Quotient Sciences

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REPORTING AND ANALYSIS PLAN

A First-in-Human, Single-Centre, Single Ascending Dose, Multiple Dose and Pilot Food Effect Study to Assess the Safety, Tolerability and Pharmacokinetics of MMV367 in Healthy Participants

Quotient Study Number: QSC207031

Sponsor Study Number: MMV_MMV367_21_01

Sponsor:

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Version Number	Reason for Update	Updated By:	Date
v1.0	Initial version	Claire Wilson	11 Jul 2022
v2.0	Amended to include protocol v3.0 updates	Claire Wilson	15 Dec 2022

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2 List of Abbreviations

ADaM	analysis data model
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
CI	confidence interval
COVID-19	Coronavirus disease 2019
CS	clinically significant
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
F	absolute bioavailability
Frel	relative bioavailability
GMR	geometric mean ratio
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

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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
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
MPR	metabolite to parent ratio
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
PI	principal investigator
PK	pharmacokinetic
PT	preferred term
QC	quality control
QTcB	QT interval corrected for heart rate using Bazett's correction
QTcF	QT interval corrected for heart rate using Fridericia's correction
RAP	reporting and analysis plan
SAC	safety advisory committee
SAE	serious adverse event

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SD	standard deviation
SDTM	study data tabulation model
SF	significant figure
SI	substantial increase in QTcF interval from baseline
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TFL	tables, figures and data listings
WHO	World Health Organisation

Abbreviations used for pharmacokinetic parameters and associated flags are defined in Section 9.1.1, and Section 9.1.3 respectively.

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3 Introduction

This document details the following for Quotient Sciences (Quotient) Study QSC207031 (MMV_MMV367_21_01):

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

This document has been compiled according to the Quotient standard operating procedure (SOP) “Production of Reporting and Analysis Plans” and has been written based on information contained in the final study protocol (v3.0) dated 08 Sep 2022.

The v1.0 RAP was amended to incorporate updates from the v3.0 protocol, which included increasing the window of the end of study visit in each study part, from ± 1 h to ± 1 day. Thus, ensuring sufficient time to complete all agreed procedures. Furthermore, additional clarification relating to the collection of urine for PK assessments has also been included.

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, safety and PK outputs; including all TFLs, and formal statistical analysis; and the clinical study report (CSR).

Quotient will provide two sets of TFLs during the study:

- Post database lock TFLs (draft) for MMV 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).

All Holter ECGs will be collected electronically using a Mortara H12+ Holter Recorder and analysed by Banook. The reporting of the ECG Holter data is not the responsibility of Quotient and will be subject of a separate analysis plan and will not be part of the final study CSR.

If required, metabolite profiling and genetic testing will the responsibility of The Doctors Laboratory and will be the subject of a separate analytical work plan should the analysis be required. Metabolite profiling may be included in the CSR as an addendum, however genetic testing will be reported separately.

3.2 Definitions

3.2.1 Subject Definitions

During the clinical phase of the study, an evaluable participant in Part 1 and Part 3 is defined as a participant who received the study drug and completed safety and PK

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assessments up to 96 h post-dose (Part 1)/post-final dose (Part 3). In Part 2, a participant will be considered evaluable if they have received the study drug and completed safety and PK assessments up to 96 h post-dose in both periods. This will be monitored during the clinical phase to identify any requirement for replacement subjects. This definition will not be used during the reporting phase including the identification of analysis populations and datasets which are defined in Section 5.7.

In all study parts, an enrolled participant is defined as a participant who signed the informed consent, qualified per the inclusion/exclusion criteria, and was randomised.

3.2.2 Definition of Treatments

Throughout the reporting of the study, the test product will be referred to as MMV367 and the investigational medicinal products (IMPs) relating to each study part are presented in Table 1, Table 2 and Table 3, respectively.

Table 1 Description of Regimens: Part 1

SAD Cohort	Regimen	IMP	Dose	Route of Administration	TFL Label
1A	1	MMV367 or placebo	100 mg	Oral, Fasted	100 mg
1B	2	MMV367 or placebo	300 mg[a]	Oral, Fasted	300 mg
1C	3	MMV367 or placebo	750 mg[a]	Oral, Fasted	750 mg
1D	4	MMV367 or placebo	1500 mg[a]	Oral, Fasted	1500 mg
1E Optional	*5*	*MMV367 or placebo*	*2000 mg[a]*	*Oral, Fasted*	*2000 mg*

[a] Predicted dose

Table 2 Description of Regimens: Part 2

Food Effect Cohort	Period	Regimen	IMP	Dose[a]	Route of Administration	TFL Label
2A	1 and 2 (randomised)	6	MMV367	XX mg	Oral, Fasted	XX mg Fast
		7	MMV367	XX mg	Oral, Fed	XX mg Fed

[a] The dose administered in Part 2 will be determined once predicted human therapeutic concentrations of MMV367 and a safe exposure window has been established in Part 1. The dose for Regimens 6 and 7 will be the same.

Table 3 Description of Regimens: Part 3

Multiple Dose Cohort	Regimen	IMP	Dose[a]	Route of Administration	TFL Label
3A	8	MMV367 or placebo	XX mg for 3 days	Oral, Fasted	XX mg
3B Optional	*9*	*MMV367 or placebo*	*XX mg for 3 days*	*Oral, Fasted*	*XX mg*
3C Optional	*10*	*MMV367 or placebo*	*XX mg for 3 days*	*Oral, Fasted*	*XX mg*

[a] The dose(s) administered in Part 3 will be determined after review of the data from Part 1.

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Where pooling of active or placebo subjects is required within a study part (i.e., safety summaries in Part 1 and Part 3) these will be presented as All Active and All Placebo respectively.

3.2.3 Definition of Visits

For clinical data, visits will be referred to as Day throughout this document, and each Day will be stated as screening, Day -1 (Admission), with the following duration based on study Part:

- Part 1: Day 1 through to Day 5, with a return visit on Day 7 and an end of study visit on Day 15
- Part 2: Day 1 through to Day 7 Period 1, and Day 8 through to Day 12 in Period 2, with an end of study visit on Day 14 (The actual dosing days within Period 2 may change if the washout period is extended – see Section 8.1.2 of the study protocol)
- Part 3: Day 1 through to Day 7, with a return visit on Day 9 and an end of study visit on Day 17.

Time points within these days are detailed in the schedule of assessments for each study part Appendix 4 (Part 1), Appendix 5 (Part 2) and Appendix 6 (Part 3).

Baseline is defined as nominally the last measurement recorded prior to the first dose of IMP, for each dosing period.

4 Objectives and Endpoints

Objectives	Endpoints
Primary To assess the safety and tolerability of single and multiple oral doses of MMV367 in healthy participants	Incidence of adverse events (AEs), physical examination findings, and change from baseline for vital signs, electrocardiograms (ECGs) and laboratory safety tests.
Secondary To assess the pharmacokinetics (PK) of single and multiple doses of MMV367 in plasma (Parts 1, 2 and 3)	PK parameters such as AUC, Tmax, Cmax, CL/F, Vz/F, T1/2 and AR, when applicable
To assess the effect of a high-fat meal on the PK of a single dose of MMV367 in healthy participants (Part 2 only)	PK parameters such as AUC, Tmax, Cmax and Frel, as appropriate, under fed and fasted conditions
Exploratory To assess the PK of single dose of MMV367 in urine (Part 1 only) of healthy participants (optional)[a]	Urine PK parameters such as Ae, and derived plasma PK parameters such as CLr, when applicable
To assess exposure response relationship for potential effects of MMV367 on ECG intervals (QT, QTcF, QTcB, PR, QRS)[b]	ECG intervals, MMV367 plasma concentrations (time-matched)
To investigate metabolite(s) of MMV367 in healthy participants[a]	Metabolite characterisation for MMV367 in plasma and urine, when applicable
To evaluate the taste attributes (smell, sweetness, bitterness, flavour, mouthfeel/texture, grittiness and aftertaste) and overall acceptability of the IMP (Part 1 only)	Taste questionnaire score, based on a 9-point Likert scale assessing the acceptability for each taste attribute (smell, sweetness, bitterness, flavour, mouthfeel/texture, grittiness, and aftertaste) and overall acceptability for each dose level of MMV367

[a] Depending on availability of the data, these objectives may be reported in an addendum to the final study Clinical Study Report (CSR) or in a separate report.
[b] This objective will be reported in a separate cardiac safety report and will not be part of the final study CSR

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5 Study Design

5.1 Brief Description

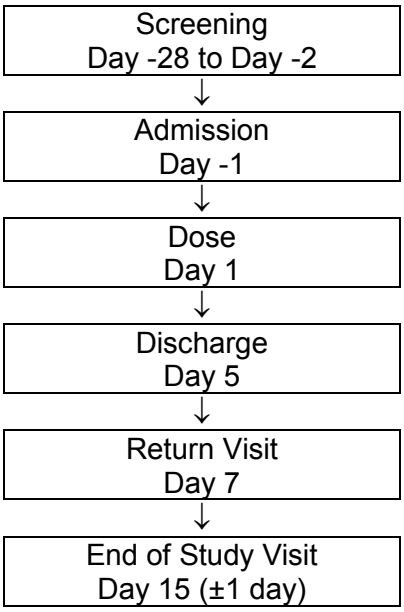
The study is divided into Parts 1, 2 and 3. For each of the three parts, participants will be screened within 28 days prior to first admission to the clinical unit on the morning of Day -1. Each participant will receive verbal and written information followed by signing of the informed consent form (ICF) prior to any screening procedures taking place.

5.1.1 Part 1 – Single Ascending Dose Cohorts

Part 1 will be a double-blinded, randomised, placebo-controlled, SAD study, which will comprise up to 5 fasted cohorts (Cohorts 1A to 1E; Cohort 1E will be optional), with 8 participants in each cohort. Participants will be randomly assigned to receive a single oral dose of either active IMP (6 participants) or placebo (2 participants) to assess its safety, tolerability and PK profile. Each participant will take part in one cohort. The data obtained from each cohort (safety, tolerability and PK) will undergo a formal review by the safety advisory committee (SAC). The SAC will determine if it is safe and appropriate to proceed with the next dose/cohort. Following review of the emerging PK data from each preceding cohort, if results suggest that the exposure plateau has been reached, the next planned cohort will not be conducted. Similarly, if PK predictions suggest that this exposure plateau would be exceeded at the next cohort/dose level, a lower dose than originally anticipated will be proposed.

It is planned to enrol 8 healthy male and female participants per cohort to ensure data in a minimum of 4 participants (per cohort) on active IMP. In each cohort, participants will be dosed on Day 1 and will remain resident in the clinical unit until discharge on Day 5. They will attend the clinical unit for a return visit on Day 7 and again on Day 15 (±1 day) for end of study assessments. Blood samples will be collected at regular intervals for PK analysis and safety from Day 1 to discharge from the study on Day 15 (±1 day), as detailed in Appendix 2. Each cohort will follow the same study design (Figure 1).

Figure 1 Study Sequence: Part 1 (Cohorts 1A to 1E)



Each participant will take part in one cohort and will receive one of the regimens presented in Table 1, according to the randomisation schedule.

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There will be a blinded interim review of the safety, tolerability and PK data after each cohort prior to the dose decision for subsequent cohorts. Full details of the interim data reviews are provided in Section 5.2.

Participants will also complete a written taste/palatability questionnaire individually and privately following administration of the IMP. In the evening of Day -1, participants will be trained to respond to a sample questionnaire using a suitable example fluid (e.g., orange juice/squash). On the morning of Day 1, participants will brush their teeth using tap water (toothpaste not permitted). In order to evaluate taste, participants will hold the IMP in their mouth and swirl it around for 10 to 15 sec before swallowing. Immediately after swallowing, they will complete a taste questionnaire individually and privately.

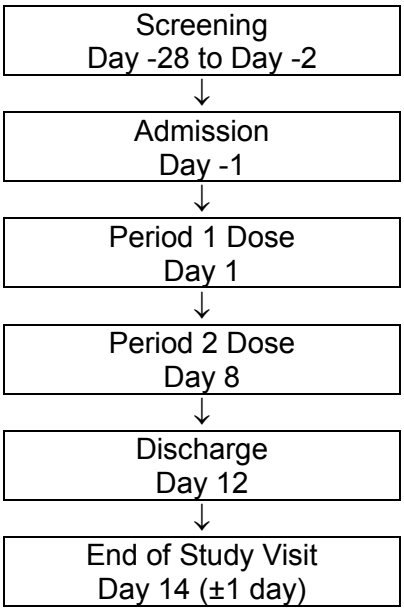
5.1.2 Part 2 – Food Effect Cohort

Part 2 will be an open-label, randomised, balanced two-period crossover, food effect evaluation. The effect of food on the PK of MMV367 will be explored in Part 2 by administering a single dose of MMV367 after a high-fat breakfast, as per FDA guidance, and a single dose of MMV367 in the fasted state.

Each participant will receive 2 single doses of MMV367. In Period 1, participants will be randomised to 1 of 2 treatment sequences (Regimen 6/Regimen 7 or Regimen 7/Regimen 6). If a participant is randomised to receive MMV367 in the fasted state (Regimen 6) in Period 1, they will receive MMV367 in the fed state (Regimen 7) in Period 2 and vice versa. It is planned to enrol 8 healthy male and female participants to ensure data in a minimum of 6 participants.

Participants will be dosed on Day 1 (Period 1 dose) and on Day 8 (Period 2 dose) and will remain resident in the clinical unit until discharge on Day 12. They will attend the clinical unit on Day 14 (±1 day) for end of study assessments. Based on emerging PK data from Part 1, the washout period between the Period 1 and Period 2 doses may be extended. Blood samples will be collected at regular intervals for PK analysis and safety from Day 1 to the end of study visit on Day 14 (±1 day), as detailed in Appendix 3. The study design for Part 2 is presented in Figure 2.

Figure 2 Study Sequence: Part 2



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Each participant will receive Regimens 6 and 7, presented in Table 2.

