16.1.9 Documentation of Statistical Methods

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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]-Rencofilstat in Healthy Male Subjects

Quotient Study Number: QSC204643
Sponsor Study Number: HEPA-CRV431-105

Sponsor: Hepion Pharmaceuticals, Inc
399 Thornall Street, First Floor
Edison
New Jersey
08837

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Author

See electronic signature at end of document	17 Feb 2023
Claire Wilson Lead Statistician (Quotient)	Date

Approvers

See electronic signature at end of document	17 Feb 2023
Carl Burdett Lead Statistical Programmer (Quotient)	Date
See electronic signature at end of document	20 Feb 2023
Anna Hunter Lead Pharmacokineticist (Quotient)	Date
See electronic signature at end of document	17 Feb 2023
Francesca Ware Lead Medical Writer (Quotient)	Date
Gemma	17/02/2023
Gemma Bullen-Clerkson Metabolism Lead (Pharmaron UK)	Date
See electronic signature at end of document	17 Feb 2023
Litza McKenzie Principal Investigator (Quotient)	Date
DocuSigned by: Jill Greytok 8CEA4A652FB24A8...	2/16/2023
Jill Greytok Senior Director Clinical Development (Hepion)	Date

1 Table of Contents

2 List of Abbreviations

^{14}C	carbon-14
ADaM	analysis data model
ADR	adverse drug reaction
AE	adverse event
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
COVID-19	Coronavirus disease 2019
CSR	clinical study report
CV%	coefficient of variation
D	'substantial' decrease from baseline for vital signs parameters
DP	decimal place
ECG	electrocardiogram
eCRF	electronic case report form
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 for Harmonisation
IMP	investigational medicinal product
ISF	Investigator Site File

L	flag used for value that is below normal reference range
LLOQ	lower limit of quantification
LOCF	last observation carried forward
Max	maximum
MBq	megabecquerel
MedDRA	Medical Dictionary for Regulatory Activities
µCi	microcurie
Min	minimum
n	number of subjects with an observation
N	number of subjects in the dataset
NA	not applicable
NC	not calculated
NR	not reportable/no result
NS	no sample
PK	pharmacokinetic
PT	preferred term
QC	quality control
QTcF	QT interval corrected for heart rate using Fridericia's correction
RAP	reporting and 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
SMEDDS	self-microemulsifying drug delivery system
SOC	system organ class
SOP	standard operating procedure

TEAE	Treatment -emergent adverse event
TFL	tables, figures and data listings
WHO	World Health Organisation

Abbreviations used for mass balance and pharmacokinetic parameters and associated flags are defined in Section 9.1.1, Section 10.1.1, and Section 10.1.3 respectively.

3 Introduction

This document details the following for Quotient Sciences (Quotient) Study QSC204643 (HEPA-CRV431-105):

- Criteria to be used for the definition of the populations and analysis sets relating to mass balance, pharmacokinetic (PK) and safety data
- Handling of missing data
- Proposed tables, figures and data listings (TFLs) for demographic, dosing, mass balance, PK and safety data
- Methods for PK parameter estimation

This document has been compiled according to the Quotient standard operating procedure (SOP) “Production of Reporting and Analysis Plans” and has been written based on information contained in the final study protocol (v1.0) dated 21 Dec 2022.

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, PK and safety 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 Hepion Pharmaceuticals, Inc (Hepion) review
- 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 14.2).

Metabolite profiling and structural identification will be the responsibility of Pharmaron UK 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 21 days after drug administration or have demonstrated >90% mass balance recovery or have <1% of the administered dose eliminated in excreta for two consecutive days, whichever is sooner. This definition will not be used during the reporting phase including the identification of analysis populations and datasets which are defined in Section 6. No replacement subjects are planned for this study.

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.

3.2.2 Definition of Treatments

Throughout the reporting of the study, investigational medicinal product (IMP) will be reported as detailed in Table 1 below:

Table 1 Study Treatments

IMP Name	Dose	Route of Administration	Label to be used for reporting
[^{14}C]CRV431 SMEDDS Concentrate for Oral Emulsion, 225 mg (NMT 6.4 MBq)	225 mg	Oral administration, Fasted	*225* mg [14C]CRV431

^{14}C: carbon-14, MBq: megabecquerel, NMT: not more than, SMEDDS: self-microemulsifying drug delivery system

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), Day 1 through to discharge between Day 22 and Day 26, and return visits on Day 28, and Day 35 (if required). Time points within these days are detailed in the schedule of assessments in Appendix 1.

Baseline is defined as nominally the last measurement recorded prior to the dose of IMP.

4 Objectives and Endpoints

Objectives	Endpoints
Primary To determine the mass balance recovery after a single oral dose of carbon-14 ([^{14}C])-rencofilstat	Mass balance recovery of total radioactivity (TR) in all excreta (urine and faeces): CumAe and Cum%Ae
To determine % parent drug unchanged versus metabolites	Evaluation of whole blood parent: whole blood TR ratios for AUC
To perform metabolite profiling and structural identification from whole blood, urine and faecal samples[a]	Collection of whole blood, urine and faeces samples for metabolite profiling, structural identification, and quantification analysis
Secondary To determine the routes and rates of elimination of [^{14}C]-rencofilstat	Mass balance recovery of TR in urine and faeces separately: Ae, %Ae, CumAe and Cum%Ae by interval
To identify the chemical structure of each metabolite accounting for more than 10% of circulating TR or accounting for 10% or more of the dose in excreta	Identification of the chemical structure of each metabolite accounting for more than 10% by AUC of circulating TR or accounting for 10% or more of the dose in excreta
To evaluate the extent of distribution of TR into blood cells	Evaluation of whole blood:plasma concentration ratios for TR
To provide additional safety and tolerability information for rencofilstat	To provide additional safety and tolerability information for rencofilstat by assessing: incidence of adverse events (AEs), physical examinations and change from baseline for vital signs, electrocardiograms (ECGs), and laboratory safety tests
To further explore the oral pharmacokinetics (PK) of rencofilstat	PK parameters for rencofilstat in whole blood and TR in plasma and whole blood following a single oral dose, including but not limited to: Tlag, Tmax, Cmax, AUC(0-last), AUC(0-inf), Lambda-z, T1/2, CL/F, Vz/F, MRT(0-last) and MRT(0-inf) as applicable

[a] Metabolite profiling and identification will be reported separately from the clinical study report as a standalone document.

5 Study Design

5.1 Brief Description

This is a single centre, open-label, non-randomised, single period, single dose study in healthy male subjects designed to assess the mass balance recovery, PK, metabolite profile and metabolite identification of rencofilstat. It is planned to enrol a single cohort of 6 subjects.

All subjects will receive a single 225 mg oral dose of [^{14}C]-rencofilstat, as a self-microemulsifying drug delivery system (SMEDDS) oral emulsion, containing NMT 6.4 MBq, in the fasted state.

Subjects will undergo preliminary screening procedures for the study at the screening visit (Day -28 to Day -2). Subjects will be admitted in the evening on the day before dosing (Day -1).

Whole blood, plasma, urine and faeces samples will be collected at regular intervals for PK analysis, TR analysis, metabolite profiling, mass balance and safety as applicable, from pre-dose to discharge from the clinical unit. Urine and faeces samples may be collected at return visits or home visits if mass balance criteria has not been met by a subject.

Subjects will be dosed on the morning of Day 1 following an overnight fast (minimum 8 h) and will remain resident in the clinical unit until up to 504 h after dosing (up to Day 22) (Figure 1).

It is planned that subjects will be released as a group when all subjects have achieved a mass balance cumulative recovery of >90% or if <1% of the dose administered has been collected in urine and faeces within two separate, consecutive 24 h periods. This may result in the subjects being discharged as a group prior to completion of the planned residency period.

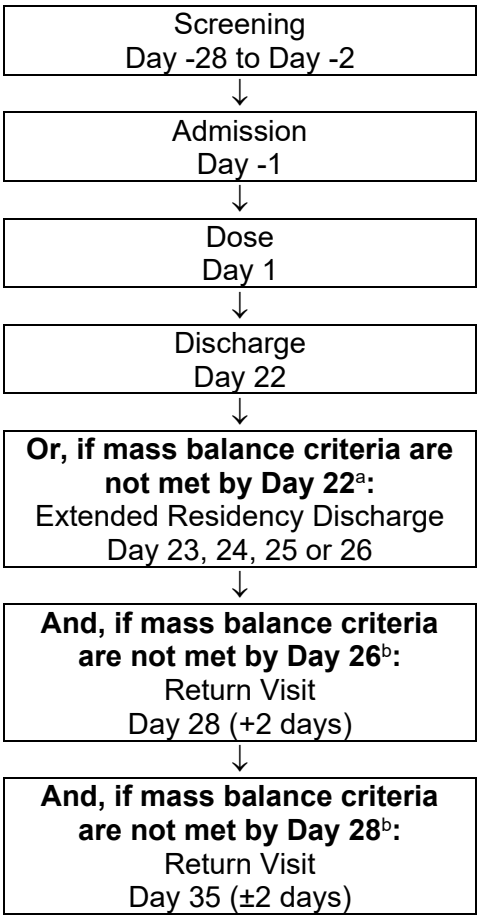
If the mass balance criteria are achieved during the planned residency period, collection of all samples (blood, urine and faeces) will be stopped once the current 24 h collection period is complete, and subjects will undergo discharge assessments.

