REPORTING AND ANALYSIS PLAN

An Open-Label, Single-Dose, Single-Period Study Designed to Assess the Mass Balance Recovery, Metabolite Profile and Metabolite Identification of [^{14}C]-MD1003 in Healthy Males Subjects

Quotient Study Number:	QSC201639
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1 Table of Contents

2 List of Abbreviations

^{14}C	carbon-14
ADaM	analysis data model
ADR	adverse drug reaction
AE	adverse event
Ae	amount of total radioactivity excreted
ATC	anatomical therapeutic chemical
AUC	area under the curve
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
CDISC	Clinical Data Interchange Standards Consortium
CHMP	Committee for Medicinal Products for Human Use
CSR	clinical study report
CumAe	cumulative amount of total radioactivity excreted
Cum%Ae	cumulative amount of total radioactivity excreted, expressed as a percentage of the radioactive dose administered
CV%	coefficient of variation
D	'substantial' decrease from baseline for vital signs parameters
DP	decimal place
ECG	electrocardiogram
h	hour
H	flag used for value that is above normal reference range
HR	heart rate
I	'substantial' increase from baseline for vital signs parameters / increase in QTcF interval from baseline

ICH	International Council on Harmonisation
IP	investigational product
L	flag used for value that is below normal reference range
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LOD	limit of detection
Max	maximum
MBq	megabecquerel
MedDRA	Medical Dictionary for Regulatory Activities
µCi	microcurie
Min	minimum
MPR	metabolite to parent ratio
MW	molecular weight
n	number of subjects with an observation
N	number of subjects in the dataset
NA	not applicable
NC	not calculated
ND	not detected
NMT	not more than
NR	no result
NS	no sample
PI	principal investigator
PK	pharmacokinetic
PT	preferred term
QC	quality control

QTcF	QT interval corrected for heart rate using Fridericia's correction
RAP	reporting analysis plan
SAE	serious adverse event
SD	standard deviation
SDTM	study data tabulation model
SF	significant figure
SI	substantial increase in QTcF interval from baseline
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse events
TER	total exposure ratio
TFL	tables, figures and listings
WHO	World Health Organisation
%Ae	amount of total radioactivity excreted, expressed as a percentage of the radioactive dose administered

Abbreviations and flags used in reporting of mass balance and pharmacokinetic data are defined in Section 9.

3 Introduction

This document details the following for Quotient Sciences (Quotient) Study QSC201639 (MD1003CT2019-03MB):

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

This document has been compiled according to the Quotient standard operating procedure (SOP) "Production of Reporting and Analysis Plans" and has been written based on information contained in the final study protocol (version 1.0) dated 12 Sep 2019.

3.1 Responsibilities

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

Quotient will provide two sets of TFLs during the study:

- post database lock TFLs (draft) for MedDay Pharmaceuticals review, and
- post-review TFLs (final) for inclusion into the CSR

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

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

3.2 Definitions

3.2.1 Subject Definitions

During the clinical phase of the study, an evaluable subject is defined as a subject who has provided mass balance and PK samples for up to 72 h (Day 4) after IP administration, or have demonstrated >90% mass balance recovery, or have <1% of the administered dose eliminated in excreta for 2 consecutive days, whichever is sooner. This will be monitored during the clinical phase but will not be used during the reporting phase including the identification of analysis populations and datasets.

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

3.2.2 Definition of Treatment

A single oral administration of a capsule containing 100 mg MD1003 and not more than (NMT) 2.22 MBq (approximately 60 µCi) [^{14}C] will be administered to each subject and labelled as 100 mg [14C]-MD1003 in TFLs.

3.2.3 Definition of Visits

For clinical data, visits will be referred to as Day throughout this document and will be referred to as Screening, Day -1 (Admission) and Day 1 through to Day 8 (planned discharge). Time points within these days are detailed in the study flow chart in Appendix 1.

Baseline is defined as nominally the last measurement recorded prior to the first dose of investigational product (IP).

4 Objectives

4.1 Primary Objectives

The primary objectives of this study are:

- to determine the mass balance recovery after a single oral dose of carbon-14 [^{14}C]-MD1003
- to perform metabolite profiling and structural identification of MD1003 metabolites from plasma, urine and faecal samples

4.2 Secondary Objectives

The secondary objectives of this study are:

- to determine the routes and rates of elimination of [^{14}C]-MD1003
- to identify the chemical structure of each metabolite accounting for more than 10% of circulating total radioactivity
- to further explore the oral PK of MD1003 and its metabolites bisnorbiotin and biotin sulfoxide
- to evaluate the extent of distribution of total radioactivity into blood cells
- to provide additional safety and tolerability information for MD1003

4.3 Study Endpoints

4.3.1 Primary Endpoints

The primary endpoints of the study are:

- mass balance recovery of total radioactivity in all excreta (urine and faeces): Ae, %Ae, CumAe and Cum%Ae
- metabolite profiling, structural identification, and quantification of [^{14}C]-MD1003 metabolites in plasma, urine and faeces

4.3.2 Secondary Endpoints

The secondary endpoints of the study are:

- amount of total radioactivity excreted and amount of total radioactivity excreted as a percentage of the administered dose in urine and faeces at each time interval
- identification of the chemical structure of each metabolite accounting for more than 10% by AUC of circulating total radioactivity
- assessment of the oral PK profile for MD1003, bisnorbiotin, biotin sulfoxide and total radioactivity based on: Tlag, Tmax, Cmax, AUC(0-last), AUC(0-inf), AUCextrap, T1/2, Lambda-z, CL/F (MD1003 only), Vz/F (MD1003 only), MPR Cmax and MPR AUC(0-inf)
- evaluation of whole blood:plasma concentration ratios for total radioactivity
- to provide additional safety and tolerability information for MD1003 by assessing: adverse events (AEs), vital signs, electrocardiograms (ECGs), physical examinations and laboratory safety

5 Study Design

5.1 Brief Description

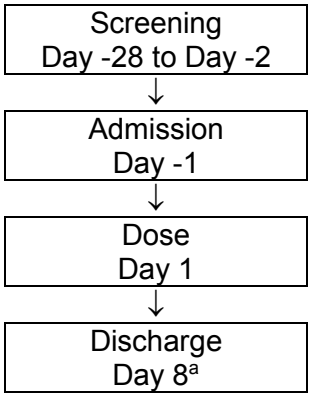
This is a single-centre, open-label, non-randomised, single oral dose study in healthy male subjects. It is planned to enrol 6 subjects.

The study design is presented in Figure 1. Subjects will be screened to participate in the study up to 28 days before dosing. Subjects will be admitted to the clinical unit on the evening of Day -1 prior to IP administration.

Subjects will be dosed in the morning of Day 1 following an overnight fast with a single oral administration of a capsule containing 100 mg MD1003 and NMT 2.22 MBq (approximately 60.0 µCi) [^{14}C]-MD1003.

Subjects 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 subject 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 planned residency period. Once the discharge criteria or the planned residency period has been achieved, collection of all samples (blood, urine and faeces) will be stopped and subjects will undergo discharge assessments. If the mass balance criteria have not been met by all subjects by Day 8, the residency period for the subjects not achieving the release criteria may be extended up to a maximum of an additional 48 h (up to Day 10) for further collection of urine and/or faeces. If the 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.

Figure 1 Study Sequence



[a] Subject may be discharged as a group earlier if a cumulative 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 criteria are not met by Day 8, this may result in the extension of the residency period for the subjects not achieving the release criteria up to a maximum of an additional 48 h (up to Day 10) for further collection of urine and/or faeces. If the criteria are still not met by Day 10, or if additional residency is not considered appropriate or necessary, then home collections of urine and/or faeces may be requested at the discretion of the investigator for individual subjects.