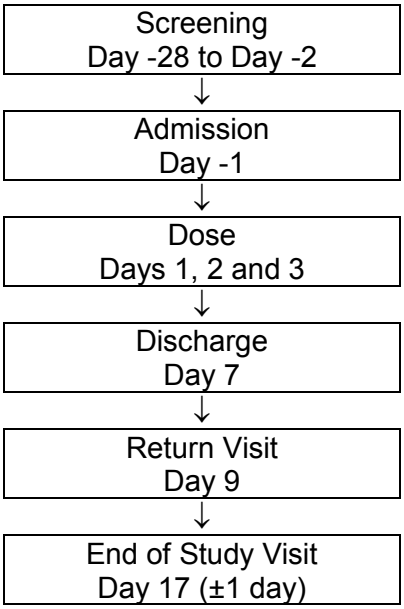
5.1.3 Part 3 – Multiple Dose Cohort(s)

Part 3 will be a double-blinded, randomised, placebo-controlled, multiple-dose study. A total of 8 participants per cohort will receive once-daily doses of MMV367 (6 participants) or placebo (2 participants) for 3 days, in the fasted state, to assess safety, tolerability and PK profile of multiple dosing.

It is planned to enrol 8 healthy male and female participants to ensure data in a minimum of 4 participants on active IMP.

Participants will receive a single dose on Days 1, 2 and 3 and will remain resident in the clinical unit until discharge on Day 7. They will attend the clinical unit for a return visit on Day 9 and again on Day 17 (±1 day) for end of study assessments. Blood samples will be collected at regular intervals for PK analysis and safety from Day 1 to discharge from the study on Day 17 (±1 day), as detailed in Appendix 4. Each cohort will follow the same study design (Figure 3).

Figure 3 Study Sequence: Part 3 (Cohorts 3A to 3C)



Each participant will receive one of the regimen(s) presented in Table 3 according to the randomisation schedule.

During the interim review of each cohort within Part 1, if it is determined that the optimal dose has been identified for the assessment of food effect, Part 2, may commence prior to the completion of Part 1, provided that this is justified by PK and safety data obtained from completed cohorts in Part 1. Similarly, Part 3 may commence prior to the completion of Part 1 if the required dose level is identified during interim review. However, the total amount of active IMP administered as multiple doses (i.e., cumulative 3-day dose) in Part 3 will be no greater than the maximum safe and well tolerated dose identified Part 1, dosed at a single dose level. Parts 2 and 3 may be conducted in parallel.

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The data obtained (safety and PK) from the multiple dose administration will undergo a formal review by the SAC after all 8 participants have completed the study. Consequently, Part 3 may be extended to evaluate a second and/or third dose level in a 3-day QD regimen.

Parts 1 and 3 will follow a sentinel dosing design. On the first day of dosing in each cohort in Part 1 and in Part 3, only 2 (sentinel) participants will be dosed. The randomisation schedule will be constructed such that 1 of the participants dosed on the first day will receive MMV367 and 1 will receive placebo. After review of the safety data up to 96 h post-dose for SAD cohorts in Part 1 and up to 96 h post-final dose in Part 3, the investigator, or medically qualified designee who is familiar with the study protocol and IB, and medical monitor or delegate (with approval from the sponsor's medical director or delegate) will decide whether to proceed with dosing the remaining participants in the cohort.

5.2 Criteria for In-Study Decisions

In-study decisions will be made by the safety advisory committee (SAC), which will always comprise the investigator, the medical monitor, the sponsor's medical director, and PK, together with appropriate representation from the partner organisation (GlaxoSmithKline plc [GSK]) where appropriate.

5.2.1 Decision Points

The following in-study decisions will be made during this study:

- Dose selection for Cohorts 1B to 1E in Part 1
- Progression from Cohort 1D to 1E in Part 1
- Washout period duration between periods in Part 2
- Dose selection for Parts 2 and 3
- Changes to safety and/or PK time points, if there is reason to believe that the change might improve the quality of the data as a consequence of review of emerging data
- Progression from Cohort 3A to further multiple dose levels in Part 3

5.2.2 Criteria for Dose Decision

Part 1: Single Ascending Dose Cohorts 1A to 1E

Progression to the next dose cohort will be permitted after review of safety, tolerability and PK data suggests that it is safe to do so. Quotient will provide data to the SAC in accordance with Quotient's standard operating procedure (SOP) on interim dose decision making and dose escalation. The decision will be documented and signed by the investigator as per Quotient's current SOP. Evidence of the decision will be retained in the ISF and Trial Master File.

For dose escalation to proceed, data must be available from a minimum of 6 participants who have completed the planned safety assessments up to 7 days after dosing and planned PK assessments up to 144 h after dosing to ensure at least 4 participants had received active IMP. Dose increases will only be made after a complete review of all data collected from the previous dose group by the SAC.

It is planned that the dose will be escalated for each subsequent cohort; however, the SAC may also agree to enrol additional participants for an intermediate dose level if

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warranted or may agree to reduce the dose with no limit on the possible extent of reduction. Any decision to investigate an intermediate or reduced dose level will be fully documented.

The decision to proceed to the next dose level will be based on safety, tolerability and available PK data. The following data are required:

- AEs
- Vital signs
- Safety laboratory results
- ECGs
- Physical examination findings
- Plasma concentrations of MMV367
- Interim PK parameter estimations (Tmax, Cmax, AUC(0-24), AUC(0-48), AUC(0last), AUC(0-inf), T1/2, where possible and appropriate)

Rules for dose decision are as follows:

- Dose increments between SAD cohorts will be a maximum of 3-fold and dose escalation may be halted in the SAD cohorts if an exposure plateau appears to have been reached
- Dose increments between multiple dose optional cohorts will be no more than 3-fold
- No dose selected for SAD or MAD will be expected to result in a mean group exposure at the next dose level (based on predicted human PK and assuming dose linearity) greater than AUC(0-inf) 376 µg.h/mL, and Cmax 23.8 µg/mL based on the NOAEL in dogs and the corresponding human therapeutic exposure
- The predicted exposure (AUC(0-inf)) of the cumulative dose after a 3-day treatment will not exceed that of a single dose evaluated in Part 1 which is safe and well tolerated
- The study will be halted (see Section 8.5 of the study protocol) and thus a further dose decision will not be made if:
    - One or more participants experience an IMP-related serious AEs (SAE)
    - Two or more participants experience an IMP-related severe or clinically significant non-serious AE at the same dose level/same cohort

If, following review by the SAC it is deemed acceptable to continue dose escalation above the defined maximal dose or exposure limit, a substantial amendment with relevant data will be submitted for approval to the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee (EC).

Progression from Part 1 (SAD) to Part 2 (Food Effect).

For the dose level decision to be made for Part 2, data must be available from a minimum of 6 participants who have completed the planned safety assessments up to 7 days after dosing and planned PK assessments up to 144 h after dosing (to ensure at least 4 participants had received active IMP), at a relevant dose level in Part 1. A “relevant dose level” is defined as a dose that demonstrated acceptable safety/tolerability (i.e., exposure levels at which no study specific criteria stopping dose progression and/or escalation were met) at a mean exposure that is not anticipated to be exceeded by the

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dosing regimen in Part 2, taking into account a potential bioavailability increase to 100% after a high-fat breakfast.

Progression from Part 1 (SAD) to Part 3 (Multiple Dose).

For the dose level decision to be made for Part 3, data must be available from a minimum of 6 participants who have completed the planned safety assessments up to 7 days after dosing and planned PK assessments up to 144 h after the final dose (to ensure at least 4 participants had received active IMP), at a relevant dose level in Part 1. The total dose in Part 3 (3 × QD dose) will not exceed a dose of MMV367 administered and evaluated as a single dose in Part 1, and the predicted exposure will not exceed an exposure observed and determined to be safe in Part 1. If a less than dose-proportional increase in exposure is observed in Part 1 (SAD), the proposed dose(s) for Part 3 may be adjusted to ensure the equivalent exposures between SAD and MAD.

8.2.1 Criteria for Sentinel Dosing Decisions

For all cohorts following a sentinel design (Parts 1 and 3) the decision to proceed with the main group will be made by the investigator, based on safety data until 96 h postdose (Part 1) or 96 h post-final dose (Part 3) in the sentinel participants. The investigator or medically qualified designee who is familiar with the study protocol and IB, and medical monitor or delegate (with approval from the sponsor's medical director or delegate) will decide whether to proceed with dosing the remaining participants in the cohort.

5.3 Study Sample Size

For Parts 1 and 3, the primary objective is an initial assessment of safety and each treatment group is therefore limited to 6 participants receiving active IMP. Administration of MMV367 to 6 participants at each dose level provides a 47%, 62%, 74%, or 82% probability of observing at least 1 occurrence of any AE, with a true incidence rate for a given dose group of 10%, 15%, 20%, or 25%, respectively.

Furthermore, it is assumed that pooling the data for the 2 participants who receive placebo in each cohort will provide an adequately sized control group to assess a possible drug effect on safety laboratory tests, vitals and ECG parameters.

Part 2 is a pilot evaluation designed to determine whether MMV367 PK is impacted by high-fat food. Historically, 8 participants have proven sufficient to characterise the preliminary effects of food on safety and PK of a new chemical entity in healthy participants. Therefore, a sample size of 8 is considered adequate at this stage of drug development.

5.4 Randomisation (including Replacement Subjects)

Parts 1 and 3 will be randomised (IMP/placebo) and double-blinded. Part 2 will be randomised (fed/fasted) and open-label. A randomisation schedule will be produced for each study part. Instructions to dispense and dose will be produced prior to dosing using the randomisation schedule and will be retained in the ISF.

For Part 2, the original randomisation schedule and proof of quality control procedures will be held by the Data Sciences department at Quotient until the study is archived, at which time the randomisation materials will be retained in the ISF.

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Using computer-generated randomisation schedules, participant numbers will be allocated to treatment regimens in a 6:2 ratio (MMV367:placebo) in each cohort (Part 1 or Part 3). In Part 2, the allocation will be balanced with 8 participants assigned to receive MMV367 in both the fed and fasted states. Participants will be randomised to 1 of 2 treatment sequences (Regimen 6/Regimen 7 or Regimen 7/Regimen 6) on Day 1 prior to dosing in the first period.

For participants in Parts 1 and 3, a sentinel group of *2* participants will be dosed ahead of the remaining participants in each cohort. For each cohort, using a computer-generated randomisation schedule, the first 2 participant numbers will be allocated to active or placebo in a 1:1 ratio (i.e., 1 participant will be randomly assigned to receive MMV367 and 1 participant will be randomly assigned to receive placebo). The remaining 6 participant numbers will be allocated to active or placebo in a 5:1 ratio (i.e., 5 participants will be randomly assigned to receive MMV367 and 1 participant will be randomly assigned to receive placebo).

Participants will be randomised immediately before administration of the first dose.

5.4.1 Participant Numbers

Participant numbers will be allocated on the morning of dosing according to the code 101 to 140 in Part 1, 201 to 208 in Part 2, and 301 to 324 in Part 3 using the lowest number available. Replacement participants will be allocated participant numbers 901 to 940 in Part 1, 801 to 808 in Part 2 and 701 to 724 in Part 3, where the last two digits are the same as those of the original participant (e.g., if Participant 105 withdraws, the replacement will have Participant Number 905 and will receive the same regimen as Participant 105).

In Part 1, up to 2 replacement participants may be used per cohort. The maximum number of participants that may be dosed is 50 (8+2 per cohort). In Part 2, up to 4 replacement participants may be enrolled into the study. The maximum number of participants that may be dosed in Part 2 is 12 (8+4). In Part 3, up to 2 replacement participants per cohort (if optional cohorts are utilised) may be enrolled into the study. The maximum number of participants that may be dosed is 30 (8+2 per cohort).

Any participant withdrawn due to an IMP related AE will not be replaced.

Participants withdrawing for other reasons may be replaced as required by agreement between the investigator and sponsor to ensure sufficient evaluable participants. Participant numbering by study part and cohort is provided in Table 4.

Table 4 Participant Numbers

Study Part	Cohort	Participant Numbers
1	1A	101–108
	1B	109–116
	1C	117–124
	1D	125–132
	1E (optional)	133–140
2	2A	201–208
3	3A	301–308
	3B (optional)	309–316
	3C (optional)	317–324

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5.5 Blinding Issues

Parts 1 and 3 of the study are double-blinded. Treatment assignment will not be known to the participants, the sponsor or the staff who are involved in the clinical evaluation of the participants and the analysis of data. If appearance matching of the placebo is not possible then masking and/or unblinded dosing teams will be used to preserve the study blind. Further details of these steps will be contained in the study specific blinding plan, which will be approved prior to dosing. The randomisation schedules and disclosure envelopes will be generated by an unblinded statistician at Quotient according to Quotient's SOPs. The unblinded statistician will not be involved in any decisions relating to populations for analysis prior to unblinding. Prior to database lock and unblinding, all original randomisation materials, including the original final signed and dated randomisation schedule, will be held by the Quality Assurance (QA) department at Quotient. The Data Sciences department will not have access to the randomisation schedule before database lock and unblinding.

Interim PK parameter estimations will be performed using bioanalytical data applied with participant aliases in order to maintain the study blind.

There may be instances where interim PK data have the potential to be treatment revealing e.g., missed blood sampling occasions. In these cases, every effort will be made by the pharmacokineticist to maintain the study blind by appropriate presentation of data to the study team. Data demonstrating extremes of exposure will always be presented, regardless of the potential to reveal the study blind. To permit selection of the dose level, individual data may be made available in full if judged necessary by the investigator or sponsor regardless of the potential to reveal study blind.

The unblinded Qualified Person or designee at the clinical site will receive a copy of the final randomisation schedule for preparation of the study drug and preparation of the instructions to dispense and dose. A copy of the randomisation schedule will also be made available to the laboratory performing the bioanalysis to allow selective analysis of drug concentrations (for Parts 1 and 3) and to the pharmacovigilance provider for analysis of pharmacovigilance.

Two sets of disclosure envelopes (i.e., sealed envelopes containing individual participant randomisation details) will be provided. One set will be held in the clinical area and the other retained in the ISF. These may be used in the event of an emergency by the investigator or delegate. Any request for information on the randomisation schedule after initial issue must be made using a randomisation disclosure form, except in the case of emergency unblinding, which must be recorded on the emergency unblinding form. Access to study drug assignment will be immediately available if the investigator deems it necessary to break the study blind in the interest of a participant's medical safety, in case of a medical emergency, or if warranted during scheduled safety reviews. The medical monitor must be contacted within 24 h following disclosure of study drug assignment.