If the mass balance criteria have not been met by all subjects on the morning of Day 22, the residency period for the subjects not achieving the mass balance criteria may be extended up to a maximum of 96 h (Day 26; 600 h post-dose). Only urine and/or faecal samples will be collected during the extended residency period.

If the mass balance criteria have not been met by all subjects on the morning of Day 26, subjects not achieving the release criteria may be required to make up to 2 return visits (each of 24 h duration) at (nominally) Day 28 (+2 days) and Day 35 (±2 days) for additional collection of excreta samples (urine and/or faecal samples).

If the mass balance criteria have not been met following the return visits, 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] If all subjects have not achieved a mass balance cumulative recovery of >90% or if a total of <1% of the dose administered has not been collected in urine and faeces within 2 separate, consecutive 24 h periods on the morning of Day 22, the residency period for the subjects not achieving the mass balance criteria may be extended up to a maximum of 96 h (Day 26). Only urine and/or faecal samples will be collected during the extended residency period.

[b] If the mass balance criteria have not been met by all subjects on the morning of Day 26, subjects not achieving the release criteria may be required to make up to 2 return visits (each of 24 h duration) at (nominally) Day 28 (+2 days) and Day 35 (±2 days) for additional collection of excreta samples (urine and/or faecal samples). If the mass balance criteria have not met following the return visits, 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

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

5.4 Randomisation (including Replacement Subjects)

This is an open-label, non-randomised study, therefore a randomisation schedule will not be produced. Instructions to dispense and dose will be produced prior to dosing with IMP, which will dictate the order in which the treatments should be administered to each subject. The instructions to dispense and dose will be retained in the investigator site file (ISF). 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 planned for 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 the IMP.

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

The safety population will be confirmed by Quotient with approval from Hepion after database lock and will be summarised 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 Hepion at the same time as the safety population and will be summarised for the analysis of demographic and baseline characteristics, and all safety data.

6.2 Mass Balance Population and Analysis Set(s)

The mass balance population will include all subjects who have received one dose of IMP and who have evaluable total radioactivity concentration (urinary or 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 the amount of urine/faeces collected or any AEs that may affect the mass balance analysis, for example:

- Spillage of urine and/or faeces
- Missing collections
- AEs that may affect the mass balance analysis*

*for example, if vomiting is observed, this will be assessed on a case-by-case basis to determine the potential impact on the mass balance recovery

The mass balance population will be confirmed by Quotient with approval from Hepion once all urinary and faecal data have been received and will be used for the analysis of the mass balance concentration data and the provision of mass balance summary tables, figures and listings.

If required, a mass balance analysis set and subset(s) will also be documented by Quotient, with approval from Hepion, at the same time as the mass balance population, if subjects are required to be excluded from the summary tables and figures (for example to exclude subjects who have incomplete collections for one matrix).

All enrolled subjects will be used for the mass balance data listings. The mass balance population will be used for the populations table. The mass balance analysis set and/or the mass balance analysis subset(s), if defined, will be used for the provision of mass balance summary tables and figures. The mass balance analysis set or subset to be

used for the provision of mass balance summary tables and figures will be documented as the same time as the mass balance population.

6.3 PK Population and Analysis Set(s)

The PK population will include all subjects who received IMP 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 Cmax
- No relevant protocol deviations which may impact the study objectives with respect to the PK endpoints
- No relevant AEs such as vomiting which suggest that the whole dose was not available for absorption for a particular subject

The PK analysis set will be defined on a per-treatment basis and will include all relevant data from the subjects included in the PK population who have received that treatment.

Individual subject profiles (ie analyte/matrix) will be excluded from the PK analysis set where deemed appropriate such as if the subject's data for the treatment affected did not meet the bullet point criteria above, or other study emergent point related to PK analysis or interpretation.

The PK population and analysis set will be confirmed by Quotient with approval from Hepion following derivation of all PK parameter estimates.

If required, a PK analysis subset(s) will also be documented by Quotient, with approval from Hepion, at the same time as the PK population and analysis set, if additional subjects are required to be excluded from the summary tables and figures.

All enrolled subjects will be used for the PK data listings. The PK population will be used for the populations table. The PK analysis set and/or the PK analysis subset(s), if defined, will be used for the provision of PK summary tables and figures. The PK analysis set or subset to be used for the provision of PK summary tables and figures will be documented as the same time as the PK population.

7 Subject Disposition, Demographics and Baseline Characteristics

No formal statistical testing will be performed on subject disposition, or on demographic or baseline data. Summaries of subject disposition and analyses populations will be based on all 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 participants who have failed screening will be databased but will not be cleaned and therefore will not be included in the SDTM or ADaM datasets or any of the TFLs or the CSR.

7.2 Subject Disposition and Withdrawals

The number and percentage of subjects enrolled, dosed, completed and discontinued will be presented overall. If any subjects discontinued from the study early then the number of subjects for each reason for discontinuation will be presented overall. However, if none of the subjects discontinued from the study early, then the reasons for discontinuation will not be populated in the summary table. A subject may be discontinued from the study early for 1 reason only.

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 population (i.e. safety, mass balance and PK) overall. The reasons for exclusion from each population will also be included in the summary table. However, if none of the subjects were excluded from a population, then the reasons for exclusion will not be populated in the summary table. A subject may be excluded from a population for more than 1 reason. The denominator for the percentage is the number of subjects enrolled.

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

7.4 Analysis Sets and Subsets

A summary table will be produced detailing the number and percentage of subjects in each of the safety, mass balance and PK analysis sets and analysis subsets (if applicable). Separate tables will be presented for safety, mass balance and PK sets and each table will be based on the relevant population the analysis set is derived from. If analysis subsets are defined they will be included on the same table as the corresponding analysis set. The reasons for exclusion from each analysis set/subset will also be included in the summary. However, if none of the subjects were excluded from an analysis set, then the reasons for exclusion will not be populated in the summary table. A subject may be excluded from an analysis set for more than 1 reason. The denominator for the percentage is the number of subjects in the relevant population.

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

7.5 Demographic Characteristics and Lifestyle Details

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

Summary statistics (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 overall. 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 (i.e., smoking history [does the subject smoke, use e-cigarettes or use nicotine replacement products?] and alcohol consumption) will be summarised by treatment as a categorical variable.

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

7.6 Medical History

Medical history will be recorded for each subject at the screening visit and updated at admission. Medical histories will be coded using Medical Dictionary for Regulatory Activities (MedDRA) v26.0 (or a more recent version) including Preferred Term (PT), and System Organ Class (SOC). All medical history data will be listed including coded terms.

7.7 Prior and Concomitant Medication

Medications (product name) will be coded using the World Health Organization (WHO) Drug Dictionary Global Drug Reference: 2023 Mar 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 first dose of IMP. All other medications will be defined as concomitant medications including those that start prior to the first dose of IMP and continue thereafter. Any medications with an unknown start or stop date will be assumed to be concomitant medications unless a partial start or stop date indicates otherwise.

All medications, including coded terms, 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 IMP will also be flagged using a “*” symbol.

7.8 Other Baseline Characteristics

All other baseline characteristics, as listed below, at screening and on admission (unless otherwise stated) will be listed:

- Carbon monoxide breath test
- Urine drug screen
- Alcohol breath test
- SARS-CoV-2 Antigen test (if required – See detail in Appendix 1)
- Virology (screening only)
- eGFR (screening only)

8 Efficacy

Not applicable.

9 Mass Balance

9.1 Mass Balance Parameter Estimation

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

- Total radioactivity concentration for urine and faeces (mass unit equivalents/g)
- Weight of urine (g)
- Faeces weight (g) i.e. 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 clinical study report. 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 is provided in Table 2.

Table 2 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 eliminated in faeces	Mass unit equiv	SF	3
%Ae(faeces)	amount of total radioactivity eliminated in faeces expressed as a percentage of the radioactive dose administered	%	DP	2
CumAe(faeces)	cumulative amount of total radioactivity eliminated in faeces	Mass unit equiv	SF	3
Cum%Ae(faeces)	cumulative amount of total radioactivity eliminated 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

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

Home collections of urine and/or faeces may be requested at the discretion of the investigator for individual subjects. For amount excreted and cumulative excretion this will be calculated for all time points including home collection, if applicable.

Dose will be used in the calculation of mass balance parameters as per Table 3.

Table 3 Mass Balance Dose Specifications

Radioactive dose level for mass balance analysis	Actual
Precision	As provided by Pharmaron

9.1.2 Rules for Mass Balance Parameter Estimation

The following will be calculated for total radioactivity in urine, faeces and 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 i.e. Ae(urine) and the amount excreted in faeces i.e. Ae(faeces) will be calculated for each collection interval the following formula (where matrix is either urine or faeces): using

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

- Following Day 26, where urine/faecal collections are no longer continuous and return visits (i.e., Day 28 [±2 days] and Day 35 [±2 days]) are scheduled, additional interpolation of A_e will be calculated to estimate amount excreted on non-collection days (i.e., between Day 26 to Day 28, and Day 28 to Day 35 if required), as follows:

  Ae(interval) = ((Ae 24h [Day x + Day y) / 2) duration of interval (days)*

  where Day x and Day y are the calculated amounts excreted for the preceding and proceeding days of the interval to be calculated.

