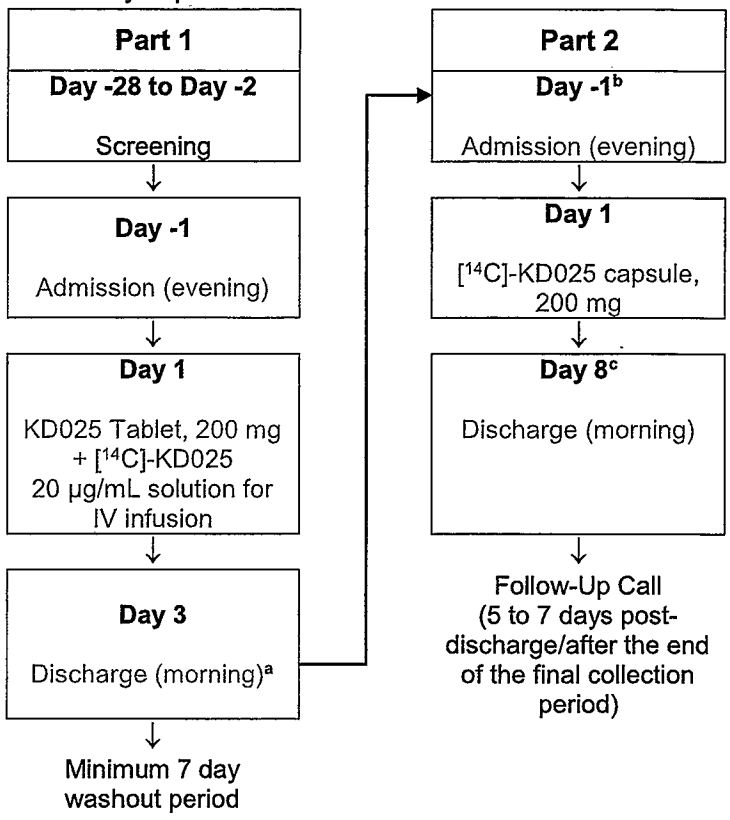
^{14}C:carbon-14, MBq: megabecquerel, µCi: Microcurie, NMT: not more than. IMP is described as free base equivalent.

Part 2 Study Design

Approximately 7 days after subjects have been discharged from Part 1 of the study, subjects will be admitted to the clinical unit on the evening of the day prior to IMP administration (Day -1) for the confirmation of eligibility and baseline procedures. Subjects will be dosed on the morning following admission (Day 1). Following an overnight fast (approximately 10 h), subjects will consume a standard breakfast and will receive a single dose of [^{14}C]-KD025 capsule (Treatment C) 30 min after the start of 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.

An overview of the study is presented below:



[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.

Number of Subjects Planned:

It is planned to enrol 6 healthy male subjects to ensure data in 4 evaluable subjects. Subjects must have participated in Part 1 in order to be eligible for Part 2. No replacement subjects are planned for this study.

Duration of Study:

Subjects will receive a single oral dose of KD025 followed by an IV infusion of [^{14}C]-KD025 administered 1.75 h after the oral dose on one occasion in Part 1 and a single oral dose of [^{14}C]-KD025 capsule on one dosing occasion in Part 2.

The estimated time from screening until the follow-up phone call is approximately 8 weeks.

Main Inclusion Criteria:

Healthy males aged 30 to 65 years
Body mass index (BMI) 18.0 to 35.0 kg/m^2

Investigational Medicinal Product, Dose and Mode of Administration:

The following IMPs will be used in this clinical study:

Part	Investigational Medicinal Product	Dose and Route of Administration
1	KD025 Tablet, 200 mg	200 mg (as 1 x 200 mg tablet), Oral
	[^{14}C]-KD025 solution for infusion, 20 µg/mL	100 µg, containing NMT 37 kBq (1000 nCi), IV infusion
2	[^{14}C]-KD025 capsule, 200 mg	200 mg, containing NMT 9.8 MBq (215 µCi) ^{14}C, Oral

^{14}C = carbon-14, IV = intravenous, kBq = kilobecquerel, MBq: megabecquerel, µCi: microcurie, nCi = nanocurie, NMT = Not more than. All IMPs are described as free base equivalent.

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

Pharmacokinetic Assessments:

Part 1

Plasma samples will be collected from pre-dose until 48 h post-dose for the analysis of KD025 and [^{14}C]-KD025. Blood samples will be collected at regular time intervals.

The concentration-time data will be analysed by Quotient Sciences using industry standard software (Phoenix WinNonlin version 8.0 or a more recent version, [Certara, Princeton, New Jersey]) using appropriate non-compartmental techniques to obtain estimates of the following parameters where possible and appropriate:

For Plasma [^{14}C]-KD025 following IV administration

- **Tmax:** Time of maximum observed concentration
- **Cmax:** The maximum observed plasma concentration
- **AUC(0-last):** Area under the curve from 0 time to the last measurable concentration
- **AUC(0-inf):** The area under the concentration-time curve from dosing extrapolated to infinity
- **AUC%extrap:** Percentage of AUC(0–inf) extrapolated beyond last measured time point
- **lambda-z:** The first order rate constant associated with the terminal (log-linear) portion of the curve
- **T1/2:** The apparent terminal elimination half-life
- **CL:** Total clearance
- **Vz:** Volume of distribution based on area
- **Vss:** Volume of distribution at steady state
- **MRT:** Mean residence time

For Plasma KD025 following oral administration

- **Tlag:** Time prior to the first measurable (non-zero) concentration
- **Tmax:** Time of maximum observed concentration
- **Cmax:** The maximum observed plasma concentration
- **AUC(0-last):** Area under the curve from 0 time to the last measurable concentration
- **AUC(0-inf):** The area under the concentration-time curve from dosing extrapolated to infinity
- **AUC%extrap:** Percentage of AUC(0–inf) extrapolated beyond last measured time point
- **lambda-z:** The first order rate constant associated with the terminal (log-linear) portion of the curve
- **T1/2:** The apparent terminal elimination half-life
- **F:** Bioavailability of oral formulation compared to IV
- **CL/F:** Apparent clearance

- **Vz/F:** Apparent volume of distribution
- **MRT:** Mean residence time

Part 2:

Plasma samples will be collected from pre-dose until 168 h post-dose for the analysis of total radioactivity, KD025, KD025m1, KD025m2 and [^{14}C]-KD025.

The concentration-time data will be analysed by Quotient Sciences using industry standard software (Phoenix WinNonlin version 8.0 or a more recent version, [Certara, Princeton, New Jersey]) using appropriate non-compartmental techniques to obtain estimates of the following parameters where possible and appropriate:

For Total Radioactivity, KD025, KD025m1 and KD025m2 in plasma:

- **Tlag:** Estimated time from dosing at which the analyte was first quantifiable in a concentration versus time profile
- **Tmax:** Time of maximum observed concentration
- **Cmax:** The maximum observed plasma concentration
- **AUC(0-last):** Area under the curve from 0 time to the last measurable concentration
- **AUC(0-inf):** The area under the concentration-time curve from dosing extrapolated to infinity
- **AUC%extrap:** Percentage of AUC(0–inf) extrapolated beyond last measured time point
- **lambda-z:** The first order rate constant associated with the terminal (log-linear) portion of the curve
- **T1/2:** The apparent terminal elimination half-life
- **Cl/F:** Apparent clearance KD025 only
- **Vd/F:** Apparent volume of distribution KD025 only
- **MRT:** Mean residence time
- Metabolite:Parent ratio for KD025m1 and KD025m2
- whole blood/plasma total radioactivity concentration at selected time points.

Mass Balance Assessments:

For Urine:

- **Ae:** Total radioactivity
- **%Ae:** Total radioactivity expressed as a percentage of the dose
- **Cum Ae:** Cumulative recovery of total radioactivity
- **Cum %Ae:** Cumulative recovery expressed as a percentage of the dose

For Faeces:

- **Ae:** Total radioactivity
- **%Ae:** Total radioactivity expressed as a percentage of the dose
- **Cum Ae:** Cumulative recovery of total radioactivity
- **Cum %Ae:** Cumulative recovery expressed as a percentage of the dose

For Mass Balance Recovery of Total Radioactivity from all excreta:

- **Ae:** Total radioactivity
- **%Ae:** Total radioactivity expressed as a percentage of the dose
- **Cum Ae (Total):** Cumulative recovery of total radioactivity
- **Cum %Ae (Total):** Cumulative recovery expressed as a percentage of the dose

Metabolite Profiling and Identification

Metabolite profiling of plasma, urine and faeces will be performed using liquid chromatography-radio-detection with subsequent mass spectrometry where appropriate. Identification of the chemical structure of each metabolite accounting for greater than 10% of circulating radioactivity in plasma ("AUC pool") and accounting for greater than 10% of the dose in the urine and faeces (from urine pools and faeces homogenate pools) will be performed. These aspects will be reported separately from the clinical study report as a standalone document.