Details of any disclosure of the randomisation schedule will be documented and retained in the ISF. The sponsor will be notified if the study blind is broken.

Part 2 of the study is open-label and therefore blinding is not required.

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5.6 Unblinding procedures

The study blind will be broken after the study database has been locked and the safety population has been defined. Any subsequent request for issue of the randomisation schedule prior to unblinding must be made using a randomisation disclosure form.

5.7 Maintaining the Blind During Interim PK Analyses

The interim PK analysis/analyses in Part 1 and Part 3 will be performed on QC checked concentration data for MMV367 in plasma using nominal sampling times and doses. Data will be received with participant aliases applied to the concentration data in order to maintain the study blind.

There may be instances where interim data has the potential to be treatment revealing eg missed blood sampling occasions. In this case every effort will be made by the pharmacokineticist to maintain the study blind by appropriate restriction/modification of data presented to the study team, such as only presenting the summary statistics e.g., mean, SD, minimum, median, maximum, geometric mean and geometric CV% for both PK parameters and concentration data.

Data demonstrating extremes of exposure will always be presented, regardless of the potential to reveal the study blind. Further details can be found in the blinding plan.

6 Populations and Analysis Sets

6.1 Safety Population and Safety Analysis Set

The safety population and safety analysis sets will be defined separately for each study part.

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

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

The safety population will be confirmed by Quotient with approval from MMV after database lock (Part 2) and prior to unblinding (Part 1 and Part 3) 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 MMV at the same time as the relevant safety population and will be summarised for the analysis of demographic and baseline characteristics, and all safety data.

6.2 Taste Population and Taste Analysis Set

The taste population will include all subjects who have received at least one regimen (i.e., active dose or placebo), in Part 1, and held it in their mouth for approximately 10 to 15 seconds. Participants will have also completed the taste questionnaire for a regimen and have no relevant protocol deviations for any taste test or AEs which confound the taste assessment.

The taste population will be determined by Quotient with approval from MMV after database lock and will be used for the taste tables and to determine the participants to be included in the taste analysis set.

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The taste analysis set will be defined on a regimen basis and will include all relevant data from the participants included in the taste population who have received that test product.

The taste analysis set will be determined by Quotient with approval from MMV at the same time as the taste population and will be used for all summary tables and formal statistical analysis of taste data.

6.3 Pharmacokinetic Population and Pharmacokinetic Analysis Set(s)

The PK population will be defined separately for study Parts 1, 2 and 3 and will include all subjects who have received at least one dose of IMP and who satisfy the following criteria for at least one profile:

- No missing samples or invalid post-dose analytical results at critical time points e.g., around Cmax
- No relevant protocol deviations that may impact the study objectives with respect to the PK endpoints
- No relevant AEs such as vomiting that suggest that the whole dose was not available for absorption for a particular participant

Handling of the urine concentration data is not currently a planned analysis in the CSR; however, should a validated method be developed and the urine concentrations be required to be reported by Quotient in Part 1, then the following should apply to the processing of the urine data. Any protocol deviations or AEs specific to the analysis of urinary PK parameters will be documented as an update to the PK population when urine data are available for analysis. Subjects who received placebo in Part 1 and 3 will not be included in the PK population.

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.

In Part 1, individual subjects will be excluded from the PK analysis set where deemed appropriate such as if the participant'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.

In Part 2, individual participant profiles (i.e., treatments) will be excluded from the PK analysis set where deemed appropriate such as if the participant'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.

In Part 3, individual subjects will be excluded from the PK analysis set where deemed appropriate such as if the participant's data for the treatment affected did not meet the bullet point criteria above for at least one individual profile (i.e., day), or other study emergent point related to PK analysis or interpretation.

Individual participant profiles in Part 3 (i.e., days) will be flagged and excluded from the PK summary statistics where deemed appropriate such as if the profile in the day 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 MMV following derivation of all PK parameter estimates.

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If required, a PK analysis subset(s) will also be documented by Quotient, with approval from MMV, at the same time as the PK population and analysis set, if additional subjects are required to be excluded from the statistical analysis (i.e., to exclude subjects who have not received both the fed and fasted treatments in Part 2).

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 as well as the formal statistical analysis and will be documented as the same time as the PK population.

7 Participant Disposition, Demographics and Baseline Characteristics

No formal statistical testing will be performed on participant disposition, or on demographic or baseline data. Summaries of participant 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

For each study part, data for subjects 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 Participant Disposition and Withdrawals

For each study part, the number and percentage of subjects randomised, dosed, completed and discontinued will be presented by sequence and overall in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. If any subjects discontinued from the study early then the number of subjects for each reason for discontinuation will be presented by sequence and overall in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. However, if none of the subjects are discontinued from the study early, then the reasons for discontinuation will not be populated in the summary table. A participant may be discontinued from the study early for 1 reason only.

Participant 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/taste/PK, as applicable) by sequence and overall in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. 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 participant may be excluded from a population for more than 1 reason. The denominator for the percentage is the number of subjects enrolled in the respective sequence in Part 2, and the number of subjects enrolled in Part 1 and Part 3.

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

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7.4 Analysis Sets and Subsets

A summary table will be produced detailing the number and percentage of subjects in each of the safety, taste and PK analysis sets and analysis subsets (if applicable) for each treatment and overall in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. Separate tables will be presented for safety, taste and PK, analysis 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 participant may be excluded from an analysis set for more than 1 reason. The denominator for the percentage is the number of subjects in each 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 (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 by sequence and overall in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. The number and percentage of subjects will be presented by sequence and overall in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3 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 participant smoke, use e-cigarettes or use nicotine replacement products?] and alcohol consumption) will be summarised by sequence and overall in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3, as a categorical variable.

Demographic and lifestyle data for all enrolled subjects will be listed. For Part 2 only, separate columns will be provided in the demographic listing for body weight at screening and admission.

7.6 Medical History

Medical history will be recorded for each participant at the screening visit and updated at admission. Medical histories will be coded using MedDRA v25.0 (or a more recent version) including Lowest Level Term, 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 version 2022 March (or more recent version) using the following Anatomical Therapeutic Chemical (ATC) classification codes

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- 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 separately for each study part:

- Carbon monoxide breath test
- Urine drug screen
- Alcohol breath test
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Antigen test
- Beck Depression Inventory (BDI-II) Questionnaire
- Virology (Screening only)
- Creatinine clearance (Admission only)
- Follicle stimulating hormone for female subjects (Screening only)
- Serum pregnancy test for female subjects (Screening only)
- Urine pregnancy test (Admission only)

8 Efficacy

Not applicable for this Phase I study.

9 Pharmacokinetics

9.1 Plasma PK Parameter Estimation

The PK parameters (Table 5 [Part 1 and 2], Table 6 [Part 3]) for MMV367 in plasma will be estimated where possible and appropriate for each participant profile (i.e., treatment/day [where relevant]) 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.

9.1.1 Definition of Plasma PK Parameters

Plasma PK parameter definitions are provided in Table 5 and Table 6.

Table 5 Plasma PK Parameter Definitions and Rounding Specifications – Part 1 and 2

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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(0-48)	Area under the curve from time 0 to 48 h post dose	mass unit.h/mL	SF	3
AUC(0-72)	Area under the curve from time 0 to 72 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 apparent body clearance calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown.	mL/min	SF	3
CLr[a]	Renal clearance calculated using plasma AUC – Part 1 only	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
Frel Cmax	Relative bioavailability based on Cmax (Part 2 fed dosing only)	%	DP	2
Frel AUC(0-last)	Relative bioavailability based on AUC(0-last) (Part 2 fed dosing only)	%	DP	2
Frel AUC(0-inf)	Relative bioavailability based on AUC(0-inf) (Part 2 fed dosing only)	%	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; NA: not applicable; SF: significant figures
* these values should be listed but omitted from the descriptive statistics
[a] Renal clearance will only be calculated in Part 1 should a validated method be developed, and the urine concentrations be required to be reported by Quotient, as an addendum to the CSR

Table 6 Plasma PK Parameter Definitions and Rounding Specifications – Part 3

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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-tau)	Area under the curve for the defined interval between doses (tau)	mass unit.h/mL	SF	3
T1/2	Terminal elimination half-life (Day 3 only)	h	DP	2
lambda-z	First order rate constant associated with the terminal (log-linear) portion of the curve (Day 3 only)	1/h	DP	4
CL/Ftau	Total body clearance calculated using AUC(0-tau) after repeated extravascular administration, where F (fraction of dose bioavailable) is unknown (Day 3 only)	mL/min	SF	3
Vz/Ftau	Apparent volume of distribution based on the terminal phase calculated using AUC(0-tau) after extravascular administration where F (fraction of dose bioavailable) is unknown (Day 3 only)	L	SF	3
AR Cmax	Accumulation ratio based on Cmax repeated dose/Cmax single dose (Day 3 only)	NA	DP	2
AR AUC	Accumulation ratio based on AUC(0-tau) repeated dose/AUC(0-tau) single dose (Day 3 only)	NA	DP	2
lambda-z lower*	Lower limit on time for values to be included in the calculation of lambda-z (Day 3 only)	h	DP	2
lambda-z upper*	Upper limit on time for values to be included in the calculation of lambda-z (Day 3 only)	h	DP	2

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

Dose will be used in the calculation of relevant PK parameters as per Table 7.

Table 7 Dose Specifications

Dose (nominal/actual)	Nominal
Precision	As per protocol

In Part 2, relative bioavailability (Frel) will be calculated as follows:

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

Frel will be calculated using Cmax, AUC(0-last) and AUC(0-inf). 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 Frel for all subjects.

The following comparisons will be made:

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- XX mg MMV367 fed [Regimen 7] (test) vs XX mg MMV367 fasted [Regimen 6] (reference)

Renal clearance (CLr) is a plasma parameter and will be calculated as follows in Part 1, if applicable:

$$\mathrm{CLr} = \frac{\mathrm{Ae}}{\mathrm{AUC}}$$

where both amount excreted (Ae) of parent in urine and AUC of parent in plasma are determined over co-incident time ranges after dosing. For example, if urinary Ae is calculated over 0-24 hours then the plasma AUC used will also be calculated over the same period. Details of methods for calculation of CumAe are included in Section 9.2.

9.1.2 Rules for Plasma PK Parameter Estimation using WinNonlin

The imputation of non-numerical (e.g., below the limit of quantification [BLQ]) 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:

- Pre-dose sample times will be entered as zero
- Values that are BLQ obtained prior to Cmax will be entered as zero
- Values that are BLQ after Cmax will be treated as missing but where BLQ concentrations are defined as parameters these will be reported as BLQ
- 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 be generally be considered missing

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 MMV has been obtained. Any exclusions of concentration values or repeat analysis of samples will be documented appropriately.

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Plasma 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 8 will be applied:

Table 8 PK Parameter Estimation Details

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

Where possible, the terminal elimination rate constant (lambda-z) will be calculated for all participant 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.

9.1.3 Plasma PK Parameter Reporting Specifications

The following parameters will be reported for each Study Part/Study Treatment/Study Day as applicable, according to the rounding specifications provided in Table 5 and Table 6:

Part 1
Tmax, Cmax, AUC(0-24), AUC(0-48), AUC(0-last), AUC(0-inf), AUCextrap, T1/2, lambda-z, CL/F, CLr*, Vz/F, lambda-z lower, lambda-z upper

Part 2 – fasted
Tmax, Cmax, AUC(0-24), AUC(0-48), AUC(0-last), AUC(0-inf), AUCextrap, T1/2, lambda-z, CL/F, Vz/F, lambda-z lower, lambda-z upper

Part 2 – fed
Tmax, Cmax, AUC(0-24), AUC(0-48), AUC(0-last), AUC(0-inf), AUCextrap, T1/2, lambda-z, CL/F, Vz/F, Frel Cmax, Frel AUC(0-last), Frel AUC(0-inf), lambda-z lower, lambda-z upper

Part 3, Day 1
Tmax, Cmax, AUC(0-tau)

Part 3, Day 3
Tmax, Cmax, AUC(0-tau), T1/2, lambda-z, CL/Ftau, Vz/Ftau, AR Cmax, AR AUC, lambda-z lower, lambda-z upper

* Renal clearance will only be calculated in Part 1 should a validated method be developed, and the urine concentrations be required to be reported by Quotient, as an addendum to the CSR

The flags/footnotes given in Table 9 will be applied to the PK parameters where relevant and will be shown in the PK parameter listings. Additional flags may be applied based on emerging data.

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Table 9 PK Parameter Flags and Footnotes

Flag	Footnote
a	Adjusted rsq of regression (the goodness of fit statistic for the elimination phase) was <0.8
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
g	Measurable pre-dose values were observed, however were considered less than 5 % of Cmax (Part 2 only)

In the event that the adjusted rsq of regression is <0.8 (“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 and formal statistical analysis.

In the event that the time period used for regression analysis is less than 2-fold the calculated half-life (“b” flag) T1/2 will be flagged, listed, and included in summary statistics and formal statistical analysis.

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 and formal statistical analysis.

In the event that there are insufficient post-Cmax data points (i.e., <3) 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.

In the event that measurable pre-dose values less than 5% of Cmax were observed (“g” flag), all parameter estimates for the profiles affected will be listed, flagged and included in summary statistics and formal statistical analysis.

Note: in the event that measurable pre-dose concentrations greater than 5% of Cmax are observed, requirements for additional flags and further action will be agreed with MMV and documented at the same time as the PK population.

9.2 Urine PK Parameter Estimation

Handling of the urine concentration data is not currently planned analysis in the CSR. However, should a validated method be developed and the urine concentrations be required to be reported by Quotient in Part 1, then the following should apply to the processing of the urine data.

In Part 1, Cohort 1C and 1D, the urine PK parameters for MMV367 may be derived for each participant and collection interval by treatment using SAS.

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9.2.1 Definition of Urine PK Parameters

Urine PK parameter definitions are provided in Table 10.