  Interpolation may also be calculated to estimate the amount excreted between home collects if required.

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

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

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

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

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

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

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

- The % amount of the total radioactive dose excreted in urine and faeces combined will be calculated for each collection interval using the following formula:

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

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

- The cumulative % amount of the total radioactive dose excreted in urine and faeces combined will be calculated for each collection interval using the following formula:

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

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

If part of a void over a particular collection interval is missing due to spillage or accidental discarding, the Ae will still be calculated providing other samples have 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, CumAe and Cum%Ae. In both scenarios the data will be flagged to highlight a missing void.

Imputation of non-numerical values reported in the urine and faecal data set (i.e. concentrations that are not detectable [ND] below the limit of quantification [BLQ]) will be entered as zero for calculation of parameters such as Ae.

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 with the approval of Hepion. The results will be reported for each subject as a single value for the whole collection period and included in the calculation of total amount excreted and % of dose recovered.

Accidental sources of elimination, e.g., vomiting, will be collected and sent for total radioactivity analysis. This will be reported on a case by case basis and details will be included in the documentation of the mass balance population.

9.2 Mass Balance Summary Tables

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

- Urine [i.e. Ae(urine) and %Ae(urine)] for total radioactivity
- Faeces [i.e. Ae(faeces) and %Ae(faeces)] for total radioactivity
- Urine and faeces combined [i.e. Ae(total) and %Ae(total)] for total radioactivity

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

- Urine [i.e. CumAe(urine) and Cum%Ae(urine)] for total radioactivity
- Faeces [i.e. CumAe(faeces) and Cum%Ae(faeces)] for total radioactivity
- Urine and faeces combined [i.e. CumAe(total) and Cum%Ae(total)] for total radioactivity

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

- Urine [i.e. CumAe(urine) and Cum%Ae(urine)] for total radioactivity
- Faeces [i.e. CumAe(faeces) and Cum%Ae(faeces)] for total radioactivity
- Urine and faeces combined [i.e. CumAe(total) and Cum%Ae(total)] for total radioactivity

If any subject withdraws prior to the end of a study visit or if subjects have differing collection intervals [(e.g. Day 10 for some subjects and Day 14 for others)] then a last observation carried forward (LOCF) approach will be used whilst calculating cumulative Ae and %Ae (i.e. CumAe and Cum%Ae), where the last observed value will be carried forward to the subsequent time point. The number of subjects included at each collection

interval will therefore remain the same regardless of subject withdrawals. The LOCF approach will be used for all summary tables detailed above.

9.3 Mass Balance Figures

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

Mean cumulative excretion (i.e. CumAe) and cumulative recovery (i.e. 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, respectively, with urine, faeces and total overlaid:

- Urine [i.e. CumAe(urine) and Cum%Ae(urine)] for total radioactivity
- Faeces [i.e. CumAe(faeces) and Cum%Ae (faeces)] for total radioactivity
- Urine and faeces combined [i.e. CumAe(total) and Cum%Ae(total)] for total radioactivity

A legend identifying each profile (i.e. urine, faeces and total) will be displayed on the mean plots. Figures will be produced using the LOCF imputation strategy (see Section 9.2) if summary tables are produced using this method (a footnote to indicate this will be added to figures as required).

9.4 Mass Balance Listings

The sample collection data (e.g. collection intervals) for all urine and faecal samples will be listed. In addition all total radioactivity concentrations, urine and faecal weights and all mass balance parameters will be listed on a per subject basis. The LOCF approach will be used for all cumulative mass balance parameters. Where LOCF values appear in the listings they will be flagged.

9.5 Statistical Analysis of Mass Balance Parameters

No formal statistical analysis will be performed for the mass balance data in this study. Descriptive statistics (i.e. n, mean, SD, median, CV%, minimum and maximum) are considered adequate for a study of this type.

10 Pharmacokinetics

10.1 Plasma and Whole Blood PK Parameter Estimation

The PK parameters for rencofilstat in whole blood and total radioactivity in plasma and whole blood will be estimated where possible and appropriate for each subject profile by non-compartmental analysis methods using Phoenix WinNonlin software (v8.3 or a more recent version, Certara USA, Inc., USA). Additional parameters may be calculated if required, depending on the data.

10.1.1 Definition of Plasma and Whole Blood PK Parameters

Plasma and whole blood PK parameter definitions are provided in Table 4.

Table 4 Plasma and whole blood PK Parameter Definitions and Rounding Specifications

Parameter	Definition	Unit	DP or SF	No. of DP/SF
Tlag	Time prior to the first measurable concentration	h	DP	2

Parameter	Definition	Unit	DP or SF	No. of DP/SF
Tmax	Time of maximum observed concentration	h	DP	2
Cmax	Maximum observed concentration	mass unit/mL	SF	3
AUC(0-24)	Area under the curve from time 0 to 24 h post-dose	Mass unit.h/mL	SF	3
AUC(0-last)	Area under the curve from time 0 to the time of last measurable concentration	mass unit.h/mL	SF	3
AUC(0-inf)	Area under the curve from time 0 extrapolated to infinity	mass unit.h/mL	SF	3
AUCextrap	Area under the curve (AUC) from time of the last measurable concentration to infinity as a percentage of the area under the curve extrapolated to infinity	%	DP	2
T1/2	Terminal elimination half-life	h	DP	2
lambda-z	First order rate constant associated with the terminal (log-linear) portion of the curve	1/h	DP	4
CL/F	Total body clearance calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown.	mL/min	SF	3
Vz/F	Apparent volume of distribution based on the terminal phase calculated using AUC(0-inf) after a single extravascular administration where F (fraction of dose bioavailable) is unknown	L	SF	3
MRT(0-last)	Mean residence time from time 0 to time of the last measurable concentration	h	DP	2
MRT(0-inf)	Mean residence time 0 extrapolated to infinity	h	DP	2
AUC Ratio	Parent to total radioactivity ratio for whole blood 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

Dose will be used in the calculation of relevant PK parameters as per Table 5.

Table 5 PK Parameter Dose Specifications

Dose Route	Nominal/Actual	Precision
Oral	Nominal	As per Protocol

Total radioactivity blood to plasma concentration ratios will be determined using SAS by the Lead Statistical Programmer (or designee) at the time points defined in the protocol. If either the blood or plasma concentration values are BLQ (i.e., <lower limit of quantification [LLOQ]) at any given timepoint the ratio will not be calculated.

When converting blood collection weights to blood volume (if required) for the calculation of the whole blood:plasma ratio, 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)*

In addition, the ratio of rencofilstat to total radioactivity in whole blood will be calculated based on AUC using AUC(0-inf):

$$\text{AUC ratio} = \left\{\frac{\text{AUC(reconfilstat)}}{\text{AUC (total radioactivity)}}\right\}$$

If for any reason the AUC(0-inf) is not calculable then an alternative or additional AUC over a partial area may be used to calculate the AUC ratio for all subjects.

10.1.2 Rules for Plasma and Whole Blood PK Parameter Estimation using WinNonlin

The imputation of non-numerical (e.g. below the limit of quantification [BLQ] or below the level of detection [LOD]) or negative values (e.g. pre-dose sampling times) reported in the input data set will be performed as follows for calculation of PK parameters:

- Predose sample times will be entered as zero
- Values that are BLQ* obtained prior to Cmax will be entered as zero and values that are BLQ* after Cmax will be treated as missing
- Values that are BLQ* after Cmax may be imputed as zero for the calculation of partial AUCs, in cases where lambda-z cannot be determined
- Values that are measurable after at least 2 consecutive BLQ* values after Cmax will be treated as missing for the calculation of PK parameters
- Values that are reported as “No Result” or “Not Reportable” (NR), “Not Calculated” (NC) or “No Sample” (NS) etc. will generally be considered missing

* values that are reported as below the LOD will be treated in the same way as samples reported as BLQ.

Missing or unusual concentration values in the input data may be queried to ascertain any underlying cause. Exclusion of missing or unusual concentration values, or repeat bioanalysis of samples, will only be performed if a definitive root cause can be established and approval from Hepion has been obtained. Any exclusions of concentration values or repeat analysis of samples will be documented appropriately.

Plasma and whole blood 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 rules specified in Table 6 will be applied:

Table 6 PK Parameter Estimation Details

Sampling times	Actual
Calculation method	Linear trapezoidal linear interpolation
Number of points used for lambda-z	At least 3, not including Cmax
Minimum requirements for AUC	At least 3 consecutive measurable concentrations

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. 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 subject profiles. 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.

10.1.3 Plasma and Whole Blood PK Parameter Reporting Specifications

The following parameters will be reported for each period as applicable, according to the rounding specifications provided in Table 4:

Tlag, Tmax, Cmax, AUC(0-24), AUC(0-last), AUC(0-inf), AUCextrap, T1/2, lambda-z, CL/F (Rencofilstat only), Vz/F (Rencofilstat only), MRT(0-last), MRT(0-inf), AUC ratio (Rencofilstat only), lambda z lower and lambda z upper

The flags/footnotes given in Table 7 will be applied to the PK parameters where relevant and will be shown in PK parameter listings. Additional flags may be applied based on emerging data.