Safety Assessments:

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

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

Statistical Methodology:

No formal statistical analysis will be performed for the safety, pharmacokinetics (PK), or mass balance data.

Sample Size and Power:

The study is exploratory and no formal sample size calculation has been made. Based on experience from previous studies of a similar design, a total of 6 subjects are to be enrolled and a minimum of 4 evaluable subjects are considered sufficient.

An evaluable subject for Part 1 is defined as a subject who has sufficient data for evaluation of the primary bioavailability objective of the study.

A subject in Part 2 will be considered evaluable if they have provided biological samples for up to 168 h after drug administration or have demonstrated >90% mass balance recovery, or have <1% of the administered dose eliminated in excreta for two consecutive days, whichever is the sooner.

4 List of Abbreviations

Abbreviation	Definition
^{14}C	carbon-14
ADR	adverse drug reaction
ADME	absorption, distribution, metabolism and elimination
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARSAC	Administration of Radioactive Substances Advisory Committee
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
cGVHD	Chronic graft versus host disease
CLcr	creatinine clearance
CTGF	connective tissue growth factor
CYP	Cytochrome P450
DMP	Data management plan
EC	ethics committee
ECG	electrocardiogram
EMA	European Medicines Agency
GCP	good clinical practice
GI	gastrointestinal
GP	general practitioner
HBsAg	hepatitis B surface antigen
HCV Ab	hepatitis C virus antibody
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IL	interleukin
IPF	idiopathic pulmonary fibrosis
IV	intravenous
MBq	megabecquerel
MedDRA	Medical Dictionary for Regulatory Activities

MHRA	Medicines and Healthcare products Regulatory Agency
µCi	microcurie
mSv	millisievert
nCi	nanocurie
NMT	not more than
PHE	Public Health England
PI	Principal Investigator
PIS	Participant Information Sheet
PK	pharmacokinetic(s)
QA	quality assurance
QD	once daily
QTc	correct QT interval
QTcF	correct QT interval by Fredericia's formula
RAP	Reporting and Analysis Plan
ROCK	Rho-associated coiled-coil protein kinase
SAE	serious adverse event
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
Th	T-helper
Treg	regulatory T cells
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
WHO	World Health Organisation

5 Background Information

5.1 Introduction

Rho-associated coiled-coil protein kinases (ROCKs) are members of the serine/threonine kinase family, often studied for their role in cell morphology, motility and shape through effects on the cytoskeleton [1][2]. Two ROCK isoforms have been identified, ROCK1 and ROCK2. Both are involved in Rho-mediated changes in the actin/myosin cytoskeletal network. ROCK1 and ROCK2 are not redundant signalling molecules and may serve different functions within cells [3][4][5]. Recent research has uncovered additional roles for ROCK signalling, particularly ROCK2, in conditions including autoimmune disease aggravated or caused by a T-helper (Th)17-polarised T cell response [6] and pulmonary fibrosis [7].

Rho GTPase-mediated signalling pathways play a central role in coordinating and balancing T cell mediated immune responses, including T cell receptor-mediated signalling, cytoskeletal reorganisation, and the acquisition of the appropriate T cell effector program [8]. Recent studies have demonstrated that aberrant activation of ROCK2 leads to induction of interleukin (IL)-17 and IL-21 via interferon regulatory factor 4-dependent mechanism [9].

In addition, ROCK activity was found to be up-regulated in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [10] and inhibition of ROCK2 effectively decreased IL-17 production in vivo and demonstrated efficacy in arthritis and lupus mouse models. Autoimmunity also involves alterations to regulatory T cells (Tregs) that suppress activation of the immune system and play a critical role in maintaining immunological tolerance to self-antigens and inhibiting autoimmune responses [11]. ROCK2 inhibition may increase the suppressive function of Tregs.

ROCK is also downstream of several major pro-fibrotic mediators, including: transforming growth factor beta (TGF-β), connective tissue growth factor (CTGF), and lysophosphatidic acid (LPA). A defining feature of pathologic fibrosis is the differentiation of fibroblasts to myofibroblasts, a process mediated by ROCK. In addition, ROCK mediates stress fibre formation and regulates the transcription of pro-fibrotic genes, including CTGF and alpha-smooth muscle actin (α-SMA). Further, ROCK inhibition has demonstrated anti-fibrotic activity in murine models [12].

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

Pre-clinical investigations have identified that KD025 is metabolised via first pass metabolism to 2 main metabolites KD025m1 and KD025m2 in the species dosed.

5.2 Investigational Medicinal Product(s)

The following investigational medicinal products (IMPs) will be used in this clinical study (Table 1).

Table 1 Investigational Medicinal Products

Part	Investigational Medicinal Product	Dose and Route of Administration
1	KD025 Tablet, 200 mg	200 mg (as 1 x 200 mg tablet), Oral
	[^{14}C]-KD025 solution for infusion, 20 µg/mL	100 µg, containing NMT 37 kBq (1000 nCi), IV infusion
2	[^{14}C]-KD025 capsule, 200 mg	200 mg, containing NMT 9.8 MBq (215 µCi) ^{14}C, Oral

^{14}C = carbon-14, IV = intravenous, kBq = kilobecquerel, MBq: megabecquerel µCi: microcurie, nCi = nanocurie, NMT = not more than. All IMPs are described as free base equivalent.

Only subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments will be stored in a secure, environmentally-controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions. Access will be limited to the investigator and authorised site staff.

Where Quotient Sciences is manufacturing the IMP(s), suitability of the manufacturing process will be documented in a Pharmaceutical Development and Control Strategy Report.

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

5.3 Previous Study Findings

5.3.1 Non-clinical Data Summary

Nonclinical pharmacology studies demonstrate the potential of KD025 to have a therapeutic benefit in a number of indications, particularly in autoimmune disease through effects on Th17-type immune responses, and idiopathic pulmonary fibrosis (IPF) through anti-fibrotic mechanisms [12].

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

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

KD025 undergoes first pass metabolism in all evaluated species after oral administration to form a ROCK2 active metabolite, KD025m1 and a metabolite that is relatively less active against ROCK2, KD025m2.

Distribution studies performed in rats with oral administration of carbon-14 [^{14}C]-KD025 demonstrated distribution primarily into tissues associated with elimination (gastrointestinal [GI], liver, kidney, urinary bladder), adrenal gland, and exocrine glandular tissue. All tissues demonstrated clearance and no appreciable radioactivity was observed in the brain. Melanin-containing tissues (uveal tract and pigmented skin) demonstrated higher tissue retention, indicating some affinity of KD025 for melanin.

[^{14}C]-KD025 excretion was similar in male and female rats and was predominantly via the faecal route (~90%), while urine accounted for a smaller proportion of excretion (<1%).

Based on in-vitro assessment, cytochrome P450 (CYP)3A4 and CYP1A2 were the predominant CYP isoforms responsible for the metabolism of KD025, although CYP2C8, CYP2D6 and Uridine 5'-diphospho-glucuronosyltransferase (UGT)1A9 may also contribute to a lesser extent. Metabolism of KD025 to KD025m1 was CYP3A4 and CYP2C8 dependent. Metabolism of KD025 to KD025m2 was CYP3A4 dependent with further metabolism of KD025m2 dependent on UGT1A1 with no to little contribution from CYP enzymes.

KD025 and the active metabolite KD025m1 is > 99% bound to human, dog and rat plasma proteins. KD025m2 is > 99% bound to human plasma protein.

Good laboratory practice (GLP)-compliant rat and dog general toxicology/toxicokinetic studies of acute, sub-chronic (1 and 3 month), and chronic (6-month rat and 9-month dog) duration have been completed. In addition, safety pharmacology studies evaluating human ether-à-go-go related gene (hERG) (in-vitro), central nervous system (rat), respiratory (rat), and cardiovascular (dog) organ systems have been completed. Embryo-foetal toxicology (rat and rabbit) and fertility (rat) studies have also been completed. Furthermore, KD025 has been evaluated in a panel of studies evaluating drug genotoxicity and phototoxicity potential. The primary non-clinical toxicology finding at/near clinically relevant exposures were limited to changes in the cardiovascular (blood pressure lowering), hepatic (transaminitis, hypertrophy/increased organ weight, and cholestasis/inflammation), renal (increased blood urea nitrogen [BUN], tubular changes, pigmentation and intracellular protein droplets in the epithelium), GI (decreased appetite), and hematopoietic/immunologic (anemia with regeneration and thymic/splenic lymphoid depletion) systems. In addition, KD025 demonstrated embryo-foetal toxicity/teratogenicity as well as reduced male fertility (reduced fertility index/sperm concentration/motility and increased abnormal sperm percentage; testes/epididymis [decreased organ weights and degenerative histopathology]). Male fertility findings were generally at higher than clinically relevant exposures.