5.2 Criteria for In-Study Decisions

Not applicable for this study.

5.3 Study Sample Size

This 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 is to be enrolled and a minimum of 4 evaluable subjects is considered sufficient.

5.4 Subject Numbers

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

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

No replacement subjects are to be used in this study.

5.5 Blinding Issues

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

6 Populations and Analysis Sets

6.1 Safety Population and Safety Analysis Set

The safety population will include all subjects who have received any amount of IP.

The safety analysis set will include all relevant data from the subjects included in the safety population.

The safety population will be confirmed by Quotient with approval from MedDay Pharmaceuticals after database lock and will be used for the populations table and to determine the subjects to be included in the safety analysis set.

The safety analysis set will be confirmed by Quotient with approval from MedDay Pharmaceuticals at the same time as the safety population and will be used for the analysis of demographic and baseline characteristics, and all safety data.

6.2 Mass Balance Population and Mass Balance Analysis Set

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

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

The mass balance analysis set will include all relevant data from the subjects included in the mass balance population.

The mass balance population will be confirmed by Quotient with approval from MedDay Pharmaceuticals once all urinary and faecal data have been received and will be used for the populations table and to determine the subjects to be included in the mass balance analysis set.

The mass balance analysis set will be confirmed by Quotient with approval from MedDay Pharmaceuticals at the same time as the mass balance population and will be used for the provision of mass balance summary tables and figures.

6.3 Pharmacokinetic Population and Pharmacokinetic Analysis Set

The PK population will include all subjects who have received IP and who satisfy the following criteria for at least 1 profile:

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

The PK analysis set will include all relevant data from the subjects included in the PK population.

The PK population will be confirmed by Quotient with approval from MedDay Pharmaceuticals following derivation of all PK parameter estimates and will be used for the populations table and to determine the subjects to be included in the PK analysis set.

The PK analysis set will be confirmed by Quotient with approval from MedDay Pharmaceuticals at the same time as the PK population and will be used for the provision of PK summary tables and figures.

7 Subject Disposition, Demographics and Baseline Characteristics

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

7.1 Screening Failures

Data for subjects who have failed screening will be databased but will not be cleaned and therefore will not be included in the SAS extracts, SDTM or ADaM datasets or any of the TFLs.

7.2 Subject Disposition and Withdrawals

The number and percentage of subjects enrolled, dosed, completed and discontinued will be presented. If any subjects discontinued from the study early then the number of subjects for each reason for discontinuation will be presented. However, if none of the subjects discontinued from the study early, then the reasons for discontinuation will not be populated in the summary table.

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

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

7.3 Analysis Populations

A summary table will be produced detailing the number and percentage of subjects in each safety, mass balance and PK population. The reasons for exclusion from each population will also be included in the summary.

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

7.4 Analysis Sets

A summary table will be produced detailing the number and percentage of subjects in each safety/mass balance/PK analysis set. The table will be based on the relevant population the analysis set is a subset of (ie the safety/mass balance/PK population). The reasons for exclusion from each analysis set will also be included in the summary.

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

7.5 Demographic Characteristics and Lifestyle Details

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

$$\text{Age (years)} = \frac{\text{Date of Informed Consent} - \text{Date of Birth}}{365.25}$$

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

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

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

Demographic and lifestyle data will be listed by subject for all enrolled subjects.

7.6 Medical/Surgical History

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

7.7 Prior and Concomitant Medication

Medications (product name) will be coded using the World Health Organization (WHO) Drug Dictionary Global Drug Reference (2019 September version or more recent version) using the following Anatomical Therapeutic Chemical (ATC) classification codes:

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

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

7.7.1 Summary Table for Prior and Concomitant Medication

If 2 or more subjects receive concomitant medications, a table will be presented to summarise concomitant medications data.

All subjects taking concomitant medications will be summarised. Counts will be given for total number (and percentage) of subjects who received concomitant medications and total number of occasions in which medications were taken.

Additionally, concomitant medication will be summarised by therapeutic subgroup, chemical subgroup and preferred name. Counts will be given for the number (and percentage) of subjects and total number of occasions in which medications were taken.

No summary table will be presented for prior medication.

7.7.2 Listing for Prior and Concomitant Medication

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

7.8 Other Baseline Characteristics

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

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

8 Efficacy

Not applicable.

9 Mass Balance and Pharmacokinetics

9.1 Mass Balance Parameter Estimation and Reporting

Pharmaron will provide the following concentration and weight data on a per subject basis for each collection period as specified in the clinical protocol:

- amount of dose received (mg) and radioactive dose received (µCi and MBq)
- total radioactivity concentration (mass unit equivalents/g)
- weight of urine (g)
- faeces weight (g) ie not faecal homogenate weight

Concentration values will be expressed in terms of mass unit equivalents of the free base form. Quotient Data Sciences will be responsible for the calculation of excretion and recovery of total radioactivity in urine, faeces and urine and faeces combined for inclusion into the CSR.

For the purposes of this document, “excretion” will be used when describing the amount of total radioactivity excreted and “recovery” will be used when describing the amount of total radioactivity expressed as a percentage of the radioactive dose administered.

9.1.1 Definition of Mass Balance Parameters

A list of mass balance parameter definitions are provided in Table 1.

Table 1 Mass Balance Parameters and Reporting Specifications

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

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

DP = decimal place
SF = significant figure

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

9.1.2 Rules for Mass Balance Parameter Estimation

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

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

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

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

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

- The cumulative amount excreted in urine, ie CumAe(urine), and the cumulative amount excreted in faeces, ie CumAe(faeces), will be calculated by the incremental summation of the Ae(<matrix>) across all collection periods (where matrix is either urine or faeces).

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

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

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

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

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

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

- The cumulative % amount of the total radioactive dose excreted in urine, ie Cum%Ae(urine), and the cumulative % amount of the total radioactive dose excreted in faeces, ie Cum%Ae(faeces), will be calculated by the incremental summation of the %Ae(<matrix>) across all collection periods (where matrix is either urine or faeces).
- The cumulative % amount of the total radioactive dose excreted in urine and faeces combined, ie Cum%Ae(total), will be calculated for each collection period using the following formula:

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

Where the collection periods for urine and faeces differ (ie, on Day 1 urine collected at 12 h intervals while faeces collected over 24 h), the total excretion and recovery (ie, urine and faeces combined) will be calculated over the larger of the intervals.

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

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

Non-numerical values reported in the urine and faecal data set (ie concentrations that are ND) will be entered as zero for calculation of mass balance parameters.

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

1.02 g of urine = 1 mL of urine

This will be calculated in SAS as follows:

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

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

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

The radioactivity associated with toilet paper may be determined at the request of the sponsor. The results will be reported for each subject as a single value for the whole collection period and included in the calculation of amount excreted and % of dose recovered.

Other unexpected sources of elimination will be collected as voided (ie, emesis) and samples will be shipped to Pharmaron for the analysis of total radioactivity. Such cases will be discussed with Med Day and details regarding the reporting will be documented.

The actual dose, as received from Pharmaron, will be used for mass balance analysis.

9.1.3 Mass Balance Summary Tables

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

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

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

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

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

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

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

9.1.4 Mass Balance Figures

Arithmetic mean cumulative excretion (ie CumAe) and cumulative recovery (ie Cum%Ae) vs time curves will be produced on a linear/linear scale and will include ± SD bars. These plots will be produced for CumAe and Cum%Ae, separately, with urine, faeces and total overlaid.