Table 7 PK parameter Flags and Footnotes

Flag	Footnote
a	Adjusted rsq of regression (the goodness of fit statistic for the elimination phase) 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 PK parameters could be calculated
f	Fewer than 3 consecutive measurable concentrations, AUCs not calculated

In the event that the adjusted rsq of regression was <0.9 (“a” flag) then lambda-z and parameter estimates derived using lambda-z and AUC(0-inf) will be deemed unreliable and will be flagged and listed but excluded from the summary statistics.

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

In the event that the extrapolated portion of AUC(0-inf) >20% (“c” flag), then AUC(0-inf) and parameter estimates derived using AUC(0-inf) will be deemed unreliable and will be flagged and listed but excluded from the summary statistics.

In the event that there are insufficient post-Cmax data points for estimation of lambda-z (“d” flag) then lambda-z and parameter estimates derived using lambda-z and AUC(0-inf) will be reported as ‘NC’.

In the event that there are fewer than 3 consecutive measurable concentrations (“f” flag) then all AUC parameter estimates will be reported as ‘NC’.

10.2 Concentration and PK Parameter Summary Tables

Summary statistics (i.e. n, mean, SD, CV%, median, minimum, maximum, geometric mean, geometric SD and geometric CV%) of concentration data will be calculated for the following analytes/matrices. The number of BLQ values (n) per time point will also be presented. Geometric statistics will not be calculated for pre-dose concentrations.

- Whole blood concentrations of rencofilstat by time point
- Plasma concentrations of total radioactivity by time point
- Whole blood concentrations of total radioactivity by time point
- Whole blood:plasma concentration ratios of total radioactivity by time point

Summary statistics (i.e. n, mean, SD, CV%, median, minimum and maximum) of whole blood PK parameters will be calculated for rencofilstat and total radioactivity. Geometric mean, geometric SD and geometric CV% will be presented for all PK parameters except Tlag and Tmax.

Non-measurable values reported in the concentration data (i.e., values that are BLQ), will be entered as zero for the determination of summary statistics with the exception of geometric means, geometric SD and geometric CV%, where BLQ values will be imputed as half the LLOQ value. This also applies to any concentrations that are defined as PK parameters (e.g., C24). Data recorded as NR, NS or NC will be handled as missing (i.e., no assumption will be made about the actual concentration).

10.3 Concentration and PK Figures

Mean, spaghetti and individual whole blood and plasma concentration vs time plots will be produced on both the linear/linear scale and on log10/linear scale. For all plots on a linear/linear scale, post-dose concentration values reported as BLQ will be set to zero, up to the point at which all concentrations fall below BLQ, after which they will be presented as missing. For all plots on a log 10/linear scale, post-dose concentration values reported as BLQ will be set to half the BLQ value, up to the point at which all concentrations fall below BLQ, after which they will be presented as missing. Where curves from multiple treatment regimens or subjects are overlaid on the same plot, symbols will be used to identify different subjects/ treatment regimens and a legend will be included on the plots to define the symbols used.

Mean concentration vs time plots (using nominal times) will be produced for:

- Rencofilstat in whole blood and total radioactivity in plasma and whole blood, on the same plot (3 profiles per plot)
- Rencofilstat in whole blood and total radioactivity in whole blood on the same plot (2 profiles per plot)
- Total radioactivity in plasma and whole blood on the same plot (2 profiles per plot)

These will be produced as follows:

- Linear/linear scale using arithmetic mean concentrations (error bars ± arithmetic SD)
- Log10/linear scale using geometric mean concentrations (error bars x/÷ geometric SD)

Separate spaghetti plots (using actual sampling time after dosing) will be produced for each matrix and analyte with each plot displaying 1 line per subject.

Individual plots (using actual sampling times after dosing) will be produced separately for each individual subject with all analytes and matrices on the same plot.

10.4 Concentration and PK Listings

The sample collection data (e.g. collection times) for PK samples will be listed. In addition, all concentration data and PK parameters will be listed on a per subject basis. Any flags used will be included as a footnote with the appropriate definition.

10.5 Statistical Analysis of PK Parameters

No formal statistical analysis will be performed for the PK data in this study. Descriptive statistics (i.e. n, mean, SD, median, CV%, minimum and maximum) are considered adequate for a study of this type.

11 Safety Assessments

Safety data summaries will be presented overall and the safety analysis set will be used throughout.

11.1 Extent of Exposure and Treatment Compliance

The total dose given (including the dose of radioactivity in microcurie [µCi] and megabequerel [MBq]) will be summarised (i.e., n, mean, SD, median, minimum and maximum) for rencofilstat.

Dosing details (including the date and time of all IMP administrations and any comments) will be listed for all enrolled subjects. Any recorded deviations from the planned dosing regimen will be listed as protocol deviations.

11.2 Adverse Events

Throughout the study, all AEs will be evaluated by the investigator and noted in the AE section of the eCRF study build specification. An AE is any untoward medical occurrence in a subject that occurs either before dosing (referred to as a pre-dose AE) or once a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

AEs will be coded using MedDRA v26.0 (or more recent version), including PT and SOC.

AEs will be classified into the following categories:

- Pre-dose AEs: AEs recorded at screening or with a start date and time prior to the first dose of IMP
- Treatment -emergent AEs (TEAEs): AEs that commence during/after the first dose of IMP or commence before first dose of IMP (i.e., a pre-dose AE or existing medical condition) but worsen in intensity during exposure to IMP

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

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

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

When summary presentation is made by maximum severity, “missing” will be handled as follows:

- If there are other events (i.e. same SOC and PT code) with a maximum severity recorded as “moderate” or “severe” for that subject, then the maximum observed severity for that subject will be categorised and presented as “moderate” or “severe”, respectively
- If there are other events (i.e. same SOP and PT code) with a maximum severity recorded as “mild” for that subject, then the maximum observed severity for that subject will be categorised and presented as “missing”

When summaries are presented by relationship to IMP, “missing” will be handled as follows:

- If there are other events (i.e. same SOC and PT code) with a most closely related association recorded as “possibly related” or “related” for that subject, then the maximum observed relationship for that subject will be categorised and presented as “possibly related” or “related”, respectively
- If there are other events (i.e. same SOP and PT code) with a most closely related association recorded as “unrelated” for that subject, then the maximum observed relationship for that subject will be categorised and presented as “missing”

Where the start date of an AE is missing and the stop date is on or after the day of first dose of IMP or both the start and stop dates are missing then a “worst-case” scenario will be assumed i.e., 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.

11.2.1 Summary Tables for Adverse Events

All pre-dose AEs (as defined in Section 11.2) 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 presented for both SOC and PT. For summaries by SOC and PT, with the exception of TEAEs by severity and relationship to IMP, the number of subjects and the number of events will be summarised. For summaries by severity and relationship only the number of subjects will be summarised.

For counts of subjects experiencing events the following will apply:

- A subject 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 i.e., most frequently reported SOC in the study and then by most frequently reported PT in the study within each SOC.

11.2.1.1 Overall Summary of Adverse Events

The following will be summarised for the safety analysis set:

- Number and percentage of subjects reporting at least 1 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 subject withdrawal
- 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 subject withdrawal
- Total number of TEAEs leading to death

11.2.1.2 Summary of Treatment-Emergent Adverse Events

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. Subjects experiencing more than 1 episode of a TEAE will be counted only once within each SOC and PT.

11.2.1.3 Summary of Treatment -Emergent Adverse Events by Severity

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

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

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

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

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

11.2.1.5 Summary of Adverse Drug Reactions (ADRs)

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. Subjects experiencing more than 1 episode of an ADR will be counted only once within each SOC and PT.

11.2.1.6 Summary of Serious Adverse Events

All subjects reporting treatment -emergent serious AEs (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 treatment -emergent SAEs will be summarised for SOC and PT. Counts will be given for number of subjects and number of events. Subjects experiencing more than 1 episode of a SAE will be counted only once within each SOC and PT.

11.2.2 Listings for Adverse Events

All pre-dose AEs (as defined in Section 11.2) will be listed including SOC and PT.

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

11.3 Laboratory Evaluations

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

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

11.3.1 Summary Tables for Laboratory Evaluations

Haematology and clinical chemistry data will be summarised (n, mean, SD, median, minimum and maximum) for each laboratory parameter at each time point, including changes from baseline (Day 1, Pre-dose) at each scheduled post-baseline time point.

Shift tables from baseline to each scheduled 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 relevant post-baseline time point.

For fasting-sensitive laboratory parameters (i.e. glucose and serum cholesterol) results taken in the non-fasted state (i.e. LBFAST=N) will not be included in summary statistics by time point or be used in derivations of changes from baseline. For tabulations (e.g. shift tables) both fasted and non-fasted results will be pooled and used in the tabulations, using the appropriate fasted or non-fasted reference range. All results (fasted or non-fasted) will be listed with non-fasted data flagged.