Data from these nonclinical studies support a thorough understanding of the potential for safety-related effects of KD025 and have facilitated the development of the current clinical trial monitoring plan. Further details of non-clinical studies can be found in the Investigator's Brochure (IB) [12].

5.3.2 Clinical Data Summary

To date, 7 clinical studies have been completed, consisting of 6 Phase I clinical studies (SLx-2119-09-01, KD025-101, KD025-102, KD025-103, KD025-105, and KD025-106) in healthy subjects, and 1 Phase IIa study (KD025-205) in subjects with psoriasis vulgaris. Additionally, a Phase II study (KD025-206) in subjects with psoriasis vulgaris has been clinically completed; however, the clinical study report is pending. In addition to the completed studies, 5 Phase II studies are ongoing in subjects with chronic graft versus host disease (cGVHD) (KD025-208 and KD025-213), IPF (KD025-207), psoriasis (KD025-211) and systemic sclerosis (KD025-209). A drug-drug interaction phase 1 study is currently ongoing (KD025-107).

KD025 was generally well-tolerated, with most adverse events (AEs) considered mild or moderate in severity and a low incidence of serious adverse events (SAEs) overall. An increase in liver function test AEs at the highest dose tested in Phase 2 studies (400 mg twice daily [BID]) (Study KD025-206) led to this dose no longer being used in subsequent studies.

The most common (≥5% overall) AEs were alanine aminotransferase (ALT) increased (10.8%), nausea (9.7%), diarrhoea (8.9%), upper respiratory tract infection (8.9%), fatigue (7.8%), aspartate aminotransferase (AST) increased (7.8%), gamma-glutamyltransferase increased (7.8%), headache (6.3%), cough (6.3%), and dyspnoea (5.2%).

The most common AEs were generally also the most common treatment related AEs. The majority of these events were mild to moderate in severity.

To date no clinically significant AEs suggestive of photo-toxicity have been reported in KD025 studies. All but one of the skin and subcutaneous tissues system organ class (SOC) events reported to date have been mild to moderate in severity (the exception being a Grade 3 "rash erythematous" likely related to progression of cGVHD). Of note, most of the subjects treated with KD025 have been enrolled into studies of psoriasis and GVHD.

No treatment related deaths have occurred to date.

The identified and potential risks noted in association with KD025, detailed in the IB [12], are balanced by the anticipated benefits that may be afforded to subjects with psoriasis vulgaris, IPF and cGVHD.

6 Rationale

6.1 Study Rationale

This study is being conducted to investigate the oral pharmacokinetics (PK), intravenous (IV) PK, mass balance recovery and metabolite profiling and identification of ^{14}C-KD025.

Kadmon Pharmaceuticals LLC. is developing KD025, a ROCK2 selective inhibitor, for the treatment of autoimmune diseases.

Part 1

Knowing the absolute bioavailability of an oral drug product is a regulatory requirement in some regions, eg Australia. In addition, understanding the bioavailability of a drug and the factors that influence absorption, may guide the formulation development strategy. The IV microtracer technique is an established methodology for measuring the IV and oral kinetics of a drug in the same individuals in a single dosing period. The technique involves concurrent administration of a microdose of the drug containing microtracer amounts of ^{14}C with a single oral therapeutic dose, which avoids the concerns of dose-dependent kinetics when extrapolating IV PK from a microdose, as the systemic exposure is at therapeutic concentrations. This design enables measurement of ^{14}C-labelled drug in the plasma following IV dosing via sensitive accelerator mass spectrometry (AMS) techniques, and measurement of the unlabelled parent in the plasma by standard high performance liquid chromatography mass spectrometry/mass spectrometry (HPLC MS/MS) techniques. Thus, it is possible to obtain the IV PK parameters with the associated variability, and calculate the absolute bioavailability. In

addition, because the IV dose administration involves giving a low volume of a low concentration of parent drug, an advantage of this approach is that it is much easier to develop an IV formulation for microdosing than it would be for a higher clinical dose.

Part 2

The current study is designed to collect samples and to generate data for the absorption, distribution, metabolism and elimination (ADME) of KD025 in humans, as well as generating samples for metabolite profiling and structural identification.

6.2 Dose Rationale

Part 1

KD025 in doses ranging from 20 to 1000 mg once daily (QD) to 500 mg BID have generally been well tolerated. A single oral dose of 200 mg of KD025 followed by an 100 µg IV dose of [^{14}C]-KD025, given 1.75 h after the oral dose has been administered (estimated to end at the time of maximum plasma concentration [Tmax] for the oral dose [2 h]), has been selected for Part 2 of this study. The 200 mg dose has been well tolerated as a single dose and in repeat dosing in healthy subjects and patients with psoriasis and cGVHD; repeat dosing at 400 mg QD has been well tolerated in patients with cGVHD and IPF. The 200 mg dose provides a clear PK profile, in the linear range, well above the lower limit of quantification, and is in the expected therapeutic range.

Part 1 is the absolute bioavailability part of the study where an IV micro dose of KD025 containing microtracer amounts of ^{14}C is administered following administration of an oral dose of KD025 to determine the bioavailability of the oral dose compared with the IV dose. According to the International Council for Harmonisation (ICH) M3 guidance, a micro dose is a dose that is <1/100th of the pharmacologically active dose up to a maximum of 100 µg. In addition, to ensure that the IV micro dose does not contribute significantly to the exposure following oral dosing, the IV dose is reduced further and in this study will be 1/1000th of the oral dose.

An IV microtracer dose is one that contains not more than (NMT) 37.0 kBq (1000 nCi). This has been selected as it is the standard radioactive dose used in this type of study and will be sufficient to meet the objectives of Part 1, but contains a low enough amount of radioactivity so as not to cause a significant risk to the subjects.

Therefore the IV dose for this study will be 100 µg [^{14}C]-KD025 containing NMT 37.0 kBq (1000 nCi). This IV dose is 1/2000th of the oral dose administered in this study and <1/100th of the likely therapeutic dose, and hence is an appropriate 'IV microtracer dose'.

Part 2

KD025 in doses ranging from 20 to 1000 mg QD to 500 mg BID have generally been well tolerated. A single dose of 200 mg [^{14}C]-KD025 has been selected for Part 2 of this study. The 200 mg dose has been well tolerated as a single dose and in repeat dosing in healthy subjects and patients with psoriasis and cGVHD; repeat dosing at 400 mg QD has been well tolerated in patients with cGVHD and IPF. The 200 mg dose provides a clear PK profile, in the linear range, well above the lower limit of quantification, and is in the expected therapeutic range.

The dose of radioactivity for Part 2 has been determined following review of human dosimetry calculations provided by Public Health England (PHE). In accordance with the 'as low as reasonably practical' principle, the lowest amount of radioactivity will be administered that gives confidence that the study objectives will be met. Based on the human dosimetry calculations, a radioactive dose of no more than 9.8 MBq (215 µCi) by the oral route will be necessary. Adequate metabolite profiling of some key plasma samples may not be possible at a radioactive dose less than this.

Subjects will be participating in both study Parts 1 and 2, therefore the radioactive dose for Part 2 will be adjusted to take into account the microtracer amount of radioactivity that the subjects will receive in Part 1 of the study (37 kBq/1000 nCi). Thus the oral dose for Part 2 will have a radioactive dose containing NMT 9.8 MBq (215 µCi). The total committed effective dose subjects will receive is 3 mSv, falling within International Commission on Radiological Protection (1992) Guidelines for Category IIb studies (1 to 10 mSv).

To ensure that the [^{14}C] drug products do not exceed the limit for radioactive dose approved by the Administration of Radioactive Substances Advisory Committee (ARSAC), the target specific activity of the [^{14}C] drug substance will be set at 90% of 90% of the threshold radioactive dosing limit. This will ensure provision for a ± 10% range on the [^{14}C] drug substance specification for specific activity and a ± 10% range on the [^{14}C] drug substance assay in the drug product, thereby providing continued assurance for compliance with the ARSAC-approved limit for drug product radioactivity dose.

A positive food effect has been reported in previous studies and current dosing instructions in on-going Phase 2 studies recommend administration of KD025 with food [12]. Therefore oral administration of KD025 in this study will be performed in the fed state, to ensure characterisation of absorption, metabolism and excretion in conditions that best mimic intended clinical use.