In addition, individual cumulative excretion (ie, CumAe) and cumulative recovery (ie, Cum%Ae) vs time curves will be produced on a linear/linear scale. These plots will be produced for CumAe and Cum%Ae, separately, with urine, faeces and total overlaid.

A legend identifying each profile (ie urine, faeces and total) will be displayed on the mean plots. Mean figures will be produced using the LOCF imputation strategy (see Section 9.1.3) if summary tables are produced using this method.

9.1.5 Mass Balance Listings

The sample collection data (eg collection times) for all urine and faecal samples will be listed by subject for enrolled subjects. In addition, all total radioactivity concentrations, urine and faecal weights and all mass balance parameters will be listed per subject.

For urine and feces, where a subject has failed to void over a particular collection interval, the amount excreted (Ae) will be listed as “NS” in the data listings.

Concentrations that are not detected (ie, < limit of detection (LOD)), will be listed as “ND” in the data listings.

9.1.6 Statistical Analysis of Mass Balance Parameters

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

9.2 Pharmacokinetic Parameter Estimation and Reporting

Charles River will provide plasma concentration data for MD1003, bisnorbiotin and biotin sulfoxide. Pharmaron will provide plasma and whole blood concentration data for total radioactivity.

The PK parameters for MD1003, bisnorbiotin, biotin sulfoxide and total radioactivity in plasma (only) will be estimated by Quotient, where possible and appropriate for each subject using Phoenix WinNonlin software (v8.0 or a more recent version, Certara USA, Inc., USA).

9.2.1 Definition of Pharmacokinetic Parameters

Plasma PK parameter definitions are provided in Table 2 and will be calculated for MD1003, bisnorbiotin, biotin sulfoxide and total radioactivity unless otherwise stated.

Table 2 Plasma Pharmacokinetic Parameters and Rounding Specifications

Parameter	Definition	Unit	DP or SF	No. of DP/SF
Tlag	Time prior to the first measurable concentration	h	DP	2
Tmax	Time of maximum observed concentration	h	DP	2
Cmax	Maximum observed concentration	mass unit/mL	SF	3
AUC(0-last)	Area under the curve from 0 time to the last measurable concentration	mass unit.h/mL	SF	3
AUC(0-inf)	Area under the curve from 0 time extrapolated to infinity	mass unit.h/mL	SF	3
AUCextrap	Percentage of AUC(0–inf) extrapolated beyond the last measurable concentration	%	DP	2
T1/2	Apparent elimination half-life	h	DP	2
lambda-z	Slope of the apparent elimination phase	1/h	DP	4
CL/F (MD1003 only)	Apparent total body clearance calculated after a single extravascular administration, where F (fraction of dose bioavailable) is unknown	mL/min	SF	3
Vz/F (MD1003 only)	Apparent volume of distribution based on the terminal phase calculated after a single extravascular administration, where F (fraction of dose bioavailable) is unknown	L	SF	3
MPR Cmax	Metabolite to parent ratio based on Cmax	NA	DP	2
MPR AUC(0-last)	Metabolite to parent ratio based on AUC(0-last)	NA	DP	2
MPR AUC(0-inf)	Metabolite to parent ratio based on AUC(0-inf)	NA	DP	2
TER Cmax	Total exposure ratio based on Cmax	NA	DP	2
TER AUC(0-last)	Total exposure ratio based on AUC(0-last)	NA	DP	2
TER AUC(0-inf)	Total exposure ratio based on AUC(0-inf)	NA	DP	2
lambda-z lower*	Lower limit on time for values to be included in the calculation of lambda-z	h	DP	2
lambda-z upper*	Upper limit on time for values to be included in the calculation of lambda-z	h	DP	2

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

9.2.2 Rules for Pharmacokinetic Parameter Estimation using WinNonlin

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

- pre-dose sample times will be entered as zero
- values that are below the limit of quantification (BLQ) or not detected (ND) will be entered as zero

- should partial AUCs be required then values that are BLQ or ND after Cmax may be imputed as zero for these partial areas if lambda-z cannot be determined
- values that are quantifiable after at least 2 consecutive BLQ or ND values after Cmax will be treated as missing for the calculation of PK parameters
- values that are reported as “No Result” (NR) or “No Sample” (NS) etc. will be treated as missing

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

Parameter Estimation	Constraint
Sampling times	Actual
Trapezoidal method	Linear trapezoidal rule
Number of points used for lambda-z	At least 3, not including Cmax
Minimum requirements for AUC	At least 3 consecutive quantifiable concentrations
Dose	Actual
Rounded dose level	3 significant figures

Prior to PK parameter estimation the bioanalytical data may be corrected to account for the proportion of administered [^{14}C] material not measured due to the use of a [^{12}C] LC-MS/MS analysis method. Data correction will only be performed if the [^{14}C]-contribution exceeds 1 % of the dose administered. If required, MD1003 bioanalytical data will be multiplied by the determined data correction factor in SAS by the lead statistical programmer (or designee).

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

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

Total radioactivity whole blood to plasma ratios will be determined using SAS by the Lead Statistical Programmer (or designee) at the time points: 1, 4, 8, 12, 24, 48, 72, 96 and 168 h. If either the blood or plasma concentration values are ND (ie <LOD) at any given time point the ratio will not be calculated.

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

1.06 g of blood = 1 mL of blood

This will be calculated in SAS as follows:

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

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

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

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

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

Correcting for molecular weight (MW):

- parent (MD1003) MW = 244.31 g/mol
- metabolite (bisnorbiotin) MW = 216.26 g/mol
- metabolite (biotin sulfoxide) MW = 260.31 g/mol

In addition, total exposure ratios (TER) will be calculated for MD1003, bisnorbiotin and biotin sulfoxide as follows using Cmax, AUC(0-last) and AUC(0-inf):

$$\mathrm{TER(parent)} = \frac{\text{AUC or Cmax (parent)}}{\text{AUC or Cmax (parent + metabolites)}}$$

$$\mathrm{TER(metabolite)} = \frac{\text{AUC or Cmax (metabolite)}}{\text{AUC or Cmax (parent + metabolites)}}$$

Note that each analyte will be corrected by it's own MW (as given above) for calculation of TER.

9.2.3 Bioanalytical and Pharmacokinetic Reporting Specifications

PK parameters for each subject will be reported according to the definitions and rounding specifications provided in Table 2. The following flags/footnotes may be applied to the PK parameters:

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

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

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

Additional flags may be applied based on emerging data.

9.2.4 Bioanalytical and Pharmacokinetic Summary Tables

Summary statistics (ie n, mean, SD, CV%, median, minimum, maximum, geometric n, geometric mean, geometric SD and geometric CV%) will be calculated for the following concentration data where possible:

- plasma concentrations of MD1003 by time point
- plasma concentrations of bisnorbiotin by time point
- plasma concentrations of biotin sulfoxide by time point
- plasma concentrations of total radioactivity by time point
- whole blood concentrations of total radioactivity by time point
- whole blood:plasma concentration ratio of total radioactivity by time point

Values reported in the plasma and whole blood concentration data (ie values that are BLQ or ND) will be entered as zero for the determination of summary statistics with the exception of geometric mean parameters where BLQ or ND values will be imputed as half the LLOQ or LOD value. Data recorded as NR or NS will be handled as missing, ie no assumption will be made about the actual concentration.