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

11.3.2 Listings for Laboratory Evaluations

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

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

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

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

11.4 Vital Signs

The details relating to the measurement of supine vital signs (i.e. systolic and diastolic blood pressure [BP], and heart rate) and non-supine vital signs (oral body temperature, respiratory rate, clinical assessment and findings) are described in the study protocol. Vital signs parameters will be reported in the order given above, i.e. both summary tables and data listings.

11.4.1 Summary Tables for Vital Signs

Vital signs data, including change from baseline (Day 1, Pre-dose) will be summarised (i.e., 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.

11.4.2 Listings for Vital Signs

All individual vital signs data including derivations, such as change from baseline, will be listed. Individual data will be flagged with an "H" or an "L" for values that are higher or lower than their reference ranges, respectively, and subjects with 'substantial' increases or decreases from baseline (as defined in Section 11.4.1) in systolic BP, diastolic BP and heart rate will be flagged with an 'I' (increase) or 'D' (decrease), respectively. If applicable, data from unscheduled vital signs assessments will also be listed and flagged with a "#" to indicate it will not be used in the summary statistics.

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

The reference ranges (from Quotient SOP "The Interpretation of the Electrocardiogram, Vital Signs and Clinical Laboratory Data During Phase I / II Clinical Trials" defined in Table 8 will be used.

Table 8 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	45 bpm	100 bpm
Oral Body Temperature	NA	35.5ºC	37.5ºC

NA=Not applicable

11.5 ECGs

The details of measurement of supine ECG parameters (i.e. ventricular rate, QT interval, Frederica's correction [QTcF] interval, PR Interval, QRS duration, QRS axis, rhythm, interpretation and clinical significance and findings) are described in the study protocol. ECG parameters will be reported in the order given above, i.e. both summary tables and data listings.

11.5.1 Summary Tables for ECGs

ECG data, including change from baseline (Day 1, Pre-dose), will be summarised (i.e., 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 QTcF and increases in QTcF intervals from baseline within the categories defined in Table 9 (based on the International Council on Harmonisation [ICH] E14 guideline [1]) will be summarised. Percentages will be based on the number of subjects with measurements at the relevant time point.

Table 9 ICH E14 Ranges for QTcF Intervals

Parameter	ICH E14 Range
QTcF interval	≤450 msec (normal)
	451--480 msec
	481--500 msec
	>500 msec
Increase in QTcF interval from baseline	≤30 msec
	31--60 msec
	>60 msec

11.5.2 Listings for ECGs

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

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

In addition, 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 the eCRF study build specification for all parameters, except QT Interval, which is from Quotient SOP “The Interpretation of the Electrocardiogram, Vital Signs and Clinical Laboratory Data During Phase I / II Clinical Trials”) and defined in Table 10 will be used.

Table 10 ECG Reference Ranges

Parameter	Lower limit	Upper limit
Ventricular Rate (HR)	45 bpm	100 bpm
QT Interval	NA	500 msec
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

11.6 Body Weight

All body weight data will be listed.

11.7 Physical Examination

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

12 Interim Statistical Analyses

No interim statistical analysis is planned for this study.

13 Changes in the Conduct of the Study or Planned Analysis

13.1 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.

13.2 Changes to the Planned Analyses

No changes to planned analysis.

13.3 Any Other Relevant Changes

Not applicable.

14 Overall Considerations

14.1 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, while continuous variables will be presented using n, mean, SD, median, minimum and maximum. For PK data additional statistics including CV%, geometric mean, geometric SD and geometric CV% will be presented, as appropriate.

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:

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

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%:

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

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 11, unless otherwise stated:

Table 11 Reporting Conventions for Summary Statistics

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

i refers to the number of decimal places reported in the eCRF study build specification 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 PK parameters will be presented are detailed in Section 10.1.1. Where data requires rounding, values ending with 1 to 4 will be rounded down and values ending with 5 to 9 will be rounded up.

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

If any baseline measurements are found to be missing then consideration will be given to imputation using the preceding time point (e.g., screening, admission, if applicable). Unscheduled assessment may be used if appropriate. Details of any such imputations will be documented as part of the safety analysis set.

There will be no other imputations for the safety data with regard to missing values or study discontinuation (i.e., 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 10.1.2, imputations for reporting mass balance data are described in Section 9.2 and for reporting PK data are described in Section 10.2.

If partial dates are available for smoking history, prior medications or medical history, there will be no date imputations. The data listings will only show the date information for the date part that is available, e.g., 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.

If all or part of this study is conducted during the Coronavirus disease 2019 [COVID-19] pandemic and there is evidence that data relating to primary and/or key secondary endpoints may have been affected in a way that may bias results, then sensitivity analyses may be conducted. Requirements for any sensitivity analyses will be documented at the same time as the related population (i.e. safety, mass balance, PK population) and details of any sensitivity analyses which were carried out would be fully documented in the CSR.

14.2 Quality Control of Summary Tables, Figures and Listings

Isolated data errors detected as a result of the QC checks that are deemed significant (i.e., 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 TFLs, including a review of SAS Software code and program log files.

14.2.1 Quality Control - Summary Tables

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

- For tables presented by treatment only (i.e., no time points), all summary statistics will be QC'd
- For tables presented by treatment and time point, at least 1 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

14.2.2 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

14.2.3 Quality Control - Data Listings

All data listings will be subjected to a 100% manual check against the eCRF study build specifications or other appropriate source data for a minimum of 2 subjects. If appropriate, the subjects checked will include at least 1 subject who withdrew early from the study.

15 SAS Data Transfer

All SAS study data used for analysis and reporting, including safety, mass balance and PK data will be transferred to Hepion on issue of the final CSR. These will be performed in compliance with CDISC (SDTM IG v3.3, ADaM IG v1.2). Quotient will provide metadata files and data will be transferred as SAS Software transport files. No define .xml output will be included.

16 Programming Conventions

Quotient standards for layout of TFLs 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 (or more recent version) documents and figures will be produced as PDF files. Listings will be sorted by subject ID number.

The mock tables (Section 21) presented are a representation of Quotient reporting standards. However, these are provided for illustrative purposes only. The numbering and titles, formatting, labelling, footnotes and cosmetic appearance of all output 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.

17 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

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Table Number	Table Title
	Excretion and Recovery – Faecal Concentrations
14.2.2.1	Excretion: Total Radioactivity Ae(Faeces) by Collection Period <(units)> Summary Statistics: <*Mass Balance Analysis Set / Mass Balance Analysis Subset*>
14.2.2.2	Excretion: Total Radioactivity Cumulative Ae(Faeces) <(units)> Summary Statistics: <*Mass Balance Analysis Set / Mass Balance Analysis Subset*>
14.2.2.3	Recovery: Total Radioactivity %Ae(Faeces) by Collection Period (%) Summary Statistics: <*Mass Balance Analysis Set / Mass Balance Analysis Subset*>
14.2.2.4	Recovery: Total Radioactivity Cumulative %Ae(Faeces) (%) Summary Statistics: <*Mass Balance Analysis Set / Mass Balance Analysis Subset*>
	Excretion and Recovery – Urine and Faeces Combined
14.2.3.1	Excretion: Total Radioactivity Ae(Total) by Collection Period <(units)> Summary Statistics: <*Mass Balance Analysis Set / Mass Balance Analysis Subset*>
14.2.3.2	Excretion: Total Radioactivity Cumulative Ae(Total) <(units)> Summary Statistics: <*Mass Balance Analysis Set / Mass Balance Analysis Subset*>
14.2.3.3	Recovery: Total Radioactivity %Ae(Total) by Collection Period (%) Summary Statistics: <*Mass Balance Analysis Set / Mass Balance Analysis Subset*>
14.2.3.4	Recovery: Total Radioactivity Cumulative %Ae(Total) (%) Summary Statistics: <*Mass Balance Analysis Set / Mass Balance Analysis Subset*>
	Cumulative Excretion and Recovery Parameters
14.2.4	Excretion and Recovery: Total Radioactivity Cumulative Excretion and Recovery Parameters Summary Statistics: <*Mass Balance Analysis Set / Mass Balance Analysis Subset*>
	Whole Blood and Plasma Pharmacokinetic Concentrations
14.2.5.1	Whole Blood Pharmacokinetic Concentrations: Rencofilstat <(units)> Summary Statistics: <*PK Analysis Set / PK Analysis Subset*>