6.3 Population Rationale

The European Medicines Agency (EMA) propose to include subjects in the age group 18 to 55 years with normal weight who are non-smokers without a history of alcohol or drug abuse. The latter criteria are proposed to avoid interaction on drug metabolism and to avoid non-compliance. In order to avoid any interaction with other medication, no co-medication except 4 g of paracetamol per day (within 24 h) will be allowed.

We acknowledge the ARSAC Notes for Guidance recommend that wherever possible, healthy subjects selected for research projects should be aged over 50 years [13]. However, Part 2 of this study is designed to generate data for supporting the investigation of the human ADME of a drug, as well as generating samples for metabolite profiling and structural identification.

There are 2 main reasons for generating these data within a clinical development programme. The first is to provide human metabolite data that can be used to interpret the metabolism profiles seen in the preclinical species employed in the longer term toxicity studies, to ensure that there is adequate toxicology coverage for the safe development of the drug in patients. The second is to provide data to understand how the drug is processed in physiologically normal subjects, because understanding the routes of metabolism and elimination in a healthy population generates the appropriate data to guide the clinical pharmacology package required to fulfil the regulatory requirements of a New Drug Application (NDA).

In order to address these 2 main aims of an ADME study, investigation of the drug under development is required in a population with normal physiological function, as it is recognised that certain physiological processes eg renal function, deteriorate with age and therefore it is preferable to use as healthy as possible population, to mitigate against factors which may make interpretation of the data difficult. Also, healthy subjects as a trial population are ideal since they have a relatively stable physiological, biochemical and hormonal status, which removes any disease-related variations and variations due to concomitant medications. Therefore given the aims of this ADME study our target age range for this study will be 30 to 65 years.

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

The purpose of this study is to investigate the oral pharmacokinetics (PK), intravenous (IV) PK, mass balance recovery and metabolite profiling and identification of ^{14}C-KD025. It is therefore an advantage to enrol a relatively homogeneous population and to minimise variability. Based on the above considerations and target population, healthy male subjects, aged 30 to 65 years are considered suitable for this study.

6.4 Risks and Benefits

6.4.1 Potential Risks associated with KD025

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

Other commonly reported events include ras**h, pruritus, upper respiratory infection, joint** aches and swelling, headache, fatigue, bac**k pain, leg weakness, diarrhoea, nausea,** vomiting, upper abdominal pain, increase in **white blood cell count, cannula site infection,** dizziness, and flatulence.

6.4.2 Risks associated with Radiation Exposure

The [^{14}C]-KD025 solution for infusion and **[^{14}C]-KD025 capsule will contain a radionuclide** (NMT 9.8 MBq [267 µCi]) so subjects will be **exposed to ionising radiation. The effective** dose that each subject will receive from one **administration will not exceed 3 mSv. This** is approximately 1 year and 1 month of the **average radiation exposure received in the** UK each year (2.7 mSv). It is believed that **any increase in the amount of radiation that** is received above natural radiation carries a risk of later developing serious and possibly fatal conditions. The risk associated with the maximum possible dose of radiation in this study is very small indeed and is considered to be acceptable.

6.4.3 Risks associated with exposure to Radiation Microdose

The IV micro dose to be administered is 2000-fold lower than the oral dose and the exposure to [^{14}C]-KD025 originating from the infused micro dose is therefore considered negligible and no AEs are expected to occur.

6.4.4 Other considerations

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

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

Although KD025 nonclinical data suggests the potential for phototoxicity, in standard reporting of AEs in Phase 1/2 clinical studies, KD025 has not demonstrated any clinically significant phototoxicity. Therefore, for this study no restrictions have been applied.

The blood volume taken for each subject will be approximately 583.5 mL in a 4 week period. To account for this, subjects with blood platelet count, haemoglobin and red blood cells lower than the reference range will be excluded from the study.

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

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

7 Objectives and Endpoints

7.1 Objectives

7.1.1 Primary Objectives

- 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)

7.1.2 Secondary Objectives

- To obtain information regarding the oral PK of total radioactivity, KD025 and its metabolites KD025m1 and KD025m2, in plasma
- To obtain information regarding the 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

7.2 Endpoints

7.2.1 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

7.2.2 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: AEs, vital signs, electrocardiograms (ECGs), physical examinations and laboratory safety tests.

8 Study Design

8.1 Study Plan

This is a single centre, non-randomised, open-label, two-part study in healthy male subjects. Six subjects will participate in both parts of the study.

8.1.1 Study Plan Part 1

Part 1 is an open-label, non-randomised single oral dose followed by an IV microtracer assessment in 6 healthy male subjects. On Day 1 subjects will receive a single dose of KD025 (Treatment A), in the fed state. Subjects will then receive an IV dose of [^{14}C]-KD025 (100 µg, a 'microdose') containing NMT 37 kBq (1000 nCi) [^{14}C], as a 15 min IV infusion (Treatment B), 1.75 h after the oral dose administration (Treatment A) ie, 15 min before the expected Tmax (2 h) for the oral dose.

Treatment	Investigational Medicinal Product (IMP)
A	KD025 Tablet, 200mg
B	[^{14}C]-KD025 solution for infusion, 20 µg/mL (100 µg in 5mL), containing NMT 37 kBq (1000 nCi) [^{14}C], as a 15 min IV infusion, 100 µg

^{14}C: carbon-14, kBq: Kilobecquerel, IV: Intravenous, µCi: Microcurie, nCi: Nanocurie, NMT: Not more than.
All IMPs are described as free base equivalent.
Details of IMPs can be found in Section 5.2

It is planned to enrol 6 subjects so there are 4 evaluable subjects. An evaluable subject for Part 1 is defined as a subject who has sufficient data for evaluation of the primary bioavailability objective of the study.

All subjects will undergo preliminary screening procedures to determine their eligibility for Parts 1 and 2 of the study at the screening visit (Day -28 to Day -2 of Part 1). Subjects will be admitted to the clinical unit on the evening prior to IMP(s) administration (Day -1) for confirmation of eligibility and baseline procedures. Subjects will be dosed on the morning following admission (Day 1). Following an overnight fast (approximately 10 h), subjects will consume a standard breakfast and will receive a single dose of KD025 (Treatment A) 30 min after the start of breakfast. One hour and 45 min post Treatment A administration, subjects will receive an IV infusion of [^{14}C]-KD025 solution (Treatment B). Subjects will remain resident in the clinic until up to 48 h post-oral dose (up to Day 3). The minimum washout period between dose administrations in Part 1 and 2 will be 7 days.

8.1.2 Study Plan Part 2

Part 2 is an open-label, non-randomised ADME assessment in 6 healthy male subjects. 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 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) on the morning of Day 1 after a standard breakfast.

Treatment	IMP Dose
C	[^{14}C]-KD025 capsule, containing NMT 9.8 MBq (215 µCi) ^{14}C, 200 mg

^{14}C:carbon-14, MBq: megabecquerel, µCi: Microcurie, NMT: not more than. IMP is described as free base equivalent.
Details of IMPs can be found in Section 5.2

A subject in Part 2 will be considered evaluable if they have provided biological samples for up to 168 h after drug administration or have demonstrated >90% mass balance recovery, or have <1% of the administered dose eliminated in excreta for two consecutive days, whichever is the sooner.

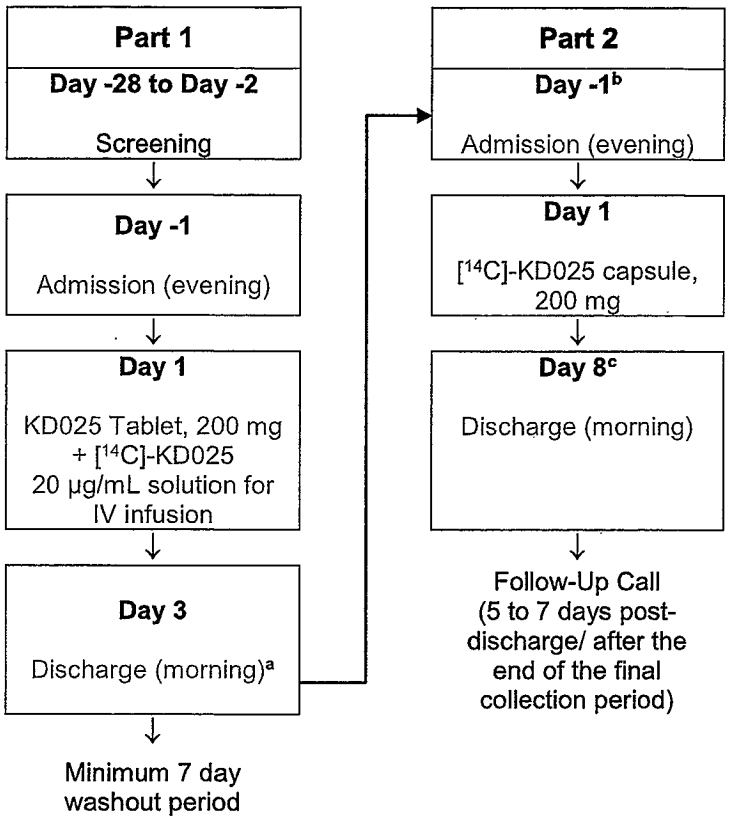
Approximately 7 days after subjects have been discharged from Part 1 of the study, subjects will be admitted to the clinical unit on the evening of the day prior to IMP administration (Day -1) for the confirmation of eligibility and baseline procedures. Subjects will be dosed on the morning following admission (Day 1). Following an overnight fast (approximately 10 h), subjects will consume a standard breakfast and will receive a single dose of [^{14}C]-KD025 capsule (Treatment C) 30 min after the start of 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.