Summary statistics (ie n, mean, SD, CV%, median, minimum and maximum) will be calculated for all plasma PK parameters. Geometric n, geometric mean, geometric SD and geometric CV% will be presented for all PK parameters except Tlag and Tmax. These summary statistics will be calculated for relevant plasma PK parameters relating to the following:

- MD1003
- bisnorbiotin
- biotin sulfoxide
- total radioactivity

If applicable, data recorded as “Not Calculated” (NC) will be handled as missing.

9.2.5 Bioanalytical and Pharmacokinetic Figures

Mean and individual concentration plots will be produced for each of the following:

- plasma concentrations of MD1003, bisnorbiotin, biotin sulfoxide and total radioactivity on same plot
- plasma and whole blood concentrations of total radioactivity on the same plot

Individual concentration vs time plots (using actual sampling times after dosing) will be produced on the linear/linear and the log10/linear scale for each individual subject.

Mean concentration vs time (using nominal times) plots will be produced on the following:

- linear/linear scale using arithmetic mean concentrations (error bars ± arithmetic SD)
- log10/linear scale using geometric mean concentrations (error bars x/÷ geometric SD)

Separate concentration vs time (using actual sampling time) plots displaying 1 line per subject will be produced on the linear/linear and the log10/linear for each of the following:

- plasma MD1003
- plasma bisnorbiotin
- plasma biotin sulfoxide
- plasma total radioactivity
- whole blood total radioactivity

Where curves from multiple analytes or subjects are overlaid on the same plot, symbols will be used to identify different analytes/subjects. A legend will be included on these plots to define the symbols used in identifying different profiles.

For all plots on a linear/linear scale, concentration values reported as BLQ or ND will be set to zero. For all plots on a log 10/linear scale then concentration values reported as BLQ will be set to ½ x LLOQ or LOD and pre-dose samples on Day 1 will not be plotted.

9.2.6 Bioanalytical and Pharmacokinetic Listings

The sample collection data (eg collection times) for PK samples will be listed by subject. In addition, all concentration data including individual ratios (total radioactivity whole blood:plasma) and PK parameters will be listed on a per subject basis. Any flags used will be provided in listings with the appropriate definition.

9.2.7 Statistical Analysis of Pharmacokinetic Parameters

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

10 Safety Assessments

Safety data summaries will be presented using the safety analysis set, throughout.

10.1 Extent of Exposure and Treatment Compliance

The total dose given, including the dose of MD1003 (in mg) and radioactivity in µCi and MBq, will be summarised (ie n, mean, SD, median, minimum and maximum).

Dosing details (including the date and time of IP administration and any comments) will be listed for all enrolled subjects. Dose will be reported to 3 significant figures in listings. Any recorded deviations from the planned dosing regimen will be listed as protocol deviations.

10.2 Meal Details

Meal details as recorded on the eCRF as sponsor data will be listed. Any recorded deviations from the planned meal times will be listed as protocol deviations.

10.3 Adverse Events

Throughout the study, all AEs will be evaluated by the principal investigator (PI) and noted in the AE section of the eCRF. 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 (referred as TEAEs), including occurrences which are not necessarily caused by or related to that product.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v22.1, or most recent version), and reported by system organ class (SOC) and preferred term (PT).

AEs will be classified into the following categories:

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

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

Adverse events will be classified as “unrelated”, “possibly related” and “related” when considering their relationship to IP. Adverse drug reactions (ADRs) are any AE where a causal relationship with the IP is at least reasonable possibility ie “possibly related” or “related”. Pre-dose AEs will always have the classification of “unrelated”.

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

If the severity or relationship to IP of a TEAE is missing, the severity/relationship will be tabulated as “severe”/”related” in the summary tables ie a worst case scenario will be assumed.

Where the start date of an AE is missing and the stop date is on or after the day of dosing of IP or both the start and stop dates are missing then a “worst-case” scenario will be assumed, ie the AE is assumed to have occurred post-dose and is therefore considered treatment-emergent. If a partial start date/time is available then the event will be considered as treatment-emergent unless the partial information suggests otherwise.

10.3.1 Summary Tables for Adverse Events

All pre-dose AEs (as defined in Section 10.3) will be excluded from the summary tables but will be listed for all enrolled subjects.

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

The number and percentage of subjects reporting each TEAE will be summarised for both SOC and PT. For summaries by SOC and PT, the number of subjects and the number of events will be summarised.

For counts of subjects experiencing events the following will apply:

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

For event counts, all events are included.

When it is necessary to calculate percentages, the denominator will be the total number of subjects in the safety analysis set and the numerator will be the total number of subjects reporting a TEAE within the relevant category.

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

10.3.1.1 Overall Summary of Adverse Events

The following will be summarised for the safety analysis set:

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

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

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

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

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

10.3.1.3 Summary of Treatment-Emergent Adverse Events by Severity

All subjects reporting TEAEs will be summarised by severity ("mild", "moderate" or "severe"). Counts will be given for number of subjects and number of events. Counts for number of subjects will be given by severity category (ie subjects experiencing more than 1 TEAE across severity categories will be counted only once by severity category).

Additionally, subjects reporting TEAEs will be summarised for SOC and PT by severity (ie "mild", "moderate" or "severe"). Counts will be given for total number of subjects and number of events. Counts for number of subjects will be given by severity category (ie subjects experiencing more than 1 TEAE across severity categories will be counted only once within each SOC and PT by severity category).

10.3.1.4 Summary of Treatment-Emergent Adverse Events by Relationship to IP

All subjects reporting TEAEs will be summarised by relationship to IP (ie "unrelated", "possibly related" or "related"). Counts will be given for number of subjects and number of events. Counts for number of subjects will be given by level of relationship to IP (ie subjects experiencing more than 1 TEAE across relationship to IP categories will be counted only once by level of relationship).

Additionally, subjects reporting TEAEs will be summarised for SOC and PT by level of relationship to IP (ie "unrelated", "possibly related" or "related"). Counts will be given for total number of subjects and number of events. Counts for number of subjects will be given by level of relationship (ie subjects experiencing more than 1 TEAE across relationship to IP categories will be counted only once within each SOC and PT by level of relationship).

10.3.1.5 Summary of Adverse Drug Reactions

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

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

10.3.1.6 Summary of Serious Adverse Events

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

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

10.3.2 Listings for Adverse Events

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

A separate data listing of all TEAEs will be provided including the SOC and PT. In addition separate listings of all TEAEs leading to deaths and SAEs will be provided.

10.4 Laboratory Evaluations

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

Where a value is provided by the safety laboratory as either above or below the LOD this will be set to the respective LOD itself for descriptive summaries. No imputations will be made in the individual listings.

10.4.1 Summary Tables for Laboratory Evaluations

Haematology and clinical chemistry data will be summarised (ie n, mean, SD, median, minimum and maximum) for each laboratory parameter at each time point, including changes from baseline (pre-dose, Day 1) at the 24 h and discharge (planned to be 168 h) post-baseline time point.

Shift tables from baseline to 24 h and discharge post-baseline time point (with respect to the number and percentage of subjects with values below, within or above the reference range) will be presented. Percentages will be based on the number of subjects with measurements at baseline and the 24 h and discharge post-baseline time points.

Note that the clinical chemistry parameters glucose (fasting) and glucose (random) are treated as separate parameters. Glucose (fasting) will be presented in the summary statistic and shift tables if there is pre-dose and post-dose readings for subjects. Glucose (random) will be listed only.