Table Number	Table Title
14.2.5.2	Whole Blood Pharmacokinetic Concentrations Total Radioactivity<(units)>: Summary Statistics: <*PK Analysis Set / PK Analysis Subset*>
14.2.5.3	Plasma Pharmacokinetic Concentrations: Total Radioactivity <(units)>: Summary Statistics: <*PK Analysis Set / PK Analysis Subset*>
14.2.5.4	Whole Blood:Plasma Concentration Ratio: Total Radioactivity <(units)> Summary Statistics: <*PK Analysis Set / PK Analysis Subset*>
	Whole Blood and Plasma Pharmacokinetic Parameters
14.2.6.1	Whole Blood Pharmacokinetic Parameters: Rencofilstat Summary Statistics: <*PK Analysis Set / PK Analysis Subset*>
14.2.6.2	Whole Blood Pharmacokinetic Parameters: Total Radioactivity Summary Statistics: <*PK Analysis Set / PK Analysis Subset*>
14.2.6.3	Plasma Pharmacokinetic Parameters: Total Radioactivity Summary Statistics: <*PK Analysis Set / PK Analysis Subset*>
	Adverse Events
14.3.1	Overall Summary of Treatment Emergent Adverse Events Summary Statistics: Safety Analysis Set
14.3.2	Treatment Emergent Adverse Events By MedDRA System Organ Class and Preferred Term Summary Statistics: Safety Analysis Set
14.3.3	Treatment Emergent Adverse Events By MedDRA System Organ Class, Preferred Term and Severity Summary Statistics: Safety Analysis Set
14.3.4	Treatment Emergent Adverse Events By MedDRA System Organ Class, Preferred Term and Relationship to IMP Summary Statistics: Safety Analysis Set
14.3.5	Adverse Drug Reactions By MedDRA System Organ Class and Preferred Term Summary Statistics: Safety Analysis Set
14.3.6	Serious Adverse Events By MedDRA System Organ Class and Preferred Term Summary Statistics: Safety Analysis Set
	Laboratory Results
14.4.1	Haematology Summary Statistics: Safety Analysis Set Parameter <units>
14.4.2	Haematology Shift Analysis: Safety Analysis Set Parameter <units>
14.4.3	Clinical Chemistry Summary Statistics: Safety Analysis Set Parameter <units>

Table Number	Table Title
14.4.4	Clinical Chemistry Shift Analysis: Safety Analysis Set Parameter <units>
	Vital Signs and ECG Results
14.5.1	Vital Signs Summary Statistics: Safety Analysis Set Parameter <units>
14.5.2.1	ECGs Summary Statistics: Safety Analysis Set Parameter <units>
14.5.2.2	ECGs QTcF Categorical Data Summary Statistics: Safety Analysis Set

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Figure Number	Figure Title
	Cumulative Excretion and Recovery
14.2.1.1	Mean Cumulative Excretion of Total Radioactivity CumAe(Urine), CumAe(Faeces) and CumAe(Total) Linear/Linear Scale Mean (± Arithmetic SD) Values: <*Mass Balance Analysis Set / Mass Balance Analysis Subset*>
14.2.1.2	Mean Cumulative Recovery of Total Radioactivity Cum%Ae(Urine), Cum%Ae(Faeces) and Cum%Ae(Total) Linear/Linear Scale Mean (±Arithmetic SD) Values: <*Mass Balance Analysis Set / Mass Balance Analysis Subset*>
	Whole Blood and Plasma Pharmacokinetic Concentrations
14.2.2.1	Whole Blood and Plasma Pharmacokinetic Concentrations: Rencofilstat and Total Radioactivity (units) Linear/Linear Scale Arithmetic Mean (±Arithmetic SD) Values: <PK Analysis Set/PK Analysis Subset> *(Programming note: Rencofilstat in whole blood and total radioactivity in plasma and whole blood - 3 profiles per plot)*
14.2.2.2	Whole Blood and Plasma Pharmacokinetic Concentrations: Rencofilstat and Total Radioactivity (units) Log10/Linear Scale Geometric Mean (×/÷ Geometric SD) Values: <PK Analysis Set/PK Analysis Subset> *(Programming note: Rencofilstat in whole blood and total radioactivity in plasma and whole blood - 3 profiles per plot)*
14.2.2.3	Whole Blood Pharmacokinetic Concentrations: Rencofilstat and Total Radioactivity (units) Linear/Linear Scale Arithmetic Mean (±Arithmetic SD) Values: <PK Analysis Set/PK Analysis Subset> *(Programming note: 2 profiles per plot)*
14.2.2.4	Whole Blood Pharmacokinetic Concentrations: Rencofilstat and Total Radioactivity (units) Log10/Linear Scale Geometric Mean (×/÷ Geometric SD) Values: <PK Analysis Set/PK Analysis Subset> *(Programming note: 2 profiles per plot)*

Figure Number	Figure Title
14.2.2.5	Whole Blood and Plasma Pharmacokinetic Concentrations: Total Radioactivity (units) Linear/Linear Scale Arithmetic Mean (±Arithmetic SD) Values: <PK Analysis Set/PK Analysis Subset> *(Programming note: 2 profiles per plot)*
14.2.2.6	Whole Blood and Plasma Pharmacokinetic Concentrations: Total Radioactivity (units) Log10/Linear Scale Geometric Mean (×/÷ Geometric SD) Values: <PK Analysis Set/PK Analysis Subset> *(Programming note: 2 profiles per plot)*
14.2.2.7	Whole Blood Pharmacokinetic Concentrations: Rencofilstat (units) Linear/Linear Scale Spaghetti Plots of All Individual Values: <PK Analysis Set/PK Analysis Subset>
14.2.2.8	Whole Blood Pharmacokinetic Concentrations: Rencofilstat (units) Log10/Linear Scale Spaghetti Plots of All Individual Values: <PK Analysis Set/PK Analysis Subset>
14.2.2.9	Whole Blood Pharmacokinetic Concentrations: Total Radioactivity (units) Linear/Linear Scale Spaghetti Plots of All Individual Values: <PK Analysis Set/PK Analysis Subset>
14.2.2.10	Whole Blood Pharmacokinetic Concentrations: Total Radioactivity (units) Log10/Linear Scale Spaghetti Plots of All Individual Values: <PK Analysis Set/PK Analysis Subset>
14.2.2.11	Plasma Pharmacokinetic Concentrations: Total Radioactivity (units) Linear/Linear Scale Spaghetti Plots of All Individual Values: <PK Analysis Set/PK Analysis Subset>
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Figure Number	Figure Title
14.2.2.13	Whole Blood and Plasma Pharmacokinetic Concentrations: Rencofilstat and Total Radioactivity (units) Linear/Linear Scale Individual Values for Subject <xxx>: <PK Analysis Set/PK Analysis Subset> *Programming note: Rencofilstat in whole blood, and total radioactivity in whole blood and plasma all on the same plot (i.e., 3 profiles per subject)*
14.2.2.14	Whole Blood and Plasma Pharmacokinetic Concentrations: Rencofilstat and Total Radioactivity (units) Log10/Linear Scale Individual Values for Subject <xxx>: <PK Analysis Set/PK Analysis Subset> *Programming note: Rencofilstat in whole blood, and total radioactivity in whole blood and plasma all on the same plot (i.e., 3 profiles per subject)*

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	Subject Informed Consent and Completion/Withdrawal
16.2.1	Subject Informed Consent and Completion/Withdrawal Individual Values: All Enrolled Subjects
	Protocol Deviations and Inclusion/Exclusion Criteria
16.2.2.1	Protocol Deviations Individual Values: All Enrolled Subjects
16.2.2.2	Inclusion/Exclusion Criteria Individual Values: All Enrolled Subjects
	Analysis Populations and Reasons for Exclusion
16.2.3.1	Analysis Populations and Reasons for Exclusion Individual Values: All Enrolled Subjects
16.2.3.2	Analysis Sets and Analysis Subsets and Reasons for Exclusion Individual Values: All Enrolled Subjects
	Demographic and Baseline Characteristics
16.2.4.1	Demographics and Baseline Characteristics Individual Values: All Enrolled Subjects
16.2.4.2	Lifestyle Details: Smoking History and Alcohol Consumption Individual Values: All Enrolled Subjects
16.2.4.3	Medical/Surgical History Individual Values: All Enrolled Subjects
16.2.4.4	Prior and Concomitant Medication Individual Values: All Enrolled Subjects
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16.2.4.6	Urine Drug Screen Individual Values: All Enrolled Subjects
16.2.4.7	Alcohol Breath Test Individual Values: All Enrolled Subjects
16.2.4.8	SARS-CoV-Antigen Test Individual Values: All Enrolled Population (Programming note: This listing will only be produced if COVID-19 testing takes place in this study)
16.2.4.9	Virology Individual Values: All Enrolled Subjects
16.2.4.10	eGFR Individual Values: All Enrolled Subjects

Listing Number	Listing Title
	Dosing Details and Meal Details
16.2.5.1.1	Dosing Details Individual Values: All Enrolled Subjects
16.2.5.1.2	Meal Details Individual Values: All Enrolled Subjects
	Urine and Faecal Concentration Data
16.2.5.2.1	Urine Collection and Weight Details Individual Values: All Enrolled Subjects
16.2.5.2.2	Urine Concentrations and Excretion: Total Radioactivity (units) Individual Values: All Enrolled Subjects
16.2.5.2.3	Faecal Collection and Weight Details Individual Values: All Enrolled Subjects
16.2.5.2.4	Faecal Concentrations and Excretion: Total Radioactivity (units) Individual Values: All Enrolled Subjects
16.2.5.2.5	Urine and Faecal Concentrations and Excretion Combined: Total Radioactivity (units) Individual Values: All Enrolled Subjects
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16.2.5.3.2	Whole Blood and Plasma Pharmacokinetic Concentrations: Total Radioactivity <*(units)*> Individual Values: All Enrolled Subjects
16.2.5.3.3	Plasma Pharmacokinetic Concentrations: rencofilstat Individual Values: All Enrolled Subjects
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16.2.6.1	Whole Blood Pharmacokinetic Parameters: Total Radioactivity Individual Values: All Enrolled Subjects
16.2.6.2	Plasma Pharmacokinetic Parameters: Total Radioactivity Individual Values: All Enrolled Subjects
16.2.6.3	Plasma Pharmacokinetic Parameters: rencofilstat Individual Values: All Enrolled Subjects
16.2.6.4	Pharmacokinetic Parameter Flags (Programming note: Details of the PK parameter flags will be added to listings 16.2.6.1-3 as footnotes if length of these details allows – in which case do not produce this listing. Otherwise display PK parameter flags in this listing).