An overview of the study is presented below (Figure 1):

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.

8.2 Criteria for In-Study Decisions

Not applicable for this study.

8.3 Subject Withdrawal

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

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

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

Subjects will be withdrawn from the study drug(s) for the following reasons:

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

For the purpose of withdrawal criteria in Parts 1 and 2, baseline will be considered as the pre-dose Day 1 measurement for each part.

8.4 Subject Replacement

No replacement subjects are to be used in this study.

8.5 Stopping Criteria

The study will be halted, and the risk to other subjects evaluated if any of the following criteria are met:

- A serious adverse reaction (ie, a serious adverse event considered at least possibly related to the IMP administration) in one subject.
- Severe non-serious adverse reactions (ie, severe non-serious adverse events considered as, at least possibly related to the IMP administration) in two subjects in the same cohort of the study, independent of within or not within the same system organ class.

Relatedness will be determined by the investigator.

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

The ARSAC Practitioner will also be informed of the temporary halt

8.6 Study Termination

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

If the study is abandoned prior to commencement of any protocol activities, the Principal Investigator (PI) or sponsor must notify the EC, MHRA, ARSAC practitioner and ARSAC (if ARSAC research application has been submitted or approved) in writing outlining the reasons for abandonment of the trial.

Once exposure to ionising radiation and/or dosing has begun, the study will be completed as planned unless the following criteria are satisfied that require a temporary halt or early termination of the study:

- The occurrence of serious or severe adverse event(s), as defined in Section 8.5, if considered to be related to the IMP, as defined in Section 14.2.
- New information regarding the safety of the IMP that indicates a change in the risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

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

If it becomes necessary to consider termination of the study after dosing has begun, dosing may be suspended pending discussion between the investigator, sponsor and potentially the ARSAC practitioner (where discussion is related to administration of radiation). Dosing will be stopped immediately on safety grounds.

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

8.7 Lost to Follow-up

A subject will be considered lost to follow-up if they fail to return for scheduled visits and cannot be contacted by the clinical unit.

If a subject fails to return to the clinical unit for a required study visit:

The clinical unit must attempt to contact the subject and reschedule the missed visit as soon as possible

Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (eg 3 telephone calls on 3 separate occasions and, if necessary, an email or letter to the participant's last known email/postal address). These contact attempts should be documented in the subject's source.

If the subject cannot be contacted, they will be considered lost to follow-up.

8.8 Treatment Allocation

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

8.8.1 Subject Numbers

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.

8.8.2 Blinding

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

9 Selection of Subjects

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

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

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

9.1 Informed Consent

Subjects will be provided with a written explanation of the study at least the day before the screening visit. A physician or nurse will explain to each subject the nature of the study, its purpose, expected duration and the benefits and risks involved in study participation. Subjects will be informed that, for safety reasons, brief details of their involvement in the study may be revealed to other units and companies that carry out clinical studies in the local area. Subjects will then be given the opportunity to ask questions and will be informed of their right to withdraw from the study without prejudice. After this explanation and before entering the study, the subject will voluntarily sign an informed consent form (ICF). Until written consent has been obtained from the subject no study specific procedure or investigation will be performed. If an amendment is made to the participant information sheet (PIS), participants will be re-consented to the most current version of the ICF(s) where appropriate.

9.2 Inclusion Criteria

1. Healthy males
2. Age 30 to 65 years of age
3. Good state of health (mentally and physically) as indicated by a comprehensive clinical assessment (detailed medical history and a complete physical examination), ECG and laboratory investigations (haematology, clinical chemistry and urinalysis)
4. Body weight ≥50 kg
5. Body mass index (BMI) of 18.0 to 35.0 kg/m^2
6. Must be willing and able to communicate and participate in the whole study

7. Must have regular bowel movements (ie, average stool production of ≥1 and ≤3 stools per day)
8. Subjects must have participated in Part 1 in order to be eligible for Part 2
9. Must provide written informed consent
10. Must agree to adhere to the contraception requirements defined in Section 9.4.

9.3 Exclusion Criteria

1. Subjects who previously participated in any other investigational study drug trial in which receipt of an investigational study drug occurred within 90 days prior to dosing
2. Subjects who have previously participated in a study where subjects were dosed with KD025 (QSC200311 and QCL117415).
3. Subjects who are study site employees, or immediate family members of a study site or sponsor employee
4. Subjects with pregnant partners
5. History of any drug or alcohol abuse in the past 2 years
6. Regular alcohol consumption in males >21 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 Units = 125 mL glass of wine, depending on type)
7. Current smokers and those who have smoked within the last 12 months. A breath carbon monoxide reading of greater than 10 ppm at screening and admission
8. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
9. Radiation exposure, including that from the present study, excluding background radiation but including diagnostic x-rays and other medical exposures, exceeding 5 mSv in the last 12 months or 10 mSv in the last 5 years. No occupationally exposed worker, as defined in the Ionizing Radiation Regulations 2017, shall participate in the study.
10. Subjects who have been enrolled in an ADME/IV microtracer study in the last 12 months
11. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening
12. Clinically significant abnormal biochemistry, haematology or urinalysis as judged by the investigator (laboratory parameters are listed in Appendix 1). Subjects with blood platelet count, haemoglobin and red blood cells lower than the reference range will be excluded
13. Confirmed positive drugs of abuse test result (drugs of abuse tests are listed in Appendix 1)
14. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) results
15. Evidence of renal impairment at screening, as indicated by an estimated creatinine clearance (CLcr) of <80 mL/min using the Cockcroft-Gault equation
16. History of clinically significant cardiovascular, renal, hepatic, chronic respiratory or GI disease, neurological or psychiatric disorder, as judged by the investigator
17. Subject has a history or presence of any of the following:
    - Active GI disease requiring therapy
    - Hepatic disease and/or ALT or AST > ULN
    - Renal disease and/or serum creatinine > ULN
    - Other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs
18. Subject has QT interval corrected using Fridericia's formula (QTcF) intervals >450 msec at screening or admission
19. Serious adverse reaction or serious hypersensitivity to any drug or the formulation excipients

20. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hayfever is allowed unless it is active
21. Donation or loss of greater than 400 mL of blood within the previous 3 months
22. Subjects who are taking, or have taken, any prescribed or over-the-counter drug (other than 4 g of paracetamol per day) or herbal remedies in the 14 days before IMP administration (See Section 11.2). Exceptions may apply on a case by case basis, if considered not to interfere with the objectives of the study, as agreed by the PI and sponsor's medical monitor.
23. Failure to satisfy the investigator of fitness to participate for any other reason

Exclusion criteria 7, 13, 18, 21, 22 and 23 from the list above will be re-assessed at admission/pre-dose for Part 1 and 2.

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

9.4 Contraception

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

- Partner's use of combined (oestrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal

- Partner's use of progestogen-only hormonal contraception:
  - oral
  - injectable/implantable
  - intrauterine hormone-releasing system

- Partner's use of implantable intrauterine device
- Surgical sterilisation (for example, vasectomy or partner's bilateral tubal occlusion)
- Partner's use of female cap or diaphragm (double barrier)

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

These contraception requirements are aligned with guidance issued by the Heads of Medicines Agency: Clinical Trials Facilitation Group [14].

9.4.1 Exposure to Partners During the Study

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

9.4.2 Sperm Donation

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

9.5 Pregnancy

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

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

9.6 Additional Study Restrictions

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

1. Subjects must abstain from alcohol during the 24 h prior to screening and the 24 h prior to each admission until discharge from each part of the study.
2. Subjects must not drink liquids or eat food containing grapefruit, cranberry, caffeine or other xanthines from 24 h prior to each admission until discharge from each part of the study.
3. Subjects should refrain from eating food containing poppy seeds for 48 h prior to screening and for 48 h prior to each admission until discharge from each part of the study.
4. Subjects must not take part in any unaccustomed strenuous exercise from the 72 h before the screening visit and then from 72 h prior to each admission until discharge from each part of the study.