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

10.4.2 Listings for Laboratory Evaluations

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

All individual subject data, for planned haematology, clinical chemistry and urinalysis data including derivations such as change from baseline will be listed. If applicable, data from unscheduled laboratory tests will also be listed and flagged with a "#" to indicate it will not be used in the summary statistics. In these listings, individual data will be flagged with an "H" or an "L" for values that are higher or lower than their reference ranges, respectively.

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

- pH: 5.0 to 8.0
- Specific gravity: 1.005 to 1.035

10.5 Vital Signs

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

10.5.1 Summary Tables for Vital Signs

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

In addition, the number of subjects with 'substantial' increases or decreases or no substantial change from baseline in systolic BP (>20 mmHg), diastolic BP (>10 mmHg) and heart rate (>15 bpm) will be summarised.

10.5.2 Listings for Vital Signs

All individual vital signs data (ie systolic and diastolic BP, heart rate and oral temperature) including derivations such as change from baseline will be listed. Individual data will be flagged with an "H" or an "L" for values that are higher or lower than their reference ranges (see Table 3), respectively, and subjects with 'substantial' increases or decreases from baseline (as defined in Section 10.5.1) in systolic BP, diastolic BP and heart rate will be flagged with an 'I' (increase) or 'D' (decrease), respectively. If applicable, data from unscheduled vital signs assessments will also be listed and flagged with a "#" to indicate it will not be used in the summary statistics.

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

The reference ranges (from Quotient SOP "The Interpretation of the Electrocardiogram, Vital Signs and Clinical Laboratory Data During Phase I / II Clinical Trials) defined in Table 3 will be used.

Table 3 Vital Signs Reference Ranges

Parameter	Split	Lower limit	Upper limit
Systolic BP	18-45 years	90 mmHg	140 mmHg
Systolic BP	>45 years	90 mmHg	160 mmHg
Diastolic BP	NA	40 mmHg	90 mmHg
Heart rate	NA	40 bpm	100 bpm
Oral Body Temperature	NA	35.5ºC	37.5ºC

NA=Not applicable

10.6 ECGs

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

10.6.1 Summary Tables for ECGs

ECG data, including change from baseline (pre-dose, Day 1), will be summarised (ie n, mean, SD, median, minimum and maximum) at each post-baseline time point.

The number and percentage of subjects with normal and prolonged QT intervals corrected for heart rate using Fridericia's correction (ie QTcF) and increases in QTcF intervals from baseline within the categories defined in Table 4 (based on the International Council on Harmonisation [ICH] E14 guideline [1]) will be summarised by time point. Percentages will be based on the number of subjects with measurements at the relevant time point.

Table 4 ICH E14 Ranges for QTcF Intervals

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

10.6.2 Listings for ECGs

All ECG measurements (ie single readings) including derivations such as change from baseline will be listed by subject for all enrolled subjects.

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

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

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

The reference ranges (from Quotient SOP "The Interpretation of the Electrocardiogram, Vital Signs and Clinical Laboratory Data During Phase I / II Clinical Trials") and defined in Table 5 will be used. Note that QT interval will not be presented with a respective reference range.

Table 5 ECG Reference Ranges

Parameter	Lower limit	Upper limit
Ventricular Rate (HR)	40	100
QTcF Interval	NA	450 msec
PR Interval	120 msec	220 msec
QRS Duration	NA	120 msec
QRS Axis	-30º	100º

HR=heart rate
NA=Not applicable

10.7 Physical Examination

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

11 Interim Statistical Analyses

No interim statistical analysis is planned for this study.

12 Changes in the Conduct of the Study or Planned Analysis

12.1 Changes in the Conduct of the Study

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

12.2 Changes to the Planned Analyses

No changes to planned analysis.

12.3 Any Other Relevant Changes

Not applicable.

13 Overall Considerations

13.1 Statistical Programming and Analysis

The Data Sciences Department at Quotient will perform the statistical programming and analysis to produce all analysis datasets and TFLs using the statistical SAS Software v9.4.

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

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

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

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

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

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

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

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

In general summary statistics will be presented as detailed in Table 6 below, unless otherwise stated:

Table 6 Reporting Conventions for Summary Statistics

Data Type	Statistic	Number of decimal places for reporting (i)
Frequency	Counts (n)	None
	Percentages (%)	1 decimal place
Summary statistic	n	None
	Mean	i + 1 decimal place
	SD	i + 1 decimal place
	CV%	1 decimal place
	Median	i + 1 decimal place
	Min	i decimal places
	Max	i decimal places
	Geometric n	None
	Geometric Mean	i + 1 decimal place
	Geometric SD	i + 1 decimal place
	Geometric CV%	1 decimal place

i refers to the number of decimal places reported in the eCRF or other appropriate source data for the original data. Where bioanalytical or PK data are received rounded in significant figures rather than decimal places, summary statistics will be supplied to the same precision.

Details of how the individual mass balance and PK parameters will be presented are detailed in Section 9.1.1 and Section 9.2.1, respectively. Where data requires rounding,

values ending with 1 to 4 will be rounded down and values ending with 5 to 9 will be rounded up.

All data listings will be based on all enrolled subjects (see Section 3.2.1). Details of age and sex will be included on all data listings.

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

There will be no other imputations for the safety data with regard to missing values or study discontinuation (ie subjects who do not complete the study). Imputation for mass balance parameter estimation using SAS Software is described in Section 9.1.2 and for PK parameter estimation using WinNonlin is described in Section 9.2.2.

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

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

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

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

13.2.1 Quality Control - Summary Tables

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

- for tables with no time points, all summary statistics will be QC'd
- for tables with time points, at least one time point in each table will be QC'd – different combinations of time point will be selected across tables
- where tables are produced using a macro for multiple parameters, a minimum of 3 tables, using treatment and time point as appropriate, will be QC'd
- for AEs, the treatment details will be 100% QC'd against the treatment allocation list for all subjects
- AE summary tables will be 100% checked using the relevant data listing

13.2.2 Quality Control - Figures

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

- all data points for treatment will be checked
- where figures are produced using a macro for individual subjects and/or multiple parameters, a minimum of 3 figures will be QC'd
- mean figures will be QC'd using the corresponding summary table

13.2.3 Quality Control - Data Listings

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

14 SAS Data Transfer

All study data used for analysis and reporting will be transferred to MedDay on issue of the final CSR. Datasets will be provided in SAS transport file format (XPT), each dataset will be in an individual transport file and will be performed in compliance with SDTM (IG v3.2) and ADaM (IG v1.1). This will include define.xml (v2.0) output as well as a Data Reviewers Guide (one for SDTM and one for ADaM) in PDF which will be linked to the ADaM define.xml. The define.xml will be issued on finalisation of the CSR.

In addition, copies of reporting SAS programs will be provided with the final data transfer (as executable files). This transfer will also include SDTM/ADaM specs, 'raw' database extract datasets, external vendor datasets (with transfer specs) and the database and dataset annotated eCRFs.

15 Programming Conventions

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

- courier new, font size 8
- landscape
- A4 paper

Tables and listings will be produced as MS Word 2016 documents and figures will be produced as RTF and PDF files. Listings will be sorted by subject ID number.

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

16 Reference List

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

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20 Mock Tables

MedDay Pharmaceuticals
Protocol: MD1003CT2019-03MB

TABLE 14.1.1
Subject Disposition by Reason
Summary Statistics: All Enrolled Subjects

	100 mg [14C]-MD1003 (N=XX) n (%)
Subjects enrolled (1)	xx (xx.x)
Subjects dosed	xx (xx.x)
Subjects completed	xx (xx.x)
Subjects discontinued	xx (xx.x)
Reason for discontinuation	
REASON 1	xx (xx.x)
REASON 2	xx (xx.x)
REASON 3	xx (xx.x)
…	…
<All categories on source>	xx (xx.x)

Note: The data in this table are presented in listing x.x
(1) An enrolled subject is defined as a subject who signed the informed consent, qualified per the inclusion/exclusion criteria and was allocated a subject number.
A subject may be discontinued for one reason only.
Percentages are based on the number of subjects enrolled.