Listing Number	Listing Title
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16.2.7.2	All Treatment -Emergent Adverse Events Individual Values: All Enrolled Subjects
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16.2.8.5	Clinical Chemistry Individual Values Outside the Reference Range: All Enrolled Subjects
16.2.8.6	Urinalysis Sample Collection Individual Values: All Enrolled Subjects
16.2.8.7	Urinalysis Individual Values: All Enrolled Subjects
16.2.8.8	Urinalysis Individual Values Outside the Reference Range: All Enrolled Subjects
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16.2.9.1.1	Vital Signs Individual Values: All Enrolled Subjects (Programming note: The order of Vital Signs parameters is to be as per Section 11.4)
16.2.9.1.2	Vital Signs Individual Values Outside the Reference Range: All Enrolled Subjects
16.2.9.2.1	ECGs Individual Values: All Enrolled Subjects (Programming note: The order of ECG parameters is to be as per Section 11.5)
16.2.9.2.2	ECGs Individual Values Outside the Reference Range: All Enrolled Subjects

Listing Number	Listing Title
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16.2.9.4	Body Weight Data Individual Values: All Enrolled Subjects

21 Mock Tables

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

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

	225 mg [14C]CRV431 (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
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
(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:\~\QSCXXXXXX\~\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

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

TABLE 14.1.2.1
Analysis Populations
Summary Statistics: All Enrolled Subjects

	225 mg [14C]CRV431 n (%)
Subjects in Safety Population	xx (xx.x)
Reasons for exclusion from Safety Population	
<All categories on source listing>	xx (xx.x)
	…
Subjects in Mass Balance Population	xx (xx.x)
Reasons for exclusion from Mass Balance Population	
<All categories on source listing>	xx (xx.x)
	…
Subjects in PK Population	xx (xx.x)
Reasons for exclusion from PK Population	
<All categories on source listing>	xx (xx.x)
	…

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
A subject may be excluded for more than 1 reason
Percentages are based on the number of subjects enrolled

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

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

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

TABLE 14.1.2.2
Safety Analysis Set
Summary Statistics: Safety Population

	225 mg [14C]CRV431 n (%)
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
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
A subject may be excluded for more than 1 reason

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

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
• Mass Balance Analysis Set, ie Table [14.1.2.3] and
• PK 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)

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

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

		225 mg [14C]CRV431 (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
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431

PROGRAM PATH: X:\~\QSCXXXXXX\~\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

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

		225 mg [14C]CRV431 n (%)
Does the subject smoke (1)	NO	xx (xx.x)
	PREVIOUSLY	xx (xx.x)
Alcohol Consumption (2)	NONE	xx (xx.x)
	YES: NOT EXCESSIVE	xx (xx.x)

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
(1) Smoked or used e-cigarettes or nicotine replacement products in the last 12 months
(2) Regular alcohol consumption (>21 units/week in males)
1 unit = 1/2 pint beer, 25 mL of 40% spirit, 1.5 to 2 units = 125 mL glass of wine depending on type

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

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

TABLE 14.1.5
Extent of Exposure
Summary Statistics: Safety Analysis Set

	225 mg [14C]CRV431 (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
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431

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

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

TABLE 14.2.1.1
Excretion: Total Radioactivity
Ae(Urine) by Collection Period <(units)>
Summary Statistics: <Mass Balance Analysis Set / Mass Balance Analysis Subset>

225 mg [14C]CRV431

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
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
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:\~\QSCXXXXXX\~\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 [14.2.1.3]
- Ae(Faeces), ie Table [14.2.2.1]
- %Ae(Faeces) (Recovery), ie Table [14.2.2.3]
- Combined (Ae[total]), ie Table [14.2.3.1] and
- Combined (%Ae[total]) (Recovery), ie Table [14.2.3.3])

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

TABLE 14.2.1.2
Excretion: Total Radioactivity
Cumulative Ae(Urine) <(units)>
Summary Statistics: <Mass Balance Analysis Set / Mass Balance Analysis Subset>

225 mg [14C]CRV431

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

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431

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

Programming note: This table will be continued for all collection periods. If required, as a result of early withdrawal or varying follow-up periods, this table will be produced using the LOCF approach. Similar tables will be produced for
- Cumulative %Ae(Urine) (Recovery), ie Table [14.2.1.4]
- Cumulative Ae(Faeces), ie Table [14.2.2.2]
- Cumulative %Ae(Faeces) (Recovery), ie Table [14.2.2.4]
- Combined Cumulative (Ae[total]), ie Table [14.2.3.2] and
- Combined Cumulative (%Ae[total]) (Recovery), ie Table [14.2.3.4]

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

TABLE 14.2.4
Excretion and Recovery: Total Radioactivity
Cumulative Excretion and Recovery Parameters
Summary Statistics: <Mass Balance Analysis Set / Mass Balance Analysis Subset>

225 mg [14C]CRV431

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

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
CumAe represents the cumulative excretion. Cum%Ae represents the cumulative recovery as a percentage of the radioactive dose administered

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

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

TABLE 14.2.5.1
Whole Blood Pharmacokinetic Concentrations: Rencofilstat <(units)>
Summary Statistics: <PK Analysis Set / PK Analysis Subset>

225 mg [14C]CRV431

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

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
n# indicates the number of subjects with a BLQ value recorded at the time point indicated
(1) For arithmetic summary statistics, concentration values reported as BLQ have been set to zero
(2) For calculation of geometric summary statistics, values reported as BLQ have been set to ½ × LLOQ, except for pre-dose values which will not be summarised. The LLOQ value was <value, units>

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

Programming note: This table will be continued for all time points. Similar tables will be produced for
- Whole Blood Concentrations: Total Radioactivity, ie Table [14.2.5.2] and
- Plasma Pharmacokinetic Concentrations: Total Radioactivity, ie Table [14.2.5.3]
- Whole Blood:Plasma Concentration Ratio: Total Radioactivity, ie Table [14.2.5.4]

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

TABLE 14.2.6.1
Whole Blood Pharmacokinetic Parameters: Rencofilstat
Summary Statistics: <PK Analysis Set / PK Analysis Subset>

225 mg [14C]CRV431

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 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
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
For concentration parameters, BLQ values have been set to zero for arithmetic statistics and to ½ × LLOQ for geometric statistics. The LLOQ value was <value, units>

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

Programming note: A similar table will be produced for
- Whole Blood Pharmacokinetic Parameters: Total Radioactivity, ie Table [14.2.6.2] and
- Plasma Pharmacokinetic Parameters: Total Radioactivity, ie Table [14.2.6.3]

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

Event	225 mg [14C]CRV431 (N=XX) n(%)	Total Number of Events
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 subject withdrawal	xx (xx.x)	xx
TEAEs leading to death	xx (xx.x)	xx

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
TEAEs are coded using MedDRA vXX.X
(1) ADR is any AE where a causal relationship with the IMP is at least a reasonable possibility ie "possibly related" or "related". n is the number of subjects reporting at least one event

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

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

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	225 mg [14C]CRV431 (N=XX) n(%)	Total Number of Events
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
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency
Subjects experiencing more than one TEAE are counted only once for number of subjects but are counted more than once for number of events. Subjects experiencing more than one TEAE are counted only once within each SOC and PT

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

Programming note: This table will be continued for all SOC and PT

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

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

System Organ Class Preferred Term	225 mg [14C]CRV431 (N=XX) Mild n(%)	 Moderate n(%)	 Severe n(%)
TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…
…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency
Counts are given for total number of subjects, not for events
Counts of number of subjects are by maximum severity, ie subjects experiencing more than one TEAE are counted only once within each SOC and PT using the most severe episode

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

Programming note: This table will be continued for all SOC and PT

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

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

System Organ Class Preferred Term	225 mg [14C]CRV431 (N=XX) Unrelated n(%)	 Possibly Related n(%)	 Related n(%)
TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…
…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency
Counts are given for total number of subjects, not for events
Counts of number of subjects are by closest relationship, ie subjects experiencing more than one TEAE are counted only once within each SOC and PT using the most closely related event

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

Programming note: This table will be continued for all SOC and PT

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

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	225 mg [14C]CRV431 (N=XX) n(%)	Total Number of Events
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
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
(1) An ADR is any AE where a causal relationship with the IMP is at least a reasonable possibility ie "possibly related" or "related". TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency
Subjects experiencing more than one ADR are counted only once for number of subjects but are counted more than once for number of events. Subjects experiencing more than one ADR are counted only once within each SOC and PT

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

Programming note: A similar table will be produced for
• Serious Adverse Events, ie Table [14.3.6]