Table 10 Urine PK Parameter Definitions and Rounding Specifications

Parameter	Definition	Unit	DP	No. of DP
Ae	Amount excreted	mass unit	DP	2
CumAe	Cumulative amount excreted	mass unit	DP	2
%Ae	Percentage of dose excreted	%	DP	2
Cum%Ae	Cumulative percentage of dose excreted	%	DP	2

DP = decimal places
Dose is defined as per Table 7

Urine PK parameters will be calculated as follows:

- 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 MMV367 concentrations in urine are provided in mass unit/g the following conversion will be performed using SAS:

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

- Ae will be derived for each collection period:

  *Ae = concentration * volume*

- CumAe, will be calculated by the incremental summation of the Ae over all collection periods. Note: The amount excreted in the pre-dose sample should not be included in the calculation of the cumulative amount excreted.
- %Ae will be derived for each collection period:

  *%Ae = 100 * Ae / Total Dose Administered*

- Cum%Ae will be calculated by the incremental summation of the %Ae over all collection periods. Note: The percentage of dose excreted in the pre-dose sample will not be included in the calculation of the cumulative percentage of dose excreted.
- Where a participant has failed to void over a particular collection interval the Ae for that collection interval 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

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been collected within the interval. Where no other samples are collected within the interval the concentration will be set to missing for the purposes of the calculation urine PK parameters. In both scenarios the data will be flagged to highlight a missing void. Affected participant(s) may be excluded from summary statistics, this will be documented as part of the PK population.

- Imputation of non-numerical values reported in the urine dataset (i.e., concentrations that are BLQ) will be entered as zero for calculation of urine PK parameters.

9.3 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 each time point and treatment for MMV367 in plasma. The number of BLQ values (n#) per time point will also be presented. Geometric statistics will not be calculated for Day 1, pre-dose concentrations.

Summary statistics (i.e., n, mean, SD, CV%, median, minimum and maximum) of plasma PK parameters will be calculated for MMV367 for each treatment and day (where appropriate). Geometric mean, geometric SD and geometric CV% will be presented for all plasma PK parameters except Tmax.

In Part 1, Cohort 1C and 1D, should a validated method be developed, and the urine concentrations be required to be reported by Quotient in Part 1, urine Ae and CumAe will be summarised using the n, mean, SD, CV%, median, minimum, and maximum) whilst %Ae and Cum%Ae will be summarised using the n, mean, SD, CV%, median, minimum and maximum only.

Non-measurable values reported in the plasma 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 lower limit of quantification (LLOQ) value. This also applies to any concentrations that are defined as PK parameters. Data recorded as NR, NS or NC will be handled as missing (i.e., no assumption will be made about the actual concentration).

9.4 Concentration and PK Figures

Mean, spaghetti and individual 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, pre-dose concentration values reported as BLQ will be set to zero. Post-dose concentration values reported as BLQ will be set to zero, up to the point at which all concentrations fall below the LLOQ, after which they will be presented as missing. For all plots on a log 10/linear scale, pre-dose concentration values reported as BLQ will be presented as missing. 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 the LLOQ, 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.

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

Part 1
- All treatments on the same plot (1 plot with up to 5 profiles)

Part 2
- Fed and Fasted treatments on the same plot (1 plot with 2 profiles)

Part 3
- All treatments on the same plot with separate plots for Day 1 and Day 3 (2 plots with up to 3 profiles per plot)
- Day 1 and Day 3 on the same plot, with separate plots for each treatment (up to 3 plots with 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 plasma concentration vs time spaghetti plots (using actual sampling time after dosing) will be produced for each treatment (and Day in Part 3) with each plot displaying 1 line per participant.

In Part 2, individual plasma concentration vs time plots (using actual sampling times after dosing) will be produced separately for each individual participant with fed and fasted treatments on the same plot in Part 2. Additionally, in Part 3, individual plasma concentration vs time plots will be produced separately for each participant and each Day, as well as each individual participant and both Days on the same plot.

For the food effect comparison in Part 2, scatter plots of individual plasma PK parameter values for Cmax, AUC(0-last) and AUC(0-inf). The PK parameter estimates will be plotted on the y-axis (linear scale) and regimen on the x-axis. Each participant's individual points will be connected with a line. In addition, the corresponding geometric mean parameter values will be plotted using a different symbol and connected with a thicker line. Separate plots will be produced for each parameter.

9.5 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 participant basis. Any flags used will be included as a footnote with the appropriate definition.

9.6 Statistical Analysis of PK Parameters

9.6.1 Part 1 and Part 3: Assessment of Dose Proportionality

Formal statistical analysis will be performed on the PK parameters Cmax, AUC(0-last) and AUC(0-inf) in Part 1, and Cmax and AUC(0-tau) in Part 3, including data from up to 5 different dose levels in Part 1 and up to 3 different dose levels, on Day 1 and Day 3 separately in Part 3 to assess dose proportionality. This will be assessed using a power model as follows:

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$$\log(AUC \text{ or } Cmax) = \mu + \beta \times \log(dose)$$

where μ and β are the intercept and the slope of the model, respectively. The PK parameters will be undergo a natural log transformation. The model will include the log dose as a fixed effect and log PK parameter as the dependent variable The analysis will be performed using SAS Software procedure PROC MIXED, the method will be specified as Restricted Maximum Likelihood and the denominator degrees of freedom for the fixed effects will be calculated using Kenward and Roger's method.

The model is usually referred to as a power model [1] as after exponentiation:

$$AUC \text{ (or } Cmax) = \alpha \times dose^{\beta}$$

The estimate obtained for β together with its 90% CI will be presented along with the number of subjects and the geometric means.

The following is an example of the SAS Software code that will be used:

```
PROC MIXED DATA=<input dataset name> METHOD=REML ORDER=INTERNAL;
      MODEL LVAR= LDOSE / SOLUTION OUTP=PRED DDFM=KR CL ALPHA=0.10;
      ODS OUTPUT SOLUTIONF=EST;
RUN;
```

Where LVAR is the log transformed PK parameter and LDOSE is the log transformed dose.

Dose proportionality will be assessed against the critical region defined by the formula below [2][3]:

$$1 + \frac{\ln(\theta_L)}{\ln(r)} < \beta < 1 + \frac{\ln(\theta_H)}{\ln(r)}$$

where: $\theta_L = 0.50$
$\theta_H = 2.00$
r = ratio highest dose level/lowest dose level
β = slope of line as a measure of dose proportionality from power model

If the 90% CI for β lie entirely within the critical region defined above, dose proportionality will be concluded over the dose range under analysis. The critical region will be calculated using SAS Software as part of the statistical analysis and presented in the analysis table as a footnote.

In addition, the power model will be used to estimate the increase in the PK parameter resulting from a doubling in the dose i.e., 2^{β} 90% CI associated with this estimate will also be provided.

This analysis will be performed if there is quantifiable plasma PK data for a minimum of 3 active dose levels. Dose levels will be included in the analysis if quantifiable plasma PK data is available for a minimum of 3 subjects within the relevant dose level.

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Where dose proportionality cannot be concluded over the full dose range then dose proportionality may be assessed over a reduced dose range to identify if dose proportionality exists over a narrower dose range.

9.6.2 Part 2: Assessment of Food Effect

Formal statistical analysis will be performed on the PK parameters Cmax, AUC(0-last) and AUC(0-inf), to assess the presence of a food effect. The null hypothesis is that there is no difference between fed and fasted treatments.

The PK parameters will undergo a natural logarithmic transformation and will be analysed using mixed effect modelling techniques. The model will include terms for fed/fasted status and period fitted as fixed effects and participant fitted as a random effect.

Only subjects who complete both the fed and fasted periods will be included in the statistical analysis. Furthermore, for AUC(0-inf) only, a participant must have reliable estimates of AUC(0-inf) for both fed and fasted periods to be included in the statistical analysis. If the number of subjects with reliable estimates for both periods is less than 4 (i.e., less than 50% of planned number of evaluable subjects) then no formal statistical analysis of AUC(0-inf) will be performed i.e., descriptive summaries only.

The adjusted means including differences from the fed/fasted comparison and the associated 90% CIs obtained from the model are back transformed on the log scale to obtain adjusted geometric mean ratios (GMRs) and 90% CIs of the ratio. These will be presented together with the p-value from the fed/fasted comparison.

The fixed effects table from the model with F-statistic and p-value for the relevant effects will be presented in a separate table.

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

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

The analysis will be performed using the SAS Software procedure PROC MIXED, the method will specified as Restricted Maximum Likelihood and the denominator degrees of freedom for the fixed effects will be calculated using Kenward-Roger method [4]. The following is an example of the SAS Software code that will be used:

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

where

- LVAR is the natural log transformed PK parameter of interest
- SUBJIDN is the numeric participant identifier variable
- APERIODN is the numeric period variable

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- FSTATUS is the numeric variable representing fasted or fed status

For each analysis, distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability (QQ) plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. If the distributional assumptions for the parametric approach are not satisfied, then additional sensitivity analyses may be performed including the removal of potential outliers or the use of non-parametric methods to assess the robustness of the original analysis. This will be documented in the CSR together with the reasoning supporting the most appropriate action taken, if applicable. In general terms the results of the original analysis will always be presented in the CSR.

9.6.3 Statistical Figures for Analysis of Pharmacokinetic Data

In Part 1, to complement the dose proportionality assessment the geometric mean values of the PK parameters used to evaluate dose proportionality, along with the geometric SDs from the mean will be presented graphically on a $\log_{10}$ scale by $\log_{10}$ (dose level).

Additionally, the individual values for PK parameters used in the evaluation of dose proportionality will also be presented graphically on a $\log_{10}$ by $\log_{10}$ (dose level) scale and the power model regression line will be included on these plots.

9.7 Interim Pharmacokinetic Analysis

The details of the planned interim PK analysis are described in this section. However, as the analysis will be performed in real time it may be necessary to change the planned analysis in response to the emerging data.

Summary tables and figures for the interim PK analysis will be presented in an Interim PK Summary Report after being exported from WinNonlin. The formatting of this output will differ slightly from the final PK output which will be produced using SAS to include in the CSR.

The interim PK analysis will be performed on QC checked concentration data for MMV367 in plasma using nominal sampling times and doses. Measures will be taken to maintain the study blind according to Section 5.7.

The following PK parameters will be calculated for the interim analysis:

Part 1:
Tmax, Cmax, AUC(0-24), AUC(0-48), AUC(0-last), AUC(0-inf), T1/2.

Part 3 Day 1:
Tmax, Cmax, AUC(0-tau)

Part 3 Day 3:
Tmax, Cmax, AUC(0-tau), T1/2, AR Cmax, AR AUC

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10 Taste Assessment

For Part 1 only, Taste/Palatability will be assessed using a questionnaire (example provided in Appendix 7 at the time points detailed in Appendix 4. The questionnaire will ask participants to rate the overall acceptability of taste/palatability, with additional questions asked on specific palatability attributes (smell, sweetness, bitterness, flavour, mouth feel/texture, grittiness, and aftertaste), on a 9-point Likert scale. The clinical staff will provide definitions and examples of each aspect that is being rated if required.

Each participant in Part 1 of the study will complete the questionnaire individually and privately, within no more than 10 min, following IMP administration.

10.1 Summary Tables for Taste Questionnaire Assessments

Acceptability of taste (overall liking of product) will be summarised (i.e., n, mean, SD, median, minimum and maximum) by treatment.

For each of the taste attributes described above, the number and percentage of subjects who selected each taste rating on the 9-point scale and/or N/A will be summarised by treatment. The safety population will be used as the denominator in the calculation of percentages.

10.2 Listings for Taste Questionnaire Assessments

All taste assessments data will be listed.

10.3 Statistical Figures for Analysis of Taste Questionnaire Data

In Part 1, to complement to assessment of the taste questionnaire data, boxplots of each dose level will be produced separately for each taste attribute and overall acceptability. Dose level will be plotted on the X axis and taste assessment score will be plotted on the Y axis (i.e., 1=Dislike extremely, 2=Dislike very much etc.).

Additionally, bubble plots of each taste attribute and overall acceptability will be produced. Each dose level will be plotted on the X axis, with the assessment score plotted on the Y axis. Each bubble will contain a count of the number of subjects which scored a particular outcome. The size of the bubble will reflect the count (i.e., The bubble associated which the most popular score will be the biggest).

11 Safety Assessments

Safety data summaries will be presented by actual treatment and the safety analysis set will be used throughout.

11.1 Extent of Exposure and Treatment Compliance

The number and percentage of subjects dosed with IMP (each day, Part 3 only), will be presented for all placebo, all active, and each active dose level separately in Part 1 and Part 3, and by treatment received in Part 2.

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. Total number of days of exposure and measures of compliance will be included in the listing (Part 3 only).

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11.2 Meal Details

For Part 2 only, meal details as recorded on the electronic case report form (eCRF) will be listed for all enrolled subjects. Any recorded deviations from the planned mealtimes will be listed as protocol deviations.

11.3 Adverse Events

Throughout the study, all AEs will be evaluated by the PI and noted in the AE section of the eCRF. An AE is any untoward medical occurrence in a participant 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 the Medical Dictionary for Regulatory Activities MedDRA v25.0 (or more recent version), and reported by SOC and PT.

AEs will be classified into the following categories:

- Pre-dose AEs: AEs recorded at screening or with a start date and time prior to the first dose of IMP
- Treatment-emergent 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

For Part 2 only, TEAEs will be assigned to the treatment of the period in which the AE first occurred. Where the severity of an AE intensifies or symptoms change in a subsequent period, this will be defined as a new AE and included under the regimen associated with the subsequent period. Adverse events that occur during the washout period will be assigned to the treatment the participant received during the period immediately before the washout period.

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

Adverse events will be classified as “unrelated”, or “related” when considering their relationship to IMP. TEAEs classified as “related”, will be defined as IMP-related events. 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 participant and regimen, then the maximum observed severity for that participant will be categorised and presented as “moderate” or “severe”, respectively

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

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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 “related” for that participant and regimen, then the maximum observed relationship for that participant will be categorised and presented as “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 participant and regimen, then the maximum observed relationship for that participant 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.

11.3.1 Summary Tables for Adverse Events

All pre-dose AEs (as defined in Section 11.3 will be excluded from the summary tables but will be listed for all enrolled subjects.