PROGRAM PATH: X:\~\QSC201639\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all reasons for discontinuation as recorded on the eCRF. If none of the subjects discontinued from the study early then reasons for discontinuation will not be populated in the summary table.)

MedDay Pharmaceuticals
Protocol: MD1003CT2019-03MB

TABLE 14.1.2.1
Analysis Populations
Summary Statistics: All Enrolled Subjects

	100 mg [14C]-MD1003 (N=XX)
Number (%) of subjects in Safety Population	xx (xx.x)
Reasons for exclusion from Safety Population	
<All categories on source listing>	xx (xx.x)
	…
Number (%) of subjects in Mass Balance Population	xx (xx.x)
Reasons for exclusion from Mass Balance Population	
<All categories on source listing>	xx (xx.x)
	…
Number (%) of subjects in PK Population	xx (xx.x)
Reasons for exclusion from PK Population	
<All categories on source listing>	xx (xx.x)
	…

Note: The data in this table are presented in listing x.x
A subject may be excluded for more than one reason.
Percentages are based on the number of subjects enrolled.

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(Programming note: This table will be continued for all reasons for exclusion. If none of the subjects were excluded from a population, then reasons for exclusion will not be populated in the summary table.)

MedDay Pharmaceuticals
Protocol: MD1003CT2019-03MB

TABLE 14.1.2.2.1
Safety Analysis Set
Summary Statistics: Safety Population

	100 mg [14C]-MD1003 (N=XX)
Number (%) of subjects in Safety Analysis Set	xx (xx.x)
Reasons for exclusion from Safety Analysis Set	
<All categories from source>	xx (xx.x)
	…

Note: The data in this table are presented in listing x.x
A subject may be excluded for more than one reason.

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(Programming note: This table will be continued for all reasons for exclusion. If none of the subjects were excluded from the safety analysis set, then reasons for exclusion will not be populated in the summary table. Similar tables will be produced for:
• PK Analysis Set, ie Table [14.1.2.3] and
• Mass Balance Analysis Set, ie Table [14.1.2.4].
Each analysis set will be a subset of their respective populations and percentages will be based on number of subjects in each population.)

MedDay Pharmaceuticals
Protocol: MD1003CT2019-03MB

TABLE 14.1.3
Demographic and Baseline Characteristics
Summary Statistics: Safety Analysis Set

		100 mg [14C]-MD1003 (N=XX)
Age (years)	n	xx
	Mean	xx.xx
	SD	xx.xx
	Median	xx.xx
	Min	xx.x
	Max	xx.x
Ethnicity n (%)	<All categories on source>	xx (xx.x)
Race n (%)	<All categories on source>	xx (xx.x)
Sex n (%)	Male	xx (xx.x)
Height (cm)	…	…
Weight (kg)	…	…
BMI (kg/m^2)	…	…

Note: The data in this table are presented in listing x.x

PROGRAM PATH: X:\~\QSC201639\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

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

MedDay Pharmaceuticals
Protocol: MD1003CT2019-03MB

TABLE 14.1.4
Lifestyle Details: Smoking History and Alcohol Consumption
Summary Statistics: Safety Analysis Set

		100 mg [14C]-MD1003 (N=XX) n (%)
Does subject smoke (1)	NO: NEVER	xx (xx.x)
	PREVIOUSLY	xx (xx.x)
Alcohol Consumption (2)	NONE	xx (xx.x)
	YES: <21 UNITS	xx (xx.x)

Note: The data in this table are presented in listing x.x
(1) Anyone who smoked, used e-cigarettes or any nicotine replacement products in the last 12 months is excluded from the study.
(2) Anyone who regularly consumes alcohol (>21 units/week in males) is excluded from the study.
1 unit = 1/2 pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type.

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MedDay Pharmaceuticals
Protocol: MD1003CT2019-03MB

TABLE 14.1.5
Concomitant Medications
Summary Statistics: Safety Analysis Set

Medications	100 mg [14C]-MD1003 (N=XX) n (%)	Number of Occasions
Any Concomitant Medication	xx (xx.x)	xx
Therapeutic subgroup 1	xx (xx.x)	xx
Chemical subgroup 1	xx (xx.x)	xx
preferred name 1	xx (xx.x)	xx
preferred name 2	xx (xx.x)	xx
…	…	…
Chemical subgroup 2	xx (xx.x)	xx
preferred name 1	xx (xx.x)	xx
preferred name 2	xx (xx.x)	xx
…	…	…
Therapeutic subgroup 1	xx (xx.x)	xx
Chemical subgroup 1	xx (xx.x)	xx
preferred name 1	xx (xx.x)	xx
preferred name 2	xx (xx.x)	xx
…	…	…

Note: The data in this table are presented in listing x.x
Medications are coded using WHODrug 2019 September version.
n is the number of subjects reporting at least one concomitant medication.
Counts are given for number of subjects and total number of occasions in which medications were taken.
Abbreviations: WHODrug=World health organisation drug dictionary global drug reference

MedDay Pharmaceuticals
Protocol: MD1003CT2019-03MB

TABLE 14.1.6
Extent of Exposure
Summary Statistics: Safety Analysis Set

	100 mg [14C]-MD1003 (N=XX)		
	mg	MBq	µCi
n	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx
SD	xx.xx	xx.xx	xx.xx
Median	xx.xx	xx.xx	xx.xx
Min	xx.x	xx.x	xx.x
Max	xx.x	xx.x	xx.x

Note: The data in this table are presented in listing x.x

PROGRAM PATH: X:\~\QSC201639\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

MedDay Pharmaceuticals Page x of y
Protocol: MD1003CT2019-03MB

TABLE 14.2.1.1.1
Excretion: Total Radioactivity
Ae(Urine) by Collection Period <(units)>
Summary Statistics: Mass Balance Analysis Set

100 mg [14C]-MD1003 (N=XX)

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

Note: The data in this table are presented in listing x.x
Where a subject has failed to void or has a ND concentration over a particular collection interval, the amount excreted (Ae) has been set to zero.

PROGRAM PATH: X:\~\QSC201639\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all collection periods. Similar tables will be produced for
- %Ae(Urine) (Recovery), ie Table [14.2.1.1.3]
- Ae(Faeces), ie Table [14.2.1.2.1]
- %Ae(Faeces) (Recovery), ie Table [14.2.1.2.3]
- Ae(total), ie Table [14.2.1.3.1] and
- %Ae(total) (Recovery), ie Table [14.2.1.3.3].)

(Programming note: Tables 14.2.1.2.1, 14.2.1.2.3, 14.2.1.3.1 and 14.2.1.3.3 will have 'ADIMISSON – 0 H' for 'PRE-DOSE'.)