10 Study Procedures

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

10.1 Screening

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

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

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

Screening safety procedures such as safety bloods, ECGs, vital signs and urinalysis can be repeated as clinically indicated under the discretion of the investigator or sub-investigator if there is a concern regarding a subject's safety or eligibility to participate in the trial.

10.1.1 Subject Re-Screening

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

10.2 Admission and Pre-dose Procedures

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

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

Admission safety procedures such as safety bloods, ECGs, vital signs, urinalysis and drugs of abuse tests can be repeated as clinically indicated under the discretion of investigator or sub-investigator if there is a concern regarding a subject's safety or eligibility to participate in the clinical trial.

Subjects will be admitted to the clinical unit on the evening before dosing (Day -1) for both Parts 1 and 2.

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

10.3 Study Day Procedures

10.3.1 Blood Volume

The total blood volume for each subject will be approximately 583.5 mL in a 4 week period. Subjects with a low blood count will be excluded from participation in this study (exclusion criterion 12). The first 0.5 mL of blood withdrawn via cannula will be discarded.

10.3.2 Timing of Procedures

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

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

As guidance, the preferred order of assessments is:

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

All safety assessments in Part 1 will be timed according to the schedule in Appendix 2. All safety assessments in Part 2 will be timed and performed relative to the start of dosing.

10.3.3 Discharge from the Clinical Unit

Part 1

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

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

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

There will be no continued provision of the study intervention or treatment for subjects as this study involves healthy volunteers only.

Part 2

A subject will be allowed to leave the premises following completion of study-specific procedures at 168 h post-dose providing that:

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

Subjects will be dosed on the morning of Day 1 following a standard breakfast, and will remain resident in the clinical unit 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, 2 additional 24 h periods). 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.

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

There will be no continued provision of the study intervention or treatment for subjects as this study involves healthy volunteers only.

10.3.4 Medical Supervision

A physician will be responsible for the clinical aspects of the study and will be available at all times during the study. In accordance with the current Association of the British Pharmaceutical Industry guidelines [15], each subject will receive a card stating the telephone number of the investigator.

10.3.5 Follow-up

A follow-up phone call will take place 5 to 7 days after discharge/after the final collection period to ensure the ongoing wellbeing of the subjects. If a subject reports any AEs which can present a cause for concern, they will be required to attend the clinic for a further follow-up assessment (as an unscheduled visit). Completion of the last follow-up call or unscheduled follow-up visit will be considered the end of the study.

11 Dosing of Subjects

11.1 Food and Fluid Intake

Subjects will be allowed water up to 1 h before the scheduled dosing time and will be provided with 240 mL of water at 1 h post-dose. Water will be allowed ad libitum after 1 h post-dose. Decaffeinated fluids will be allowed ad libitum from lunch time on the day of dosing. In Part 1, the water restrictions before and after dosing only apply to the oral dose. If, for technical reasons, dosing is delayed for more than 2 h beyond the expected dosing time, subjects will receive 200 mL of Lucozade Sport at the originally scheduled dosing time, or earlier if possible.

Breakfast will be controlled by clinical staff members on Day 1 for both study Parts. The start and stop time of the meal and the percentage consumed must be recorded in the source.

Subjects will be provided with a light snack and will fast from all food and drink (except water) until the following morning, when they will be provided with a standard breakfast.

The breakfast should be consumed over a maximum period of 25 min, with oral dosing occurring 30 min after the start of breakfast. Subjects should be encouraged to eat their meal evenly over the 25 min period. It is acknowledged that some subjects will take less time to eat, but dosing should still occur 30 min after the start of breakfast.

The acceptable deviation for the pre-dose meal from the nominal time point is:

- Pre-dose meal will be provided within ± 5 min of the nominal time point

Lunch will be provided at approximately 4 h post-dose, an evening meal at approximately 10 h post-dose and an evening snack at approximately 14 h post-dose. On subsequent days, meals will be provided at appropriate times.

Part 2 only: If an individual subject has not experienced a bowel movement in any 36-h period post-dose, fluid intake should be increased and administration of a mild laxative (eg, prune juice or a mild stool softener) should be implemented.

11.2 Administration of Test Preparations

Specific details of IMPs and doses to be administered are provided in Section 5.2 and Section 8.1.1, respectively. Subjects will be dosed on the morning of Day 1 of each study part.

Part 1

Subjects will receive a single oral dose of KD025 in the fed state. 240 mL of water will be given immediately following oral administration. One hour and 45 min after the oral dose has been administered, an ^{14}C radiolabelled IV dose will be infused over 15 min. This infusion will be in the opposite arm being used for PK sampling.

To assess tolerability of the IV administration, the first subject will be dosed at least 30 min prior to dosing the second subject. All subsequent dosing of the IV formulation will be staggered by at least 15 min.

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

Part 2

Subjects will receive a single oral dose of [^{14}C]-KD025 in the fed state on one dosing occasion. 240 mL of water will be given immediately following oral administration.

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

11.1 Dosing Compliance

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

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

Part 1 only: The IV dose will be administered by trained staff to ensure dosing compliance.

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

11.2 Prior and Concomitant Medications

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

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

12 Assessment of Efficacy

Not applicable for this Phase I study.

13 Assessment of Mass Balance, Pharmacokinetics, Metabolic Profiling and Identification and Pharmacodynamics

13.1 Assessment of Mass Balance, Pharmacokinetics and Metabolic Profiling and Identification

13.1.1 Blood Sampling

Venous blood samples will be collected from the subjects by a trained member of the clinical team. Consent will be collected from the subjects for use of these samples for the purposes of the proposed study. Pharmacokinetic analysis will be carried out on blood samples.

Blood samples are sent for laboratory testing in linked anonymised form (subject number and initials only). This information is able to be linked directly to the volunteer by the Quotient research team and study monitor, however not by the laboratory staff or sponsor.

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

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

- The pre-dose blood sample will be taken ≤1 h before dosing
- 0 to 1 h post-dose samples will be taken within ± 2 min of the nominal post-dose sampling time
- >1 to 12 h post-dose samples will be taken within ± 10 min of the nominal post-dose sampling time
- >12 h post-dose samples will be taken within ± 30 min of the nominal post-dose sampling time if subjects are resident in the clinical unit

For timings of PK sampling relative to dosing, see Appendix 2 and Appendix 3.

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

Samples will be shipped to Covance Laboratories Ltd for the analysis of KD025 (Part 1 and 2) and metabolites KD025m1 and KD025m2 (Part 2 only). Samples will be shipped to Xceleron Inc., A Pharmaron Company for the analysis of [^{14}C]-KD025 (Part 1 only). Samples will be shipped to Pharmaron for the analysis of plasma and whole blood total radioactivity.

13.1.2 Urine Sampling (Part 2 only)

Urine samples will be collected according to the time schedule presented in Appendix 3.

A single urine sample will be taken at pre-dose (the first void of the day). Where a sample is not provided, this will not be considered a deviation. All individual urine voids will be collected and shipped to the bioanalytical laboratory for analysis, according to Quotient Sciences SOPs, unless indicated otherwise by the sponsor.

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

Samples will be shipped to Pharmaron for the analysis of total radioactivity, metabolite profiling and identification in urine.

13.1.3 Faecal Sampling (Part 2 Only)

Faecal samples will be collected according to the time schedule presented in Appendix 3.

The pre-dose faecal sample will be taken from admission until dosing. If a pre-dose faecal sample cannot be obtained, the subject will still be dosed. Where a sample is not provided, this will not be considered a deviation.

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

Samples will be shipped to Pharmaron for the analysis of total radioactivity, metabolite profiling and identification in faeces.

13.1.4 Unexpected Sources of Elimination

During the study, other accidental sources of elimination will be collected as voided (eg emesis).

Samples will be shipped to Pharmaron for the analysis of total radioactivity.

13.2 Assessment of Pharmacodynamics

Not applicable for this Phase I study.

14 Assessment of Safety

14.1 Definition and Classification of Adverse Events

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

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

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

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

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

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

14.2 Assessment of Causality

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

Causality should be assessed using the following categories:

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

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

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

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

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

14.3 Recording Adverse Events

AEs will be recorded from the time of providing written informed consent until discharge from the study at the follow-up call. During each study visit the subject will be questioned directly regarding the occurrence of any adverse medical event according to the schedule in the source. All AEs, whether ascribed to study procedures or not, will be documented immediately in the source. This will include the date and time of onset, a description of the AE, severity, duration, actions taken, outcome and an investigator's current opinion on the relationship between the study drug and the event. A diagnosis and final opinion on the relationship between the study drug and the event will be provided at the end of the study by the investigator.