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

For each study part, 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:

Part 1 and Part 3:

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

Part 2:

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

For event counts, all events are included.

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When it is necessary to calculate percentages, the denominator will be the total number of subjects in the safety analysis set (and period – Part 2 only), 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 part and then by most frequently reported PT in the study part within each SOC.

11.3.1.1 Overall Summary of Adverse Events

The following will be summarised by treatment and overall, in Part 2, and by all placebo, all active, and each dose level in Part 1 and Part 3 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 IMP-related TEAEs
- Number and percentage of subjects reporting serious TEAEs
- Number and percentage of subjects reporting TEAEs leading to participant withdrawal
- Number and percentage of subjects reporting TEAEs leading to death

- Total number of TEAEs
- Total number of severe TEAEs
- Total number of IMP-related TEAEs
- Total number of serious TEAEs
- Total number of TEAEs leading to participant withdrawal
- Total number of TEAEs leading to death

11.3.1.2 Summary of Treatment-Emergent Adverse Events

All subjects reporting TEAEs will be summarised by treatment and overall in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. Counts will be given for number of subjects and number of events. Subjects experiencing more than 1 TEAE treatment will be counted only once for number of subjects but will be counted more than once for number of events.

Additionally, subjects reporting TEAEs will be summarised for SOC and PT by treatment and overall in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. Counts will be given for number of subjects and number of events. Subjects experiencing more than 1 episode of a TEAE within a treatment will be counted only once within each SOC and PT using the most severe episode.

11.3.1.3 Summary of Treatment-Emergent Adverse Events by Severity

All subjects reporting TEAEs will be summarised by severity (i.e., mild, moderate or severe) and by treatment in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. 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 within a treatment will be counted only once using the most severe episode).

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Additionally, subjects reporting TEAEs will be summarised for SOC and PT by maximum severity (i.e., mild, moderate or severe) and by treatment in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. 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 within a treatment will be counted only once within each SOC and PT using the most severe episode).

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

All subjects reporting TEAEs will be summarised by relationship to IMP (i.e., unrelated, or related) and by treatment in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. 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 within a treatment 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 or related) by treatment in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. 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 within a treatment will be counted only once within each SOC and PT using the most closely related event).

11.3.1.5 Summary of IMP-related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

All subjects reporting IMP-related TEAEs will be summarised by treatment in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. Counts will be given for number of subjects and number of events. Subjects experiencing more than 1 IMP-related TEAE within a treatment will be counted only once for number of subjects but will be counted more than once for number of events.

Additionally, subjects reporting IMP related events will be summarised for SOC and PT by treatment in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. Counts will be given for number of subjects and number of events. Subjects experiencing more than 1 episode of an IMP-related TEAE within a treatment will be counted only once within each SOC and PT using the most severe episode.

11.3.1.6 Summary of Serious Adverse Events

All subjects reporting treatment-emergent serious AEs (SAEs) will be summarised by treatment in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. Counts will be given for number of subjects and number of events. Subjects experiencing more than 1 SAE within a treatment 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 by treatment in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. Counts will be given for number of subjects and number of events. Subjects experiencing more than 1 episode of a SAE within a will be counted only once within each SOC and PT using the most severe episode.

11.3.2 Listings for Adverse Events

All pre-dose AEs (as defined in Section 11.3) will be listed including SOC and PT.

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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.

11.4 Laboratory Evaluations

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

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

11.4.1 Summary Tables for Laboratory Evaluations

For each study part, haematology, coagulation 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 (Admission, Day-1) at each scheduled post-baseline time point by treatment in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3.

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 by treatment in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3. 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) 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.

11.4.2 Listings for Laboratory Evaluations

For each study part, the sample collection data (e.g., collection times) for laboratory analysis and urinalysis data will be listed.

All individual participant 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, coagulation, clinical chemistry and urinalysis values outside their reference ranges by participant 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

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- Specific gravity: 1.000 to 1.030

11.5 Vital Signs

For each study part, the details of measurement of supine vital signs (i.e., systolic and diastolic BP, and heart rate) and non-supine vital signs (oral temperature and respiratory rate) will be measured at each scheduled timepoint.

Systolic and diastolic BP and heart rate orthostatic measurements will also be taken (1 supine and 1 standing) according to the time schedules presented in Appendix 4 (Part 1), Appendix 5 (Part 2) and Appendix 6 (Part 3). Vital signs parameters will be reported in the order given above, i.e., both summary tables and data listings.

11.5.1 Summary Tables for Vital Signs

For each study part, vital signs data (including orthostatic measurements), and change from baseline (Pre-dose, Day 1 (Period 1), Day 8 (Period 2), will be summarised (i.e., n, mean, SD, median, minimum and maximum) at each post-baseline time point by treatment in Part 2, and by all placebo, all active and each dose level in Part 1 and Part 3.

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.

Orthostatic hypotension will also be investigated at each time point. The change in systolic BP and diastolic BP between the mean of the duplicate supine measurements and the subsequent standing measurement will be calculated for each subject (i.e., standing BP- Supine BP) and summarised (i.e., mean, SD, median, minimum, maximum and n) at baseline and each post-baseline time point.

In addition, the number of subjects with 'substantial' decreases or no substantial decrease from supine to standing results in systolic BP (>20 mmHg) and diastolic BP (>10 mmHg) will be presented at each time point.

11.5.2 Listings for Vital Signs

For each study part, all individual vital signs data (including orthostatic measurements) and 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 11.5.1) in systolic BP, diastolic BP and heart rate will be flagged with an 'I' (increase) or 'D' (decrease), respectively. If applicable, data from unscheduled vital signs assessments will also be listed and flagged with a "#" to indicate it will not be used in the summary statistics.

In addition, a separate listing of all vital signs data outside their reference ranges by participant 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 11 will be used.

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Table 11 Vital Signs Reference Ranges

Parameter	Lower limit	Upper limit
Systolic BP	90 mmHg	140 mmHg
Diastolic BP	50 mmHg	90 mmHg
Heart rate	45 bpm	100 bpm
Oral Body Temperature	35.5ºC	37.5ºC
Respiration Rate	10 breaths/min	24 breaths/min

NA=Not applicable

11.6 ECGs

For each study part, the details of measurement of supine ECG parameters (i.e., ventricular rate, RR interval, QT interval, 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.

Triplicate 12-lead ECGs (2 min apart) will be obtained after the participant has been in the supine position for a minimum of 5 min.

On Day 1 of Parts 1 and 2, telemetry (continuous ECG monitoring) will commence at least 30 min before dosing until at least 12 h post-dose. As this monitoring is for safety purposes alone no data will be recorded in the source, except the start and stop time. If cardiac monitoring shows a potentially significant abnormality, a clinical assessment of the participant including a 12 lead ECG will be performed and treatment given, if appropriate.

11.6.1 Summary Tables for ECGs

For each study part and time point where triplicate ECGs are taken the arithmetic mean of the triplicate values for each 12-lead ECG measurement will be computed for each participant. These arithmetic means will then be used to compute the summary statistics for the observed values and for the change from baseline values. If 1 of the 3 measurements is missing, the mean of the 2 non-missing measurements will be used. If 2 measurements are missing, the remaining non-missing value will be used.

ECG data, including change from baseline (mean of single 12-lead measurement, Pre-dose, Day 1 of each dosing period where applicable), will be summarised (i.e., n, mean, SD, median, minimum and maximum) at each post-baseline time point by treatment in Part 2 and by all placebo, all active and each active dose in Part 1 and Part 3.

For each study part, the number and percentage of subjects with normal and prolonged QT intervals corrected for heart rate using Bazett's correction (i.e., QTcB) and Fridericia's correction (i.e., QTcF) and increases in QTcB and QTcF intervals from baseline within the categories defined in Table 12 (based on the International Council on Harmonisation [ICH] E14 guideline [5]) will be summarised by time point and overall. Percentages will be based on the number of subjects with measurements at the relevant time point.

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Table 12 ICH E14 Ranges for QTcB and QTcF Intervals

Parameter	ICH E14 Range
QTcF/ QTcB interval	≤450 msec (normal)
	>450msec
	>480 msec
	>500 msec
Increase in QTcF/ QTcB interval from baseline	≤30 msec
	>30 msec
	>60 msec

11.6.2 Listings for ECGs

For each study part, all ECG measurements (i.e., single and mean of triplicate 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, for the single values obtained from Single 12-lead measurement, and the mean values calculated from the triplicate ECG values, the number of subjects with increase in QTcF interval from baseline (>30 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 participant 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”, except QT interval which is from the eCRF) defined in Table 13 will be used.

Additionally, for Part 1 and Part 2 only, the telemetry start and stop times, as well as the nature of any potentially significant abnormality will be listed.

Table 13 ECG Reference Ranges

Parameter	Lower limit	Upper limit
Ventricular Rate (HR)	45 bpm	100 bpm
QT Interval	200 msec	600 msec
QTcB/QTcF Interval	NA	450 msec
PR Interval	120 msec	210 msec
QRS Duration	NA	120 msec
QRS Axis	-30º	100º

HR=heart rate
NA=Not applicable

11.7 Body Weight

In Part 1 and Part 3, all body weight data will be listed.

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11.8 Physical Examination

All physical examination and targeted physical examination details and comments on any findings will be listed by participant 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.

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In general summary statistics and statistical analysis results will be presented as detailed in Table 14, unless otherwise stated:

Table 14 Reporting Conventions for Summary Statistics and Statistical Analysis

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

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

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

All data listings will be based on all enrolled subjects (as defined in Section 3.2.3). Details of age and sex will be included on all data listings.

For the assessment of food effect in Part 2, statistical tests relating to PK parameters will be 2-sided and will be performed using a 10% significance level, leading to 90% (2-sided) confidence intervals (CIs).

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 PK parameter estimation using WinNonlin is described in Section 9.1.2. Imputations for reporting PK data are described in Section 9.1.3.

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

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Separate summary TFLs will be produced for Part 1, Part 2 and Part 3 of this study, respectively. The different parts will be identified by a sub-title indicating the relevant part. The text in the remainder of this document refers to both parts, unless specified otherwise. All summary tables within a study part relating to Part 1 or 3, except for the plasma PK concentration and plasma and urine PK parameter summary tables will be presented by all placebo subjects combined (i.e., all placebo subjects pooled over all dose levels), all active doses combined (i.e., all active subjects pooled over all dose levels) and all active dose levels separately. Summary tables relating to Part 2 will be presented by treatment. For the plasma PK concentration and plasma and urine PK parameter summary tables, these will be presented by all treatments separately. Placebo subjects will not be included on the PK concentration and plasma and urine PK parameter summary tables. TFLs of the same type will have the same TFL numbering with the inclusion of a .1 for Part 1 of the study and a .2 for Part 2 of the study etc. 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 /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 and Statistical Analysis

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

- Where tables are presented by sequence or treatment (Part 2), or dose group (Part 1 and Part 3) (i.e., no time points), QC will alternate between sequence or treatment (Part 2) or dose group (Part 1 and Part 3) to avoid the same sequence or treatment (Part 2) or dose group (Part 1 and Part 3) being QC'd every timeFor tables presented by sequence or treatment (Part 2) or dose group (Part 1 and Part 3) only (i.e., no time points), all summary statistics for 1 sequence or treatment (Part 2) or dose group (Part 1 and Part 3) will be QC'd
- Where tables are presented by treatment, or dose group (Part 1 and Part 3 only) and time point, QC will alternate between treatment, or dose group (Part 1 and Part 3 only) to avoid the same treatment, or dose group (Part 1 and Part 3 only) being QC'd every time
- For tables presented by treatment, or dose group (Part 1 and Part 3 only) and time point, a single treatment, or dose group (Part 1 and Part 3 only) at 1 time point in

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each table will be QC'd
- Where tables are produced using a macro for multiple parameters, a minimum of 3 tables, using different treatment, or dose group (Part 1 and Part 3 only) or combinations of treatment, or dose group (Part 1 and Part 3 only) and time point as appropriate, will be QC'd
- For AEs, the treatment details will be 100% QC'd against the randomisation schedule 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:

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

14.2.3 Quality Control - Data Listings

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

In Part 1 and Part 3, all data listings will be subjected to a 100% manual check against the eCRF or other appropriate source data for a minimum of 2 subjects. If appropriate, the subjects checked will include at least 1 participant who withdrew early from the study.

The study treatment allocation details on the dosing data listing will be 100% QC checked against the study randomisation schedule.

14.2.4 Quality Control - Statistical Analysis

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

15 SAS Data Transfer

The SDTM and ADaM datasets will be transferred to MMV at the following times:
- Prior to database lock (SDTM transfer of safety/eCRF data only)
- On the finalisation of the CSR, with the define.xml

The SDTM and ADaM datasets will be programmed according to a pre-defined set of specifications following Quotient SOP DOC-028861, with reference to SDTM IG 3.2 and ADaM IG 1.1. Quotient will provide metadata files and data will be transferred as SAS Software transport files. No define .xml output will be included.

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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 participant ID number and sequence or treatment (Part 2 only) or dose group (Part 1 and Part 3) i.e., all subjects in sequence 1 will be presented first, followed by subjects in sequence 2, etc.

The mock tables (Section 21) and titles of all TFLs and the formatting, labelling, footnotes and cosmetic appearance of tables may be modified, or additional labelling/footnotes may need to be added during analysis and reporting, for clarification purposes. Any such changes will not be regarded as changes to planned analyses.

17 Reference List

[1] Gough K, Hutchison M, Keene O, et al. Assessment of dose proportionality: report from the statisticians in the pharmaceutical industry/pharmacokinetics UK joint working party. *Drug Info J.* 1995; 29(3): 1039–1048

[2] Smith BP, Vandenhende FR, DeSante KA, et al. Confidence interval criteria for assessment of dose proportionality. *Pharmaceutical Research.* 2000; 17(10): 1278–1283.

[3] Hummel J, McKendrick S, Brindley C, et al. Exploratory assessment of dose proportionality: review of current approaches and proposal for a practical criterion. *Pharmaceutical Statist.* 2009; 8: 38–49

[4] Brown, Prescott. Repeated measures data. In: Brown H and Prescott R, 3rd edition. *Applied Mixed Models in Medicine.* Chichester, UK: John Wiley & Sons Ltd; 2015: 242–243.