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TABLE 14.2.1.1.2
Excretion: Total Radioactivity
Cumulative Ae(Urine) <(units)>
Summary Statistics: Mass Balance Analysis Set

100 mg [14C]-MD1003 (N=XX)

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

Note: The data in this table are presented in listing x.x

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(Programming note: This table will be continued for all collection periods. If required, as a result of early withdrawal or varying follow-up periods, a further set of tables will be produced for LOCF values. Table numbers will be incremented by .1 for observed values and .2 for LOCF. Similar tables will be produced for
• Cumulative %Ae(Urine) (Recovery), ie Table [14.2.1.1.4]
• Cumulative Ae(Faeces), ie Table [14.2.1.2.2]
• Cumulative %Ae(Faeces) (Recovery), ie Table [14.2.1.2.4]
• Cumulative Ae(total), ie Table [14.2.1.3.2] and
• Cumulative %Ae(total) (Recovery), ie Table [14.2.1.3.4].)
(Programming note: Tables 14.2.1.2.2, 14.2.1.2.4, 14.2.1.3.2 and 14.2.1.3.4 will have 'ADIMISSON – 0 H' for 'PRE-DOSE'.)

MedDay Pharmaceuticals
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TABLE 14.2.1.4
Excretion and Recovery: Total Radioactivity
Cumulative Excretion and Recovery Parameters
Summary Statistics: Mass Balance Analysis Set

100 mg [14C]-MD1003 (N=XX)

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

Note: The data in this table are presented in listing x.x
CumAe represents the cumulative excretion. Cum%Ae represents the cumulative recovery as a percentage of the radioactive dose administered.

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MedDay Pharmaceuticals
Protocol: MD1003CT2019-03MB

TABLE 14.2.1.5.1
Plasma Pharmacokinetic Concentrations: Total Radioactivity <(units)>
Summary Statistics: PK Analysis Set

100 mg [14C]-MD1003 (N=XX)

	Arithmetic (1)						Geometric (2)			
Time Point	n	Mean	SD	CV%	Median	Min	Max	n	Mean	SD	CV%
PRE-DOSE	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x	NC	NC	NC	NC
0.5 H	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.x
1 H	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.x
1.5 H	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.x
…	…	…	…	…	…	…	…	…	…	…	…
<All other time points>	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.x

Note: The data in this table are presented in listing x.x
(1) For arithmetic summary statistics, concentration values reported as BLQ are set to zero.
(2) For calculation of geometric summary statistics, values reported as BLQ are set to ½ × LLOQ, except for pre-dose values which will not be summarised. The LLOQ value was <value, units>.

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(Programming note: This table will be continued for all time points. Similar tables will be produced for
- Plasma Pharmacokinetic Concentrations: Bisnorbiotin, ie Table [14.2.1.5.2]
- Plasma Pharmacokinetic Concentrations: Biotin Sulfoxide, ie Table [14.2.1.5.3]
- Plasma Pharmacokinetic Concentrations: Total Radioactivity, ie Table [14.2.1.5.4]
- Whole Blood Concentrations: Total Radioactivity, ie Table [14.2.1.5.5]
- Whole Blood: Plasma Concentration Ratio, ie Table [14.2.1.5.6].)

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TABLE 14.2.2.1
Plasma Pharmacokinetic Parameters: Total Radioactivity
Summary Statistics: PK Analysis Set

100 mg [14C]-MD1003 (N=XX)

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

Note: The data in this table are presented in listing x.x
For concentration parameters, BLQ values will be set to 0 for arithmetic statistics and to ½ × LLOQ for geometric statistics.
The LLOQ value was <value, units>

PROGRAM PATH: X:\~\QSC201639\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

(Programming note: A similar table will be produced for
- Plasma Pharmacokinetic Parameters: Bisnorbiotin, ie Table [14.2.2.2])
- Plasma Pharmacokinetic Parameters: Biotin Sulfoxide, ie Table [14.2.2.3])
- Plasma Pharmacokinetic Parameters: Total Radioactivity, ie Table [14.2.2.4].)

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TABLE 14.3.1
Overall Summary of Treatment-Emergent Adverse Events
Summary Statistics: Safety Analysis Set

Event	100 mg [14C]-MD1003 (N=XX) n (%)	Events n
TEAEs	xx (xx.x)	xx
Severe TEAEs	xx (xx.x)	xx
ADRs (1)	xx (xx.x)	xx
Serious TEAEs	xx (xx.x)	xx
TEAEs leading to death	xx (xx.x)	xx

Note: The data in this table are presented in listing x.x
TEAEs are coded using MedDRA vXX.X
(1) ADR is any AE where a causal relationship with the IP is classified as 'possibly related' or 'related'.
n is the number of subjects reporting at least one event.

PROGRAM PATH: X:\~\QSC201639\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

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TABLE 14.3.2
Treatment-Emergent Adverse Events
By MedDRA System Organ Class and Preferred Term
Summary Statistics: Safety Analysis Set

System Organ Class Preferred Term	100 mg [14C]-MD1003 (N=XX) n (%)	Events n
TEAEs	xx (xx.x)	xx
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx
etc	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx
etc	…	…
…	…	…

Note: The data in this table are presented in listing x.x
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency.
Subjects experiencing more than one episode of a TEAE are counted only once within each SOC and PT.

PROGRAM PATH: X:\~\QSC201639\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all SOC and PT.)
(Programming note: Counts of number of subjects are by maximum severity, ie subjects experiencing more than one episode of TEAE are only counted once within each SOC and PT using the most severe episode.)

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TABLE 14.3.3
Treatment-Emergent Adverse Events
By MedDRA System Organ Class, Preferred Term and Severity
Summary Statistics: Safety Analysis Set

100 mg [14C]-MD1003
(N=XX)

System Organ Class Preferred Term	Mild n (%)	Events n	Moderate n (%)	Events n	Severe n (%)	Events n
TEAEs	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
etc	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
etc	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

Note: The data in this table are presented in listing x.x
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency.
Counts are given for number of subjects and number of events
Counts for number of subjects are given by severity category (ie subject experiencing TEAEs across different severity categories will be counted once for each severity category).

PROGRAM PATH: X:\~\QSC201639\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all SOC and PT.)
(Programming note: Counts of number of subjects are by severity i.e. subjects experiencing more than 1 episode of a TEAE at the same level of severity will be counted only once within each SOC and PT for that level of severity, subjects experiencing at least 2 TEAEs at different levels of severity will be counted once in each level of severity.)

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TABLE 14.3.4
Treatment-Emergent Adverse Events
By MedDRA System Organ Class, Preferred Term and Relationship to IP
Summary Statistics: Safety Analysis Set

100 mg [14C]-MD1003
(N=XX)

System Organ Class / Preferred Term	Unrelated n (%)	Unrelated Events n	Possibly Related n (%)	Possibly Related Events n	Related n (%)	Related Events n
TEAEs	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
etc	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
etc	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

Note: The data in this table are presented in listing x.x
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency.
Counts are given for total number of subjects and number of events.
Counts for number of subjects are given by relationship to IP category (ie subject experiencing TEAEs across different relationship categories will be counted once for each relationship category).

PROGRAM PATH: X:\~\QSC201639\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all SOC and PT.)
(Programming note: Counts of number of subjects are given by closest relationship i.e. subjects experiencing more than 1 episode of a TEAE at the same level of relationship to IP will be counted only once within each SOC and PT for that level of relationship to IP,subjects experiencing at least 2 TEAEs at different levels of relationship to IP will be counted once in each level of relationship to IP.)

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TABLE 14.3.5
Adverse Drug Reactions
By MedDRA System Organ Class and Preferred Term
Summary Statistics: Safety Analysis Set

System Organ Class Preferred Term	100 mg [14C]-MD1003 (N=XX) n (%)	Events n
ADRs (1)	xx (xx.x)	xx
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx
etc	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx
etc	…	…
…	…	…

Note: The data in this table are presented in listing x.x
(1) An ADR is any AE where a causal relationship with the IP is classified as 'possibly related' or 'related'.
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency.
Counts are given for total number of subjects and number of events.