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

14.4 Serious Adverse Events

14.4.1 Definition of Serious Adverse Events

A SAE is defined as any untoward medical occurrence that at any dose:

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

SAEs must be immediately reported to the sponsor.

14.4.2 Definition of Suspected Unexpected Serious Adverse Reactions

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

14.5 Laboratory Measurements

Venous blood, urine and faecal samples will be collected from the subjects by a trained member of the clinical team. Consent will be collected from the subjects for use of these samples for the purposes of the proposed study.

Blood, urine and faecal samples are sent for laboratory testing in linked anonymised form (subject number, initials, and the subjects' gender and date of birth for analytical reasons). This information is able to be linked directly to the volunteer by the Quotient research team and study monitor, however not by the laboratory staff or sponsor.

Safety laboratory tests and virology will be carried out on blood samples, and drugs of abuse tests and urinalysis will be carried out on urine samples. Urine and faecal samples will be analysed for total radioactivity. The research will not involve analysis or use of human DNA.

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

14.5.1 Haematology and Clinical Chemistry

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

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

- The pre-dose blood sample will be taken ≤2 h before dosing

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

CLcr will be calculated at screening by The Doctors Laboratory using the Cockcroft-Gault equation and body weight.

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

14.5.2 Urinalysis

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

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

- The pre-dose urine sample will be taken ≤3 h before dosing or the first void of the day
- Post-dose urine samples will be taken ± 2 h from the nominal urine sampling time

14.5.3 Drug Screen

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

14.5.4 Alcohol Breath Test

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

14.5.5 Carbon Monoxide Breath Test

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

14.5.6 Abnormal Laboratory Findings

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

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

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

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

14.6 Vital Signs Measurements

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

- The pre-dose vital signs measurements will be taken ≤2 h before dosing
- Post-dose vital signs measurements will be taken ± 15 min from the nominal post-dose time points
- Discharge vital signs measurements will be taken ± 1 h from the nominal time point

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

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

14.7 ECG Measurements

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

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

- The pre-dose ECG measurements will be taken ≤2 h before dosing
- Post-dose ECG measurements will be taken ± 15 min from the nominal post-dose time point
- Discharge ECG measurements will be taken ± 1 h from the nominal time point.

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

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

14.8 Body Weight and Height

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

14.9 Physical Examination

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

14.10 Additional Safety Procedures

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

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

15 Statistics and Data Analysis

15.1 Sample Size Justification

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 is considered appropriate to meet the objectives of the study.

15.2 Data Management

Data management will be performed by Quotient Sciences.

All study data recorded in the source, will be recorded in a validated study database that has an audit trail to log all subsequent changes to the data. All queries will be resolved within the study database.

AEs and medications will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (v22.0 or a more recent version) and the World Health Organisation (WHO) Drug Dictionary Global Drug Reference (2019 or a more recent version), respectively. An independent coding review will also be performed within the Data Sciences department.

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

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

Further details are addressed in the DMP.

15.3 Mass Balance and Pharmacokinetic Data Analysis

15.3.1 Mass Balance Data Analysis

Urine and faecal samples will be collected for the analysis of total radioactivity in Part 2. The following mass balance parameters will be calculated by Quotient Sciences from urine and faeces separately and total (urine and faeces combined): Ae, %Ae, Cum Ae and Cum %Ae.

Ae(urine), Cum Ae(urine), Ae(faeces), Cum Ae(faeces), Ae(total) and **Cum Ae(total):** amount excreted and cumulative amount excreted in urine, faeces and total (urine and faeces combined).

%Ae(urine), Cum %Ae(urine), %Ae(faeces), Cum %Ae(faeces), %Ae(total) and **Cum %Ae (total):** amount excreted and cumulative amount excreted in urine, faeces and total (urine and faeces combined) expressed as a percentage of the administered dose.

For Urine:

- **Ae:** Total radioactivity
- **%Ae:** Total radioactivity expressed as a percentage of the dose
- **Cum Ae:** Cumulative recovery of total radioactivity
- **Cum %Ae:** Cumulative recovery expressed as a percentage of the dose

For Faeces:

- **Ae:** Total radioactivity
- **%Ae:** Total radioactivity expressed as a percentage of the dose
- **Cum Ae:** Cumulative recovery of total radioactivity
- **Cum %Ae:** Cumulative recovery expressed as a percentage of the dose

For Mass Balance Recovery of Total Radioactivity from all excreta:

- **Ae:** Total radioactivity
- **%Ae:** Total radioactivity expressed as a percentage of the dose
- **Cum Ae (Total):** Cumulative recovery of total radioactivity
- **Cum %Ae (Total):** Cumulative recovery expressed as a percentage of the dose

Further analysis details will be included in the Reporting and Analysis Plan (RAP).

15.3.2 Pharmacokinetic Data Analysis

The plasma concentration data for KD025, KD025m1 and KD025m2 provided by Covance Laboratories Ltd, the plasma [^{14}C]-KD025 concentration data provided by Xceleron Inc., A Pharmaron Company and the plasma and whole blood total radioactivity data provided by Pharmaron will be analysed by Quotient Sciences, using Phoenix WinNonlin v8.0 or a more recent version (Certara USA, Inc., USA).

Calculated KD025, KD025m1 and KD025m2 concentrations in plasma may be corrected for specific activity of the administered radiolabelled oral dose by the Data Sciences department at Quotient Sciences.

Part 1

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

For Plasma [^{14}C]-KD025 following IV administration

- **Tmax**: Time of maximum observed concentration
- **Cmax:** The maximum observed plasma concentration
- **AUC(0-last):** Area under the curve from 0 time to the last measurable concentration
- **AUC(0-inf):** The area under the concentration-time curve from dosing extrapolated to infinity

- **AUC%extrap:** Percentage of AUC(0–inf) extrapolated beyond last measured time point
- **lambda-z:** The first order rate constant associated with the terminal (log-linear) portion of the curve
- **T1/2:** The apparent terminal elimination half-life
- **CL:** Total clearance
- **Vz:** Volume of distribution based on area
- **Vss:** Volume of distribution at steady state
- **MRT:** Mean residence time

For Plasma KD025 following oral administration

- **Tlag:** Time prior to the first measurable (non-zero) concentration
- **Tmax:** Time of maximum observed concentration
- **Cmax:** The maximum observed plasma concentration
- **AUC(0-last):** Area under the curve from 0 time to the last measurable concentration
- **AUC(0-inf):** The area under the concentration-time curve from dosing extrapolated to infinity
- **AUC%extrap:** Percentage of AUC(0–inf) extrapolated beyond last measured time point
- **lambda-z:** The first order rate constant associated with the terminal (log-linear) portion of the curve
- **T1/2:** The apparent terminal elimination half-life
- **F:** Bioavailability of oral formulation compared to IV
- **CL/F:** Apparent clearance
- **Vz/F:** Apparent volume of distribution
- **MRT:** Mean residence time

Part 2

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

For Total Radioactivity, KD025, KD025m1 and KD025m2 in plasma:

- **Tlag:** Estimated time from dosing at which the analyte was first quantifiable in a concentration versus time profile
- **Tmax:** Time of maximum observed concentration
- **Cmax:** The maximum observed plasma concentration
- **AUC(0-last):** Area under the curve from 0 time to the last measurable concentration
- **AUC(0-inf):** The area under the concentration-time curve from dosing extrapolated to infinity
- **AUC%extrap:** Percentage of AUC(0–inf) extrapolated beyond last measured time point
- **lambda-z:** The first order rate constant associated with the terminal (log-linear) portion of the curve
- **T1/2:** The apparent terminal elimination half-life
- **Cl/F:** Apparent clearance KD025 only
- **Vd/F:** Apparent volume of distribution KD025 only
- **MRT:** Mean residence time

- Metabolite:Parent ratio for KD025m1 and KD025m2
- whole blood/plasma total radioactivity concentration ratios will be calculated at selected time points.

Further details of the PK data analysis will be included in the RAP.

15.3.3 Metabolite Profiling and Identification

Metabolite profiling of plasma, urine and faeces will be performed using liquid chromatography-radio-detection with subsequent mass spectrometry where appropriate.

Identification of the chemical structure of each metabolite accounting for greater than 10% of circulating radioactivity in plasma ("AUC pool") and accounting for greater than 10% of the dose in the urine and faeces (from urine pools and faeces homogenate pools) will be performed.

These aspects will be reported separately from the clinical study report as a standalone document.