[5] 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

[6] Beck A, Ward C, Mendelson M, et al. An inventory for measuring depression. *Archives of General Psychiatry*. 1961; 4: 561-571

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21 Mock Tables

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.1.1.1
Participant Disposition by Reason
Summary Statistics: All Enrolled Subjects
Part 1

			Active Dose of MMV367		
	ALL PLACEBO (N=XX) n (%)	ALL ACTIVE (N=XX) n (%)	100 mg (N=XX) n (%)	300 mg (N=XX) n (%)	.....
Subjects randomised	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
Subjects dosed	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
Subjects completed	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
Subjects discontinued	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
Reason for discontinuation					
REASON 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
REASON 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
REASON 3	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
…	…	…	…	…	…
<All categories on source>	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 dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
A participant may be discontinued for 1 reason only.

PROGRAM PATH: X:\~\QSC207031\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

Programming note: This table will be continued for all reasons for discontinuation as recorded on the source. If none of the subjects discontinued from the study early then reasons for discontinuation will not be populated in the summary table
Percentages are based on the number of subjects enrolled
A similar table will be produced for Part 3, i.e., Table [14.1.1.3]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.1.1.2
Participant Disposition by Reason
Summary Statistics: All Enrolled Subjects
Part 2

	Treatment Sequence		
	Fed/Fasted (N=X) n (%)	Fasted/Fed (N=X) n (%)	Overall (N=X) n (%)
Subjects randomised	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects dosed	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects completed	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects discontinued	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for discontinuation			
REASON 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
REASON 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
REASON 3	xx (xx.x)	xx (xx.x)	xx (xx.x)
…	…	…	…
<All categories on source>	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: The data in this table are presented in listing x.x
All subjects were to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions
A participant may be discontinued for one reason only

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

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.1.2.1.2
Analysis Populations
Summary Statistics: All Enrolled Subjects
Part 1

			Active Dose of MMV367		
	ALL PLACEBO (N=XX) n (%)	ALL ACTIVE (N=XX) n (%)	100 mg (N=XX) n (%)	300 mg (N=XX) n (%)	.....
Subjects in Safety Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
Reasons for exclusion from Safety Population					
<All categories from source>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
	…	…	…	…	…
Subjects in Taste Population	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
Reasons for exclusion from PK Population					
<All categories from source>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
		…	…	…	…
Subjects in PK Population		xx (xx.x)	xx (xx.x)	xx (xx.x)	…
Reasons for exclusion from PD Population					
<All categories from source>		xx (xx.x)	xx (xx.x)	xx (xx.x)	…
	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
A participant may be excluded for more than 1 reason

PROGRAM PATH: X:\~\QSC207031\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

Programming note: Percentages are based on the number of subjects enrolled
A similar table will be produced for Part 3, i.e., Table [14.1.2.3.2]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.1.2.2.2
Analysis Populations
Summary Statistics: All Enrolled Subjects
Part 2

	Treatment Sequence		
	Fed/Fasted (N=X) n (%)	Fasted/Fed (N=X) n (%)	Overall (N=X) n (%)
Subjects in safety population	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for exclusion from safety population			
<All categories on source listing>	xx (xx.x)	xx (xx.x)	xx (xx.x)
	…	…	…
Subjects in PK population	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for exclusion from PK population			
<All categories on source listing>	xx (xx.x)	xx (xx.x)	xx (xx.x)
	…	…	…

Note: The data in this table are presented in listing x.x
All subjects were to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions
A participant may be excluded for more than one reason

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Programming note: Percentages are based on the number of subjects enrolled in the respective sequence

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.1.2.1.3
Safety Analysis Set
Summary Statistics: Safety Population
Part 1

			Active Dose of MMV367		
	ALL PLACEBO (N=XX) n (%)	ALL ACTIVE (N=XX) n (%)	100 mg (N=XX) n (%)	300 mg (N=XX) n (%)	.....
Subjects in safety analysis set	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
Reasons for exclusion from safety analysis set					
<All categories from source>	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 dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
A participant may be excluded for more than 1 reason

PROGRAM PATH: X:\~\QSC207031\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

Programming note: A similar table will be produced for the Taste and PK Analysis Sets(and Subsets if applicable), i.e., Tables [14.1.2.1.4] and [14.1.2.1.5]. Each analysis set/subset will be a subset of their respective population and percentages will be based on number of subjects in each population
Similar tables will be produced for Part 3, i.e., Tables [14.1.2.3.3], [14.1.2.3.4]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.1.2.2.3
Safety Analysis Set
Summary Statistics: Safety Population
Part 2

	XX mg FAST (N=X) n (%)	XX mg FED (N=X) n (%)	Overall (N=X) n (%)
Subjects in safety analysis set	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reasons for exclusion from safety analysis set			
<All categories from source>	xx (xx.x)	xx (xx.x)	xx (xx.x)
	…	…	…

Note: The data in this table are presented in listing x.x
All subjects were to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions
A participant may be excluded for more than one reason

PROGRAM PATH: X:\~\QSC207031\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

Programming note: A similar table will be produced for the PK Analysis Set (and Subset[s], if required), i.e., Table [14.1.2.2.4]
Each analysis set/subset will be a subset of their respective population and percentages will be based on number of subjects in each population

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.1.3.1
Demographic and Baseline Characteristics
Summary Statistics: Safety Analysis Set
Part 1

				Active Dose of MMV367		
		ALL PLACEBO (N=XX)	ALL ACTIVE (N=XX)	100 mg (N=XX)	300 mg (N=XX)	.....
Age (years)	n	xx	xx	xx	xx	…
	Mean	xx.x	xx.x	xx.x	xx.x	…
	SD	xx.x	xx.x	xx.x	xx.x	…
	Median	xx.x	xx.x	xx.x	xx.x	…
	Min	xx	xx	xx	xx	…
	Max	xx	xx	xx	xx	…
Ethnicity n(%)	<All categories on source>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
Race n(%)	<All categories on source>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
Sex n(%)	Male	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
	Female	xx (xx.x)	xx (xx.x)	xx (xx.x)	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 dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively

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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 included in the table, as applicable
A similar table will be produced for Part 3, i.e., Table [14.1.3.3]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.1.3.2
Demographic and Baseline Characteristics
Summary Statistics: Safety Analysis Set
Part 2

		Treatment Sequence		
		Fed/Fasted (N=X)	Fasted/Fed (N=X)	Overall (N=X)
Age (years)	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
Ethnicity n(%)	<All categories on source>	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race n(%)	<All categories on source>	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sex n(%)	Male	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Female	xx (xx.x)	xx (xx.x)	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 to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions

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

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TABLE 14.1.4.1
Lifestyle Details: Smoking History and Alcohol Consumption
Summary Statistics: Safety Analysis Set
Part 1

				Active Dose of MMV367		
		ALL PLACEBO (N=XX) n (%)	ALL ACTIVE (N=XX) n (%)	100 mg (N=XX) n (%)	300 mg (N=XX) n (%)	.....
Does the participant smoke (1)	NO	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
	PREVIOUSLY	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
Alcohol Consumption (2)	NONE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
	YES: NOT EXCESSIVE	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 dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
(1) Smoked or used e-cigarettes or nicotine replacement products in the last 12 months
(2) Regular alcohol consumption (>21 units/week in males and >14 units/week in females)
1 unit = 1/2 pint beer, 25 mL of 40% spirit, 1.5 to 2 units = 125 mL glass of wine depending on type

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Programming note: A similar table will be produced for Part 3, i.e., Table [14.1.4.3]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.1.4.2
Lifestyle Details: Smoking History and Alcohol Consumption
Summary Statistics: Safety Analysis Set
Part 2

		Treatment Sequence		
		Fed/Fasted (N=X)	Fasted/Fed (N=X)	Overall (N=X)
Does the participant smoke? (1)	NO	xx (xx.x)	xx (xx.x)	xx (xx.x)
	PREVIOUSLY	xx (xx.x)	xx (xx.x)	xx (xx.x)
Alcohol Consumption (2)	NONE	xx (xx.x)	xx (xx.x)	xx (xx.x)
	YES: NOT REGULARLY	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: The data in this table are presented in listing x.x
All subjects were to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions
(1) Smoked or used e-cigarettes or nicotine replacement products in the last 12 months
(2) Regular alcohol consumption (>21 units/week in males and >14 units/week in females)
1 unit = 1/2 pint beer, 25 mL of 40% spirit, 1.5 to 2 units = 125 mL glass of wine depending on type

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.1.5.1
Extent of Exposure
Summary Statistics: Safety Analysis Set
Part 1

Treatment	Subjects Dosed (N=XX) n (%)
ALL PLACEBO	xx (xx.x)
ALL ACTIVE	xx (xx.x)
100 mg	xx (xx.x)
…	…

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.1.5.2
Extent of Exposure
Summary Statistics: Safety Analysis Set
Part 2

Treatment	Subjects Dosed (N=X) n (%)
XX mg FAST	xx (xx.x)
XX mg FED	xx (xx.x)

Note: The data in this table are presented in listing x.x
All subjects were to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.1.5.3.1
Extent of Exposure: Subjects Dosed by Day
Summary Statistics: Safety Analysis Set
Part 3

Day	ALL PLACEBO (N=xx) n (%)	XX mg (N=xx) n (%)	XX mg (N=xx) n (%)	XX mg (N=xx) n (%)
DAY 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
DAY 2	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 dose of either MMV367 or matching placebo over 3 days
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively

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Medicines for Malaria Venture Page x of y
Protocol: MMV_MMV367_21_01

TABLE 14.2.1.1.1
Excretion: MM367
Ae(Urine) by Collection Period <(units)>
Summary Statistics: PK Analysis Set
Part 1

MMV367 (N=XX)

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

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
Where a participant has failed to void or has a ND concentration over a particular collection interval, the amount excreted (Ae) has been set to zero

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(Programming Note: This table will be continued for all collection periods
A similar table will be produced for:
• %Ae(Urine) (Recovery), i.e., Table [14.2.1.1.3]

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Medicines for Malaria Venture Page x of y
Protocol: MMV_MMV367_21_01

TABLE 14.2.1.1.2
Excretion: MMV367
Cumulative Ae(Urine) <(units)>
Summary Statistics: PK Analysis Set
Part 1

MMV367 (N=XX)

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

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively

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(Programming note: This table will be continued for all collection periods. If required, as a result of early withdrawal or varying follow-up periods, this table will be produced using the LOCF approach. A similar table will be produced for
• Cumulative %Ae(Urine) (Recovery), i.e., Table [14.2.1.1.4]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.2.1.1.5
Plasma Pharmacokinetic Concentrations: MMV367(<units>)
Summary Statistics: <PK Analysis Set/PK Analysis Subset>
Part 1

				Arithmetic (1)						Geometric (2)		
Treatment	Time Point	n	n#	Mean	SD	CV%	Median	Min	Max	Mean	SD	CV%
100 mg	PRE-DOSE	xx	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x	NC	NC	NC
(N=XX)	TIMEPOINT 1	xx	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x	xx.xx	xx.xx	xx.x
	TIMEPOINT 2	xx	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x	xx.xx	xx.xx	xx.x
	…	…	…	…	…	…	…	…	…	…	…	…
300 mg	PRE-DOSE	xx	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x	NC	NC	NC
(N=XX)	TIMEPOINT 1	xx	xx	xx.xx	xx.xx	xx.x	xx.xx	xx.x	xx.x	xx.xx	xx.xx	xx.x
	TIMEPOINT 2	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 dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
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>

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Programming note: This table will be continued for all treatments and time points
Similar tables will be produced for Part 2 i.e., Table [14.2.1.2.1] and Part 3 i.e.,[14.2.1.2.3], with a column for Visit included before time point column.

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.2.2.1.1
Plasma Pharmacokinetic Parameters: MMV367
Summary Statistics: <PK Analysis Set/PK Analysis Subset>
Part 1

Treatment	Statistic	Parameter 1 (units)	Parameter 2 (units)	Parameter 3 (units)		All Other PK Parameters (units)
100 mg	n	xx	xx	xx	…	xx
(N=XX)	Mean	xx.x	xx.x	xx.x	…	xx.x
	SD	xx.x	xx.x	xx.x	…	xx.x
	CV%	xx.x	xx.x	xx.x	…	xx.x
	Median	xx.x	xx.x	xx.x	…	xx.x
	Min	xx	xx	xx	…	xx
	Max	xx	xx	xx	…	xx
	Geometric Mean	xx.x	xx.x	xx.x	…	xx.x
	Geometric SD	xx.x	xx.x	xx.x	…	xx.x
	Geometric CV%	xx.x	xx.x	xx.x	…	xx.x
					…	
300 mg	…	…	…	…	…	…
(N=XX)	…	…	…	…	…	…
…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
For concentration parameters, BLQ values will be set to 0 for arithmetic statistics and to ½ × LLOQ for geometric statistics>
The LLOQ value was <value, units

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Programming note: This table will be continued for all treatments and PK parameters
Similar tables will be produced for Part 2 i.e., Table [14.2.2.1.2] and Part 3, i.e., Table [14.2.2.1.3]
with a column for Visit included before statistic column.