PROGRAM PATH: X:\~\QSC201639\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

(Programming note: A similar table will be produced for
• Serious Adverse Events, ie Table [14.3.6].)
(Programming note: Subjects experiencing more than one episode of an ADR/SAE are counted only once within each SOC and PT.)

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TABLE 14.4.1
Haematology
Summary Statistics: Safety Analysis Set

100 mg [14C]-MD1003 (N=XX)
<Parameter> (<units>) [ref range xxx - xxx (male)]

	Result						Change from Baseline					
Time Point	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x						
24 H	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x
DISCHARGE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x

Note: The data in this table are presented in listing x.x
BASELINE is defined as Day 1, Pre-dose. DISCHARGE is planned to be 168 h.

PROGRAM PATH: X:\~\QSC201639\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all haematology parameters and all time points.
A similar table will be produced for
• Clinical Chemistry, ie Table [14.4.3].
Parameter may be added as the first column in this table.)

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TABLE 14.4.2
Haematology
Shift Analysis: Safety Analysis Set

100 mg [14C]-MD1003 (N=XX)
<Parameter> (<units>) [ref range xxx - xxx (male)]

Time Point Assessment	N#	Baseline Below n(%)	Baseline Within n(%)	Baseline Above n(%)
24 H	xx			
Below		xx (xx.x)	xx (xx.x)	xx (xx.x)
Within		xx (xx.x)	xx (xx.x)	xx (xx.x)
Above		xx (xx.x)	xx (xx.x)	xx (xx.x)
DISCHARGE	xx			
Below		xx (xx.x)	xx (xx.x)	xx (xx.x)
Within		xx (xx.x)	xx (xx.x)	xx (xx.x)
Above		xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: The data in this table are presented in listing x.x
BASELINE is defined as Day 1, Pre-dose. DISCHARGE is planned to be 168 h.
N# is the total number of subjects that have a value at baseline and each given time-point and is used in the denominator for calculating the percentages of subjects, n indicates the number of subjects with a baseline and a post baseline assessment at the time point indicated. Below/within/above indicate the number (%) of subjects with assessments below/within/above the normal reference range.

PROGRAM PATH: X:\~\QSC201639\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all haematology parameters and all time points.
A similar table will be produced for
• Clinical Chemistry, ie Table [14.4.4].
Parameter may be added as the first column in this table

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TABLE 14.5.1
Vital Signs
Summary Statistics: Safety Analysis Set

100 mg [14C]-MD1003 (N=XX)
<Parameter> (<units>) [ref range xxx - xxx (age xx - xx), xxx - xxx (age > xx)]

	Result						Change from Baseline						Substantial Change		
Time Point	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max	DEC	NONE	INC
BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x									
1 H	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx
4 H	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx
24 H	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx
72 H	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx
DISCHARGE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx

Note: The data in this table are presented in listing x.x
BASELINE is defined as Day 1, Pre-dose. DISCHARGE is planned to be 168 h.
Substantial change is defined as: > ± 20 mmHg Systolic BP, > ± 10 mmHg Diastolic BP and > ± 15 bpm HR.
DEC: number of subjects with substantial decrease from baseline, NONE: number of subjects with no substantial change from baseline, INC: number of subjects with substantial increase from baseline.

PROGRAM PATH: X:\~\QSC201639\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all vital signs parameters.
Parameter may be added as the first column in this table.)

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TABLE 14.5.2.1
ECGs
Summary Statistics: Safety Analysis Set

100 mg [14C]-MD1003 (N=XX)
<Parameter> (<units>) [<ref range xxx - xxx (age xx - xx), xxx - xxx (age > xx)> / <ref range xxx - xxx (male)>]

	Result						Change from Baseline					
Time Point	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x						
1 H	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x
4 H	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x
24 H	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x
DISCHARGE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x

Note: The data in this table are presented in listing x.x
BASELINE is defined as Day 1, Pre-dose. DISCHARGE is planned to be 168 h.

PROGRAM PATH: X:\~\QSC201639\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

(Programming note: This table will be continued for all ECG parameters, which will follow the order given in the RAP text. Parameter may be added as the first column in this table.)

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TABLE 14.5.2.2
ECGs
QTcF Categorical Data
Summary Statistics: Safety Analysis Set

100 mg [14C]-MD1003 (N=XX)

		QTcF Intervals (msec)				QTcF Interval Increase (msec)		
Time Point	N#	<=450 n(%)	451-480 n(%)	481-500 n(%)	>500 n(%)	<30 n(%)	30-60 n(%)	>60 n(%)
BASELINE	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)			
1 H	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
4 H	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
24 H	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
DISCHARGE	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: The data in this table are presented in listing x.x
BASELINE is defined as Day 1, Pre-dose. DISCHARGE is planned to be 168 h.
Categories for QTcF interval and QTcF interval increases are based on ICH E14 guidelines.
N# is the total number of subjects at the relevant time point and is used in the denominator for calculating the percentages of subjects, n indicates the number of subjects with observations at the given time point.

PROGRAM PATH: X:\~\QSC201639\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

Appendix 1: Study Flow Chart

Study Day	-28 to -2	-1	1											2		3	4	5	6	7	8
			Times After Dosing (h)																		
	Screening	Admission	Pre-dose	0	0.5	1	1.5	2	3	4	6	8	12	18	24	36	48	72	96	120	144	168[a]
General Assessments																						
Informed Consent	X																					
Medical History	X	X																				
Weight and Height	X																					
Vein Assessment	X																					
Carbon Monoxide Breath Test	X	X																				
Drug Screen	X	X																				
Alcohol Breath Test	X	X																				
IP Administration				X																		
Safety Assessments																						
Physical Examination	X													X[b]								X[b]
Safety Labs[c]	X		X											X								X
Urinalysis	X		X											X								X
ECG	X		X			X				X				X								X
Vital Signs[d]	X		X			X				X				X			X					X
Adverse Events	◄																					►
Prior and Concomitant Medication	◄																					►
Mass Balance and PK Assessments																						
Plasma Samples for MD1003, bisnorbiotin and biotin sulfoxide			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma Samples for TR			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
Plasma Samples for Metabolite Profiling and ID			X			X		X		X		X	X									
Urine Samples for TR and Metabolite Profiling and Identification[e]			◄																			►
Faecal Samples for TR and Metabolite Profiling and Identification[f]			◄																			►

ECG: Electrocardiogram; ID: Identification; IP: Investigational Product; TR: total radioactivity

[a] Discharge from clinical unit; subjects may be discharged 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 criteria are not met by Day 8, this may result in the extension of the residency period for the subjects not achieving the release criteria up to a maximum of an additional 48 h (up to Day 10) for further collection of urine and/or faeces. If the criteria are 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
[b] Targeted (symptom driven) physical examination
[c] Haematology and clinical chemistry at each time point including virology at screening (see protocol for a full list of clinical laboratory parameters). Creatinine clearance will be estimated at screening from plasma creatinine using the Cockcroft-Gault equation for eligibility purposes
[d] Blood pressure and heart rate. Oral temperature will be measured at screening, pre-dose and any unscheduled assessments as required
[e] A single urine sample will be collected at pre-dose (the first void of the day) and then at the following collection periods: 0 to 12 h, 12 to 24 h, and then daily (24 h intervals) until discharge
[f] Faeces will be collected pre-dose (sample to be taken between admission and pre-dose) and then daily (24 h intervals) until discharge