15.4 Statistical Data Analysis

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

No formal statistical analysis will be performed for this study. Descriptive statistics (eg mean, median, standard deviation [SD], minimum, maximum and number of subjects with an observation [n]) are considered adequate for a study of this type. Additional statistics will be provided for PK-related data, including coefficient of variation (CV%), geometric mean, geometric CV% and geometric n (ie number of subjects with an observation that are included in the natural logarithmic transformation).

Populations for analysis will be determined for safety, PK, and mass balance data after database lock using the criteria defined in the RAP; the RAP will be signed off prior to database lock.

All populations will be defined after database lock when the relevant data are available.

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

- Criteria to be used to define each of the analysis populations
- Additional detail covering the analyses and/or description of primary and secondary analyses and safety data
- Handling of missing data, unused or spurious data
- Handling of data from withdrawn subjects

All safety, mass balance recovery and PK data will be listed.

15.5 Interim Analysis

No formal interim analyses are planned for this study.

16 Safety Reporting to Ethics Committees and Regulatory Authorities

16.1 Events Requiring Expedited Reporting

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

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

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

16.2 Urgent Safety Measures

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

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

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

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

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

16.3 Reporting

16.3.1 Reporting Serious Adverse Events

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

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

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

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

Sanjay Aggarwal, MB BChir (Cantab) MRCP (UK).
Kadmon Corporation, LLC
55 Cambridge Parkway, Suite 300E
Cambridge, MA 02142
Telephone: Direct: 724-778-6129
Mobile: 857-253-8642
E-mail: Sanjay.Aggarwal@kadmon.com

16.3.2 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

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

16.3.3 Expedited Reporting of Events

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

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

Fatal or life-threatening SUSARs

It is the responsibility of the sponsor to report fatal or life-threatening SUSARs to the MHRA and EMA as soon as possible, but no later than 7 calendar days after they first became aware of the reaction. Any additional relevant information should be sent within 8 days of the report. This responsibility may be delegated to the pharmacovigilance provider.

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

The ARSAC Practitioner will be notified of any SUSAR that is considered related to the exposure to radioactivity

Other SUSARs

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

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

The ARSAC Practitioner will be notified of any SUSAR that is considered related to the exposure to radioactivity

16.3.4 Reporting of Urgent Safety Issues

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

16.4 Serious Breaches

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

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

17 Protocol Amendments and Deviations

17.1 Amendments

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

All substantial amendments will be submitted to the MHRA and/or EC for an opinion as required by current regulations. Any amendments relating to the administration of radioactive substances will be reviewed by the ARSAC practitioner prior to submission to ARSAC as required by the current ARSAC Notes for Guidance. The ARSAC practitioner will also be notified of any substantial amendments to the PIS and ICF and/or protocol.

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

17.2 Protocol Deviations

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

Protocol waivers are not acceptable.

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

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

18 Regulatory

18.1 Compliance

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

- International Council for Harmonisation Good Clinical Practice (GCP) Guidelines approved by the Committee for Medicinal Products for Human Use (CHMP) on 17 Jul 1996, which came into force on 17 Jan 1997, updated Jul 2002, Integrated Addendum E6 (R2) dated 09 Nov 2016 [16]
- The Medicines for Human Use (Clinical Trials) Regulations. Statutory Instruments 2004 No. 1031 [17]
- The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2006 No. 1928 [18]
- The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations. Statutory Instruments 2006 No. 2984 [19]
- The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2008 No. 941 [20]
- Health and Safety. The Ionising Radiations Regulations 2017. Statutory Instrument 2017 No. 1075 [21]
- Health and Safety. Ionising Radiation (Medical Exposure) Regulations 2017. Statutory Instrument 2017 No. 1322 [22]

In addition, the study will be performed according to the ethical principles outlined in the World Medical Association Declaration of Helsinki and its amendments [23].

18.2 Ethics Approval

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

18.3 MHRA Approval

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

18.4 Administration of Radiation

Dr Stuart Mair will be the ARSAC practitioner for this study, which includes the administration of radiation at Quotient Sciences. Administration will be conducted in accordance with Dr Mair's ARSAC practitioner licence (P66) and Quotient's ARSAC Employer licence (E8). Additionally a research application will be submitted to ARSAC to obtain approval for the conduct of the study before dosing.

Before submitting to the ARSAC, a summary of available nonclinical tissue distribution and excretion information on [^{14}C]-KD025 will be submitted to the Radiation Protection Division of PHE for human dosimetry calculations in order to facilitate the selection of the dose of radioactivity to be administered. The final report from the PHE will be included in the application to the ARSAC.

The protocol will be reviewed and the final version will be approved by the ARSAC practitioner, Dr Stuart Mair.

18.5 Source Data

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

For this study, electronic data capture will be used where possible and data will be automatically recorded into an electronic case report form. In instances where paper source documents are used, data to be transcribed into the electronic case report form will be identified using a Source Document Identification List, as governed by Quotient Sciences SOPs.

18.6 Declaration of the End of the Study

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

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

ARSAC and the ARSAC Practitioner will also be notified of the end of trial or early termination of the trial in writing within an appropriate timeframe.

18.7 Document Storage and Archiving

All documentation and correspondence pertaining to the study (source data, raw data, letters etc) will be kept in accordance with the ICH guidelines for Good Clinical Practice 1996, updated 2002 (ICH GCP Section 4.9.5) [16], The Medicines for Human Use (Clinical Trials) Regulations 2004 [17] and The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 [18][19].

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

18.8 Protection of Personal Data and Confidentiality

Personal data are securely stored to prevent unauthorised access, disclosure, dissemination, alteration or loss of information and unauthorised personal data processing. Access to personal information is restricted so that only personnel who are required to access personal data as part of their job role can do so. All personnel who access personal information are bound by a duty of confidentiality.

Technical arrangements surrounding the electronic storage and use of data are as follows:

- Computers storing electronic personal data are protected by antivirus software and the network on which computers are linked are protected by industry grade firewalls
- Off-site personnel can only access networked computers through a virtual private network (VPN)

- Electronic access of data is limited according to user roles
- All data are stored on password protected computers

Organisational arrangements are as follows:

- All buildings are secured by key-card access
- Manual files of personal data are stored within locked cabinets that can only be accessed by authorised personnel
- Data security and/or confidentiality provisions are utilised in agreements with third parties
- Documented Back-up and disaster recovery procedures are in place
- Internal audit and compliance functions provide regulatory oversight

The personal data of volunteers will be pseudonymised in that they will only include health, initials, date of birth and demographics (gender and ethnicity) and cannot be linked back to the individual by the recipient. The Sponsor shall be the data controller in respect of the personal data of the study subjects collected in connection with the study, and shall act in accordance with the relevant data protection laws in relation to the collection and processing of those personal data. The study subjects' pseudonymised personal data shall be collected and processed for the purposes of the study and may also be added to research databases and used in the future by the Sponsor and its affiliates for certain additional clinical research, for product regulation and safety reporting purposes and for ensuring compliance with legal requirements. The study subjects' pseudonymised personal data may be processed for such purposes by other parties including: the Sponsor's affiliates and licensing partners, its business partners, regulatory agencies and other health authorities, and ECs. The study subjects' authorisation for such use and disclosure shall be obtained by the study subjects signing the ICF for the study.

Additionally, Quotient personnel are contractually bound by a duty of confidentiality and receive training in this matter.

18.9 Data Security Breach

Quotient has a comprehensive process in place for identifying, assessing, resolving and reporting any potential data security breach. All staff are trained in the identification of potential data security breaches. Potential breaches are managed by appropriately trained quality assurance (QA) personnel in accordance with Quotient Sciences standard operating procedures. After robust assessment of data breaches, those deemed serious will be reported to the Sponsor and Information Commissioner's Office, as applicable.

19 Quality Control and Quality Assurance

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

19.1 Monitoring

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

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

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

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

20 Finance and Insurance

The sponsor (Kadmon Corporation LLC) has funded this study. A no-fault clinical trials insurance has been obtained by the sponsor. The sponsor insurance will compensate subjects in accordance with the Association of the British Pharmaceutical Industry Guidelines for Phase I Clinical Trials 2018 edition [15].

21 Publication

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

22 References

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[14] Heads of Medicines Agency: Clinical Trials Facilitation Group. Recommendations related to contraception and pregnancy testing in clinical trials. 15 Sep 2014 http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

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

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

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

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

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

[21] Health and Safety. The Ionising Radiations Regulations 2017. Statutory Instrument 2017 No. 1075.

[22] Health and Safety. Ionising Radiation (Medical Exposure) Regulations 2017. Statutory Instrument 2017 No. 1322.

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

Appendix 1 Clinical Laboratory Parameters

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

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

Appendix 2 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 2 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 3 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.