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

TABLE 14.4.1
Haematology
Summary Statistics: Safety Analysis Set

225 mg [14C]CRV431
<Parameter> (<units>) [ref range xxx - xxx (male)]

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

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
BASELINE is defined as Day 1, Pre-dose

PROGRAM PATH: X:\~\QSCXXXXXX\~\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]

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

TABLE 14.4.2
Haematology
Shift Analysis: Safety Analysis Set

225 mg [14C]CRV431
<Parameter> (<units>) [ref range xxx - xxx (male)]

		Baseline		
Time Point Assessment	N#	Below n(%)	Within n(%)	Above n(%)
TIME POINT 1	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)
TIME POINT 2	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)
<All other time points>	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
BASELINE is defined as Day 1, Pre-dose
N# is the total number of subjects that have a value at baseline and each given time-point and is used in the denominator for calculating the percentages of subjects, n indicates the number of subjects with a baseline and a post baseline assessment at the time point indicated. Below/within/above indicate the number (%) of subjects with assessments below/within/above the normal reference range

PROGRAM PATH: X:\~\QSCXXXXXX\~\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]

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

TABLE 14.5.1
Vital Signs
Summary Statistics: Safety Analysis Set

225 mg [14C]CRV431
<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									
TIME POINT 1	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx
TIME POINT 2	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx
TIME POINT 3	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx
…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…
<All other time points>	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx	xx

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
BASELINE is defined as Day 1, Pre-dose
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:\~\QSCXXXXXX\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

Programming note: This table will be continued for all vital signs parameters, which will follow the order given in the RAP text

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

TABLE 14.5.2.1
ECGs
Summary Statistics: Safety Analysis Set

225 mg [14C]CRV431
<Parameter> (<units>) [ref range xxx - xxx (male)]

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

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
BASELINE is defined as Day 1, Pre-dose

PROGRAM PATH: X:\~\QSCXXXXXX\~\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

Hepion Pharmaceuticals, Inc
Protocol: HEPA-CRV431-105

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

225 mg [14C]CRV431

		QTcF Interval (msec)				QTcF Interval Increase (msec)		
Time Point	N#	<=450 n(%)	451-480 n(%)	481-500 n(%)	>500 n(%)	<=30 n(%)	31-60 n(%)	>60 n(%)
BASELINE	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)			
TIME POINT 1	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TIME POINT 2	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
TIME POINT 3	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	…	…	…	…	…	…	…	…
<All other time points>	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single oral dose of 225 mg [14C]CRV431
BASELINE is defined as Day 1, Pre-dose
Categories for QTcF interval and QTcF interval increases are based on ICH E14 guidelines
N# is the total number of subjects at the relevant time point and is used in the denominator for calculating the percentages of subjects, n indicates the number of subjects with observations at the given time point

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

Appendix 1: Schedule of Assessments

Study day	-28 to -2	-1		1											2	3	4	5	6	7	8
				Times after dosing (h)																	
	S	A[a]	P[a]	0	0.5	1	1.5	2	3	4	6	8	12	16	24	48	72	96	120	144	168
General Assessments																					
Informed Consent	X																				
Medical History	X	X[b]																			
Weight, Height and BMI	X	X[c]																			
Vein Assessment	X																				
Carbon Monoxide Breath Test	X	X																			
Drug Screen	X	X																			
Alcohol Breath Test	X	X																			
SARS-CoV-2 Antigen[d]		X																			
IMP Administration				X																	
Safety Assessments																					
Physical Examination	X																				
Targeted (symptom driven) Physical Examination[e]			X																		
Safety Blood Samples[f]	X		X												X						
eGFR[g]	X																				
Urinalysis	X		X							X					X						
Single 12-Lead ECGs	X		X			X				X					X						
Vital Signs[h]	X		X			X				X					X						
Adverse Events	←----------X----------→																				
Prior and Concomitant Medication	←----------X----------→																				
Mass Balance, PK and Met Prof and ID Assessments																					
Whole Blood Samples for Rencofilstat			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
Whole Blood Samples for TR			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Whole Blood Samples for Met Prof and ID			X					X		X		X	X		X	X	X	X	X		X
Urine Samples for TR and Met Prof and ID[i]			←----------X----------→																		
Faecal Samples for TR and Met Prof and ID[j]		←----------X----------→																			

Appendix 1: Schedule of Assessments (continued)

Study day	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	28 (+2 days)	35 (±2 days)	Home Collections[n]
	Times after dosing (h)																				
	192	216	240	264	288	312	336	360	384	408	432	456	480	504[k]	528[l]	552[l]	576[l]	600[l]	Return Visits[m]		
General Assessments																					
SARS-CoV-2 Antigen[d]																			X	X	
Safety Assessments																					
Targeted (symptom driven) Physical Examination[e]														X[ko]							
Safety Labs[f]														X[ko]							
Urinalysis														X[ko]							
Single 12-Lead ECGs														X[ko]							
Vital Signs[h]														X[ko]					X	X	
Adverse Events	←----------X----------→																				
Prior and Concomitant Medication	←----------X----------→																				
Mass Balance, PK and Met Prof and ID Assessments																					
Whole Blood Samples for Rencofilstat	X	X		X		X		X		X		X		X[p]							
Plasma Samples for TR	X	X		X		X		X		X		X		X[p]							
Whole Blood Samples for TR	X	X		X		X		X		X		X		X[p]							
Urine Samples for TR and Met Prof and ID[i]	←----------X----------→																				
Faecal Samples for TR and Met Prof and ID[j]	←----------X----------→																				

A: admission; BMI: body mass index; ID: identification; Met Prof: Metabolite Profiling; P: pre-dose; PK: pharmacokinetic(s); S: screening; TR: total radioactivity

[a] Eligibility will be re-assessed at admission/pre-dose

[b] Update only

[c] Weight only

[d] Testing for SARS-CoV-2 may be performed based on current infection rates and availability of tests. If required, it is planned that testing will comprise an antigen test performed on Day -1 prior to admission to the clinical unit and at return visits. The decision on COVID-19 testing and the definition of the testing time points are subject to change based on the current risk mitigation in place and will be agreed by the study team and documented in the ISF via the Clinical Kick-Off Meeting minutes

[e] Targeted (symptom driven) physical examination of the relevant body system(s) as clinically indicated, as per the investigator's judgement

[f] Haematology and clinical chemistry at each time point including virology at screening

[g] eGFR will be calculated at screening using the CKD-EPI equation for eligibility purposes

[h] Blood pressure and heart rate will be measured at every time point; oral temperature will be checked at screening, pre-dose and at first return residential visit (Day 28 +2 days) only

[i] Urine will be collected for the following intervals: A single urine sample will be collected at pre-dose (or the first void of the day), then at: 0-12 h, 12-24 h and then for 24 h intervals until mass balance criteria have been met (see Section 5.1for details of mass balance criteria)

[j] Faeces will be collected at pre-dose (sample will be taken between admission and pre-dose), then at 24 h intervals until mass balance criteria have been met (see Section 5.1 for details of mass balance criteria)

[k] Discharge from clinical unit. Discharge assessments will be performed at the time of actual discharge. It is planned that subjects will remain resident in the clinical unit until 504 h post-dose (Day 22). Subjects will be discharged from the clinical unit on Day 22 provided they have met the following mass balance discharge criteria: mass balance cumulative recovery of >90% OR <1% of the dose administered collected in urine and faeces within 2 separate, consecutive 24 h periods. It is also planned that subjects will be discharged from the clinical unit as a group if all subjects have achieved the mass balance discharge criteria

[l] If mass balance discharge criteria have not been met by all subjects by Day 22, the residency period for the subjects not achieving the mass balance criteria may be extended up to a maximum of 96 h (Day 26). Urine and/or faeces will be collected during the additional residency period

[m] If mass balance discharge criteria have not been met by all subjects by the end of the additional residency (Day 26), subjects not achieving the mass balance criteria may be required to make up to 2 return visits (each of 24 h duration) at (nominally) Day 28 (+2 days) and Day 35 (±2 days) for additional collection of excreta samples. Only urine and/or faeces will be collected during the return visits

[n] If the mass balance criteria are not met following the return visits, then home collections of urine and/or faeces may be requested at the discretion of the investigator for individual subjects

[o] In the event of early withdrawal, all safety discharge assessments should be completed

[p] If the residency period for subjects not achieving the mass balance criteria is extended, a further sample will be taken at actual discharge

Document Approvals

Approved Date: 20 Feb 2023

Approval Task Verdict: Approve	Claire Wilson, Senior Statistician (Claire.Wilson@quotientsciences.com) Approval 17-Feb-2023 09:08:40 GMT+0000

Approval Task Verdict: Approve	Carl Burdett, Statistical Programmer (Carl.Burdett@quotientsciences.com) Approval 17-Feb-2023 10:05:25 GMT+0000

Approval Task Verdict: Approve	Francesca Ware, Medical Writer (Francesca.Ware@quotientsciences.com) Approval 17-Feb-2023 13:11:41 GMT+0000

Approval Task Verdict: Approve	Litza McKenzie, Senior Clinical Research Physician (Litza.McKenzie@quotientsciences.com) Approval 17-Feb-2023 16:30:30 GMT+0000

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Document Author(s): Rory McMurray