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.2.2.2.1
Plasma Pharmacokinetic Parameters: MMV367
Statistical Analysis Results - Assessment of Dose Proportionality: <PK Analysis Set/PK Analysis Subset>
Part 1

PK Parameter		Active Dose of MMV367 100 mg (N=XX)	300 mg (N=XX)	750mg (N=XX)	1500mg (N=XX)	2000mg (N=XX)
Cmax (units)	n	xx	xx	xx	xx	xx
	Geometric Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	ß (90% CI)			x.xx	(x.xx	x.xx)
	2^ß (90% CI)			x.xx	(x.xx	x.xx)
AUC (0-last) (units)	n	xx	xx	xx	xx	xx
	Geometric Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	ß (90% CI)			x.xx	(x.xx	x.xx)
	2^ß (90% CI)			x.xx	(x.xx	x.xx)
AUC (0-inf) (units)	n	xx	xx	xx	xx	xx
	Geometric Mean	xx.x	xx.x	xx.x	xx.x	xx.x
	ß (90% CI)			x.xx	(x.xx	x.xx)
	2^ß (90% CI)			x.xx	(x.xx	x.xx)

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single dose of either MMV367 or matching placebo over 3 days
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
Results obtained from log-transformed PK parameters using a power model
The model includes a term for log dose fitted as a fixed effect
The geometric means presented are the same as the geometric means presented in Table [14.2.x.x]. N = total number of subjects in dose group, n = number of subjects with non-missing, valid data, ß (ie the slope parameter) and its 90% CI are a measure of dose proportionality, 2^ß represents the increase in exposure for a 2-fold increase in dose
Dose proportionality can be concluded if the 90% CI for ß lie entirely within the critical region (x.xx, x.xx)

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.2.2.2.2
Plasma Pharmacokinetic Parameters: MMV367
Statistical Analysis Results - Assessment of Food Effect: <PK Analysis Set/PK Analysis Subset>
Part 2

	XX mg FAST (N=XX)		XX mg FED (N=XX)					
Parameter	n	Adj Geo Mean (1)	n	Adj Geo Mean (1)	Ratio (%) (2)	90% CI (3)	P-value (4)	CVw (%) (5)
Cmax (units)	xx	xx.xx	xx	xx.xx	xx.xx	(xx.xx, xx.xx)	0.xxx	xx.xxx
AUC(0-last) (units)	xx	xx.xx	xx	xx.xx	xx.xx	(xx.xx, xx.xx)	0.xxx	xx.xxx
AUC(0-inf) (units)	xx	xx.xx	xx	xx.xx	xx.xx	(xx.xx, xx.xx)	0.xxx	xx.xxx

Note: The data in this table are presented in listing x.x
All subjects were to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions
Results obtained from mixed effects model of natural log transformed PK parameters including terms for fed/fasted Status, and period fitted as fixed effects and participant as a random effect
(1) Adj geo mean = adjusted geometric mean from model (2) Ratio of adj geo means with comparison presented as test/reference (3) CI = confidence interval for ratio of adj geo means (4) p-value from two-sided test (null hypothesis of no difference) (5) CVw = Intra-participant variability

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.3.1.1
Overall Summary of Treatment-Emergent Adverse Events
Summary Statistics: Safety Analysis Set
Part 1

					Active Dose of MMV367			
	ALL PLACEBO (N=XX)		ALL ACTIVE (N=XX)		100 mg (N=XX)		.....	
Event	n(%)	E	n(%)	E	n(%)	E	.....	
TEAEs	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…	
Severe TEAEs	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…	
IMP-related TEAEs	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…	
Serious TEAEs	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…	
TEAEs leading to participant withdrawal	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…	
TEAEs leading to death	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…	

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
E = Total Number of Events
TEAEs are coded using MedDRA vXX.X
n is the number of subjects reporting at least one event

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Programming note: A similar table will be produced for Part 3, i.e., Table [14.3.3.1]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.3.2.1
Overall Summary of Treatment-Emergent Adverse Events
Summary Statistics: Safety Analysis Set
Part 2

	XX mg FAST (N=X)		XX mg FED (N=X)		Overall (N=X)	
Event	n(%)	E	n(%)	E	n(%)	E
TEAEs	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Severe TEAE	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
IMP-related TEAEs	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Serious TEAE	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
TEAE leading to participant withdrawal	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
TEAE leading to death	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx

Note: The data in this table are presented in listing x.x
All subjects were to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions
E = Total Number of Events
TEAEs are coded using MedDRA vXX.X
n is the number of subjects reporting at least one event

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.3.1.2
Treatment-Emergent Adverse Events
By MedDRA System Organ Class and Preferred Term
Summary Statistics: Safety Analysis Set
Part 1

					Active Dose of MMV367		
	ALL PLACEBO (N=XX)		ALL ACTIVE (N=XX)		100 mg (N=XX)		.....
System Organ Class Preferred Term	n(%)	E	n(%)	E	n(%)	E	.....
TEAEs	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…
etc	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…
etc	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
E = Total Number of Events
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency
Subjects experiencing more than one TEAE within a treatment are counted only once for number of subjects but will be counted more than once for number of events. Subjects experiencing more than one TEAE within a treatment are counted only once within each SOC and PT

PROGRAM PATH: X:\~\QSC207031\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

Programming note: This table will be continued for all SOC and PT
A similar table will be produced for Part 3, i.e., Table [14.3.3.2]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.3.2.2
Treatment-Emergent Adverse Events
By MedDRA System Organ Class and Preferred Term
Summary Statistics: Safety Analysis Set
Part 2

	XX mg FAST (N=X)		XX mg FED (N=X)		Overall (N=X)	
	n(%)	E	n(%)	E	n(%)	E
TEAEs	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
etc	…	…	…	…	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
etc	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects were to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions
E = Total Number of Events
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency
Subjects experiencing more than one TEAE within a treatment are counted only once for number of subjects but will be counted more than once for number of events. Subjects experiencing more than one TEAE within a treatment are counted only once within each SOC and PT

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TABLE 14.3.1.3
Treatment-Emergent Adverse Events
By MedDRA System Organ Class, Preferred Term and Severity
Summary Statistics: Safety Analysis Set
Part 1

	ALL PLACEBO (N=XX)			ALL ACTIVE (N=XX)			.....
System Organ Class Preferred Term	Mild n(%)	Moderate n(%)	Severe n(%)	Mild n(%)	Moderate n(%)	Severe n(%)	.....
TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
etc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
etc	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 dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
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 within a treatment are counted only once within that treatment or each SOC and PT using the most severe episode

PROGRAM PATH: X:\~\QSC207031\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

Programming note: This table will be continued for all SOC and PT
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Protocol: MMV_MMV367_21_01

TABLE 14.3.2.3
Treatment-Emergent Adverse Events
By MedDRA System Organ Class, Preferred Term and Severity
Summary Statistics: Safety Analysis Set
Part 2

	XX mg FAST (N=X)			XX mg Fed (N=X)		
	Mild n(%)	Moderate n(%)	Severe n(%)	Mild n(%)	Moderate n(%)	Severe n(%)
TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…	…	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects were to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions
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, i.e., subjects experiencing more than one TEAE within a treatment are counted only once within that treatment or each SOC and PT using the most severe episode

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

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TABLE 14.3.1.4
Treatment-Emergent Adverse Events
By MedDRA System Organ Class, Preferred Term and Relationship to IMP
Summary Statistics: Safety Analysis Set
Part 1

	ALL PLACEBO (N=XX)		ALL ACTIVE (N=XX)		100 mg (N=XX)		.....
System Organ Class Preferred Term	Unrelated n(%)	Related n(%)	Unrelated n(%)	Related n(%)	Unrelated n(%)	Related n(%)	.....
TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
etc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
etc	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 dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
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, i.e., subjects experiencing more than one TEAE within a treatment are counted only once within that treatment or each SOC and PT using the most closely related event

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Programming note: This table will be continued for all SOC and PT
A similar table will be produced for Part 3, i.e., Table [14.3.3.4]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.3.2.4
Treatment-Emergent Adverse Events
By MedDRA System Organ Class, Preferred Term and Relationship to IMP
Summary Statistics: Safety Analysis Set
Part 2

	XX mg FAST (N=XX)		XX mg FED (N=XX)	
System Organ Class Preferred Term	Unrelated n(%)	Related n(%)	Unrelated n(%)	Related n(%)
TEAEs	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PREFERRED TERM 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc	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 to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions
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 within a treatment are counted only once within that treatment or each SOC and PT using the most closely related event

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

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TABLE 14.3.1.5
Treatment Emergent Adverse Events Related to IMP
By MedDRA System Organ Class and Preferred Term
Summary Statistics: Safety Analysis Set
Part 1

					Active Dose of MMV367			
	ALL PLACEBO (N=XX)		ALL ACTIVE (N=XX)		100 mg (N=XX)		.....	
System Organ Class Preferred Term	n(%)	E	n(%)	E	n(%)	E	.....	
TEAEs	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…	
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…	
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…	
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…	
etc	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…	
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…	
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…	
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…	
etc	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx	…	

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
E = Total Number of Events
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency
Subjects experiencing more than one TEAE within a treatment are counted only once for number of subjects but will be counted more than once for number of events. Subjects experiencing more than one TEAE within a treatment are counted only once within each SOC and PT

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Programming note: A similar table will be produced for Serious Adverse Events, i.e., Table [14.3.1.6]
Similar tables will be produced for Part 3, i.e., Tables [14.3.3.5] and [14.3.3.6]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.3.2.5
Treatment Emergent Adverse Events Related to IMP
By MedDRA System Organ Class and Preferred Term
Summary Statistics: Safety Analysis Set
Part 2

	XX mg FAST (N=X)		XX mg FED (N=X)	
	n(%)	E	n(%)	E
TEAEs (1)	xx (xx.x)	xx	xx (xx.x)	xx
SYSTEM ORGAN CLASS 1	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx
etc	…	…	…	…
SYSTEM ORGAN CLASS 2	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 1	xx (xx.x)	xx	xx (xx.x)	xx
PREFERRED TERM 2	xx (xx.x)	xx	xx (xx.x)	xx
etc	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects were to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions
E = Total Number of Events
TEAEs are coded using MedDRA vXX.X and are presented in descending order of frequency
Subjects experiencing more than one TEAE within a treatment are counted only once for number of subjects but will be counted more than once for number of events. Subjects experiencing more than one TEAE within a treatment are counted only once within each SOC and PT

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Programming note: A similar table will be produced for Serious AEs, i.e., Table [14.3.2.6]

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Protocol: MMV_MMV367_21_01

TABLE 14.4.1.1
Haematology and Coagulation
Summary Statistics: Safety Analysis Set
Part 1

<Parameter> (<units>) [ref range xxx-xxx (male), xxx-xxx (female)]

		Result						Change from Baseline					
Treatment	Time Point	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
ALL PLACEBO	BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x						
(N=XX)	TIMEPOINT 1	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x
	TIMEPOINT 2	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x
	…	…	…	…	…	…	…	…	…	…	…	…	…
ALL ACTIVE	BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x						
(N=XX)	TIMEPOINT 1	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x
	TIMEPOINT 2	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 dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
BASELINE is defined as Day -1, Admission

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Programming note: This table will be continued for all dose levels, time points and parameters
A similar table will be produced for Clinical Chemistry, [14.4.1.3]. Similar tables will be produced for Part 3, with a column for Visit included before time point column, i.e., Tables [14.4.3.1] and [14.4.3.3]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.4.2.1
Haematology and Coagulation
Summary Statistics: Safety Analysis Set
Part 2

<Parameter> (<units>) [ref range xxx-xxx (male), xxx-xxx (female)]

		Result						Change from Baseline					
Treatment	Time Point	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
XX mg FAST	BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x						
(N=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
XX mg FED	BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x						
(N=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 to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions
BASELINE is defined as Day -1, Admission

PROGRAM PATH: X:\~\QSC207031\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

Programming note: This table will be continued for all haematology <and coagulation> parameters and all time points
A similar table will be produced for Clinical Chemistry, i.e., Table [14.4.2.3]

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TABLE 14.4.1.2
Haematology and Coagulation
Shift Analysis: Safety Analysis Set
Part 1

<Parameter> (<units>) [ref range xxx-xxx (male), xxx-xxx (female)]

			Baseline		
	Time Point		Below	Within	Above
Treatment	Assessment	N#	n(%)	n(%)	n(%)
ALL PLACEBO	TIMEPOINT 1	xx			
(N=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 ACTIVE	TIMEPOINT 1	xx			
(N=XX)	Below		xx (xx.x)	xx (xx.x)	xx (xx.x)
	Within		xx (xx.x)	xx (xx.x)	xx (xx.x)
	Above		xx (xx.x)	xx (xx.x)	xx (xx.x)
…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
BASELINE is defined as Day -1, Admission
N# is the total number of subjects that have a value at baseline and the relevant 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 n (%) of subjects with assessments below/within/above the normal reference range

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Programming note: Continue this table for all dose levels, time points and parameters
A similar table will be produced for Clinical Chemistry, [14.4.1.4]. Similar tables will be produced for Part 3, with a column for Visit included before time point column, i.e., Tables [14.4.3.2] and [14.4.3.4]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.4.2.2
Haematology and Coagulation
Shift Analysis: Safety Analysis Set
Part 2

<Parameter> (<units>) [ref range xxx-xxx (male), xxx-xxx (female)]

		XX mg FAST (N=X) Baseline				XX mg FED (N=X) Baseline		
Time Point Assessment	N#	Below n(%)	Within n(%)	Above n(%)	N#	Below n(%)	Within n(%)	Above n(%)
TIME POINT 1	xx				xx			
Below		xx (xx.x)	xx (xx.x)	xx (xx.x)		xx (xx.x)	xx (xx.x)	xx (xx.x)
Within		xx (xx.x)	xx (xx.x)	xx (xx.x)		xx (xx.x)	xx (xx.x)	xx (xx.x)
Above		xx (xx.x)	xx (xx.x)	xx (xx.x)		xx (xx.x)	xx (xx.x)	xx (xx.x)
TIME POINT 2	xx				xx			
Below		xx (xx.x)	xx (xx.x)	xx (xx.x)		xx (xx.x)	xx (xx.x)	xx (xx.x)
Within		xx (xx.x)	xx (xx.x)	xx (xx.x)		xx (xx.x)	xx (xx.x)	xx (xx.x)
Above		xx (xx.x)	xx (xx.x)	xx (xx.x)		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 to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions
BASELINE is defined as Day -1, Admission of the corresponding study period
N# indicates the number of subjects with a baseline and a post baseline assessment at the time point indicated
Below/within/above indicate the n(%)=number(%) of subjects with assessments below/within/above the normal reference range at baseline

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Programming note: This table will be continued for all haematology and coagulation parameters and all time points
A similar table will be produced for Clinical Chemistry, i.e., Table [14.4.2.4]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.5.1.1
Vital Signs
Summary Statistics: Safety Analysis Set
Part 1

<Parameter> (<units>) [ref range xxx - xxx (age xx - xx), xxx - xxx (age > xx)]

		Result						Change from Baseline						Substantial Change		
Treatment	Time Point	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max	DEC	NONE	INC
ALL PLACEBO	BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x									
(N=XX)	TIMEPOINT 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
	TIMEPOINT 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
	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…
ALL ACTIVE	BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x									
(N=XX)	TIMEPOINT 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
	TIMEPOINT 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
	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
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:\~\QSC207031\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

Programming note: Continue this table for all dose levels, time points and parameters (which will follow the order given in the RAP text)
A similar table will be produced for Part 3, with a column for Visit included before time point column, i.e., Table [14.5.1.3]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.5.1.2
Vital Signs
Summary Statistics: Safety Analysis Set
Part 2

<Parameter> (<units>) [ref range xxx - xxx (age xx - xx), xxx - xxx (age > xx)]

		Result						Change from Baseline						Substantial Change (1)		
Treatment	Time Point	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max	DEC	NONE	INC
XX mg FAST	BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x									
(N=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
XX mg FED	BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x									
(N=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 to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions
BASELINE is defined as Day 1, Pre-dose of the corresponding study period
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

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

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.5.2.1.1
ECGs
Summary Statistics: Safety Analysis Set
Single 12-Lead
Part 1

<Parameter> (<units>) [<ref range xxx - xxx (age xx - xx), xxx - xxx (age > xx)> / <ref range xxx - xxx (male), xxx-xxx (female)>]

		Result						Change from Baseline					
Treatment	Time Point	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
ALL PLACEBO	BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x						
(N=XX)	TIMEPOINT 1	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x
	TIMEPOINT 2	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x
	…	…	…	…	…	…	…	…	…	…	…	…	…
ALL ACTIVE	BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x
(N=XX)	TIMEPOINT 1	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x
	TIMEPOINT 2	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 dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
BASELINE is defined as Day 1, mean of 3 Pre-dose measurements

PROGRAM PATH: X:\~\QSC207031\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

Programming note: This table will be continued for all dose levels, time points and parameters (which will follow the order given in the RAP text)
A similar table will be produced for triplicate readings i.e., Table [14.5.2.1.2]
Similar tables will also be produced for Part 3, with a column for Visit included before time point column, i.e., Tables [14.5.2.3.1] and [14.5.2.3.2]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.5.2.2.1
ECGs
Summary Statistics: Safety Analysis Set
Single 12-Lead
Part 2

<Parameter> (<units>) [<ref range xxx - xxx (age xx - xx), xxx - xxx (age > xx)> / <ref range xxx - xxx (male), xxx-xxx (female)>]

		Result						Change from Baseline					
Treatment	Time Point	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
XX mg FAST	BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x						
(N=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
XX MG FED	BASELINE	xx	xx.xx	xx.xx	xx.xx	xx.x	xx.x						
(N=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 to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions
BASELINE is defined as Day 1, Pre-dose of the corresponding study period

PROGRAM PATH: X:\~\QSC207031\~\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
A similar table will be produced for triplicate readings i.e., Table [14.5.2.2.2]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.5.2.1.3
ECGs
QTcB and QTcF Categorical Data
Summary Statistics: Safety Analysis Set
Part 1

			QTcF Interval (msec)				QTcF Interval Increase (msec)			…
Treatment	Time Point	N#	<=450 n(%)	451-480 n(%)	481-500 n(%)	>500 n(%)	=<30 n(%)	31-60 n(%)	>60 n(%)	…
ALL PLACEBO	BASELINE	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)				
(N=XX)	TIMEPOINT 1	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
	TIMEPOINT 2	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
	…	…	…	…	…	…	…	…	…	
ALL ACTIVE	BASELINE	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
(N=XX)	TIMEPOINT 1	xx	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
	TIMEPOINT 2	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 dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively

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:\~\QSC207031\~\TFLS\PRODUCTION\TAB-XX DDMMMYYYY HH:MM

Programming note: This table will be continued for QTcB
A similar table will be produced for Part 3, with a column for Visit included before time point column, i.e., Table [14.5.2.3.3]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.5.2.2.3
ECGs
QTcB and QTcF Categorical Data
Summary Statistics: Safety Analysis Set
Part 2

			QTcF Interval (msec)				QTcF Interval Increase (msec)			
Treatment	Time Point	N#	<=450 n(%)	451-480 n(%)	481-500 n(%)	>500 n(%)	<=30 n(%)	31-60 n(%)	>60 n(%)	…
XX mg FAST	BASELINE		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)				
(N=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)	…
XX mg FED	BASELINE		xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)				
(N=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 to receive both treatments (i.e., Regimen 6 and Regimen 7) in a randomised manner over the two separate dosing occasions
BASELINE is defined as Day 1, Pre-dose of the corresponding study period
Categories for QTcF interval and QTcF interval increases are based on ICH E14 guidelines
N# is the number of subjects with a value at baseline and the relevant post-dose time point. It is the denominator for calculating the percentages of subjects, n indicates the number of subjects with observations at the given time point

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Programming note: This table will be continued for QTcB

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Medicines for Malaria Venture Page x of y
Protocol: MMV_MMV367_21_01

TABLE 14.6.1.1
Taste Assessments: Taste Aspect
Summary Statistics: Taste Analysis Set
Part 1

<Taste Aspect>

		MMV367		
Statistic	Pooled Placebo (N=XX)	100 mg (N=XX)	300 mg (N=XX)	....
n	xx	xx	xx	…
Mean	xx.x	xx.x	xx.x	…
SD	xx.x	xx.x	xx.x	…
Median	xx.x	xx.x	xx.x	…
Min	xx.x	xx.x	xx.x	…
Max	xx.x	xx.x	xx.x	…
GRADE 1 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
GRADE 2 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
GRADE 3 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
GRADE 4 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
GRADE 5 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
GRADE 6 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
GRADE 7 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
GRADE 8 n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)	…
GRADE 9 n (%)	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 dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
Key for grade: 1=Dislike extremely, 2=Dislike very much, 3=Dislike moderately, 4=Dislike slightly, 5=Neither like nor dislike, 6=Like slightly, 7=Like moderately, 8=Like very much, 9=Like extremely

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Programming note: This table will be continued for all dose levels.
A separate page will be used for each taste aspect with the relevant subheading
A similar table will be produced for Overall Acceptability, i.e., Table [14.6.1.2]

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Medicines for Malaria Venture
Protocol: MMV_MMV367_21_01

TABLE 14.6.1.3
Taste Assessments: Taste Aspects including Overall Acceptability
Statistical Analysis Results: Taste Analysis Set
Part 1

Wilcoxon Rank Sum Test: <Taste Aspect>

	Test		Reference		Difference	90% CI	p-value
Comparison	n	Median	n	Median	(1)	(2)	(3)
100 mg vs Pooled Placebo	xx	xxx	xx	xxx	xxx	(xx.xx, xx.xx)	0.xxx
300 mg vs Pooled Placebo	xx	xxx	xx	xxx	xxx	(xx.xx, xx.xx)	0.xxx
…	…	…	…	…	…	…	…

Note: The data in this table are presented in listing x.x
All subjects were planned to receive a single dose of either MMV367 or matching placebo
All Placebo/All Active relate to placebo or active subjects pooled over all cohorts, respectively
Results obtained from non-parametric Wilcoxon rank sum test
(1) Hodges-Lehmann median difference for test (Regimens 1 to 5 – Pooled Placebo), (2) Confidence interval for Hodges-Lehmann median difference (3) p-value from Wilcoxon rank sum test for the null hypothesis that the Hodges-Lehmann median difference is zero
Hodges-Lehmann median difference is not necessarily the same as the difference between medians

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Programming note: This table will be continued for all dose level comparisons

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Appendix 1 Schedule of Assessments: Part 1 (Cohorts 1A to 1E)

	Screening	Admission	Resident In-clinic					Return Visit[b]	End of Study Visit[b]
Study Day	**-28 to -2**	**-1**	**1**	**2**	**3**	**4**	**5[a]**	**7**	**15**
General Assessments									
Informed Consent	X								
Medical History	X	X[c]							
Weight, Height and BMI	X	X[d]						X[d]	X[d]
Vein Assessment	X								
Carbon Monoxide Breath Test	X	X							
Drug Screen	X	X							
Alcohol Breath Test	X	X							
SARS-CoV-2 Antigen[e]	X	X							
Randomisation[f]			X						
IMP Administration[g]			X						
Safety Assessments									
BDI-II Questionnaire	X	X							
Physical Examination	X	X							
Targeted (symptom driven) Physical Examination[h]			X	X	X	X	X	X	X
Safety Labs[i]	X	X		X			X	X	X
Urinalysis[i]	X	X		X			X	X	X
Follicle-stimulating Hormone (FSH) Test[j]	X								
Serum Pregnancy Test[k]	X								
Urine Pregnancy Test[k]		X						X	X
Single 12-Lead ECGs[l]	X	X	X	X					X
Triplicate 12-Lead ECGs[l]					X	X	X	X	
Holter Periods[m]			X	X					
Telemetry[n]			X						
Vital Signs[o]	X	X	X	X	X	X	X	X	X
Orthostatic Vital Signs[o]	X		X	X				X	
Adverse Events	< ----------X---------->								
Prior and Concomitant Medication	< ----------X---------- >								
PK/Metabolite ID/Pharmacogenetic Assessments									
Plasma Samples for MMV367[p]			X	X	X	X	X	X	
Urine Samples for MMV367[pq]			X	X	X				

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Study Day	Screening	Admission	Resident In-clinic					Return Visit[b]	End of Study Visit[b]
	-28 to -2	-1	1	2	3	4	5[a]	7	15
Blood Sample for CYP/UGT polymorphism[r]			X						
Taste/Palatability Assessments									
Taste/Palatability Questionnaire[s]									

Eligibility will be re-assessed at admission/pre-dose on Day 1.
[a] Discharge from clinical unit
[b] Participants will return for an outpatient visit on Day 7 and an end of study visit on Day 15 (±1 day).
[c] Update only
[d] Weight only
[e] It is planned that testing will comprise an antigen test performed at screening and on Day -1 prior to admission to the clinical unit. The definition of the COVID-19 testing time points are participant 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.
[f] Participants will be randomised on the morning of Day 1 prior to dosing
[g] Participants will receive a single dose of MMV367 or placebo on Day 1
[h] Targeted (symptom driven) physical examination of the relevant body system(s) as clinically indicated, as per the investigator's judgement
[i] Haematology, coagulation and clinical chemistry and urinalysis at each time point, including virology and FSH (post-menopausal female participants only) at screening. See study protocol for safety blood sample time points.
[j] Post-menopausal female participants only
[k] All female participants
[l] See study protocol for single and triplicate 12-lead ECG time points. For triplicate ECGs, participants will be required to rest in the supine position with no external stimuli (e.g. music or television) for 15 min prior to the nominal time point where a triplicate ECG is scheduled.
[m] Continuous Holter monitoring will commence at least 1.5 h prior to dosing until at least 24 h post-dose. Participants will be required to rest in the supine position with no external stimuli (e.g. music or television) for 15 min prior to the nominal time point where an ECG extraction is scheduled. See study protocol for Holter extraction time points.
[n] Telemetry (continuous ECG monitoring) will commence at least 30 min before dosing until at least 12 h post-dose.
[o] Blood pressure, heart rate and respiratory rate at all time points. Oral temperature will be measured at screening/admission only. See study protocol for vital signs and orthostatic vital signs time points.
[p] See study protocol for PK sample time points. Metabolite profiling of MMV367 in plasma and urine will be performed using existing PK samples (pooled residual samples).
[q] Urine collection in Cohorts 1C and 1D only.
[r] Sample will be taken prior to IMP administration (≤2 h before dosing).
[s] The taste/palatability questionnaire will be completed immediately after IMP administration, see study protocol for details.

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Appendix 2 Schedule of Assessments: Part 2

			Resident in Clinic												End of Study Visit
	Screening	Admi-ssion	Period 1							Period 2					
Study Day	-28 to -2	-1	1	2	3	4	5	6	7	8	9	10	11	12[a]	14[b]
General Assessments															
Informed Consent	X														
Medical History	X	X[c]													
Weight, Height and BMI	X	X[d]													
Vein Assessment	X														
Carbon Monoxide Breath Test	X	X													
Drug Screen	X	X													
Alcohol Breath Test	X	X													
SARS-CoV-2 Antigen[e]	X	X													
Randomisation[f]			X												
IMP Administration[g]			X							X					
Safety Assessments															
BDI-II Questionnaire	X	X													
Physical Examination	X	X													
Targeted (symptom driven) Physical Examination[h]			X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Labs[i]	X	X		X			X		X		X			X	X
Urinalysis[i]	X	X		X			X		X		X			X	X
Follicle-stimulating Hormone (FSH) Test[j]	X														
Serum Pregnancy Test[k]	X														
Urine Pregnancy Test[k]		X													X
Single 12-Lead ECGs[l]	X	X	X	X						X	X				X
Triplicate 12-Lead ECGs[l]					X	X	X		X			X	X	X	
Holter Periods[m]			X	X						X	X				
Telemetry[n]			X							X					
Vital Signs[o]	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Adverse Events	< ----------X---------- >														
Prior and Concomitant Medication	< ----------X---------- >														

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PK/Pharmacogenetic Assessments															
Plasma Samples for MMV367[p]			X	X	X	X	X		X	X	X	X	X	X	X
Blood Sample for CYP/UGT polymorphism[q]			X												

Eligibility will be re-assessed at admission/pre-dose on Day 1.
[a] Discharge from clinical unit
[b] Participants will return for an end of study visit on Day 14 (± 1 day).
[c] Update only
[d] Weight only
[e] It is planned that testing will comprise an antigen test performed at screening and on Day -1 prior to admission to the clinical unit. The definition of the COVID-19 testing time points are participant 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.
[f] Participants will be randomised on the morning of Period 1, Day 1 prior to dosing
[g] Participants will receive a single dose of MMV367 on Day 1 and Day 8 in the fed or fasted state
[h] Targeted (symptom driven) physical examination of the relevant body system(s) as clinically indicated, as per the investigator's judgement
[i] Haematology, coagulation, clinical chemistry and urinalysis at each time point, including virology and FSH (post-menopausal female participants only) at screening.
[j] Post-menopausal female participants only
[k] All female participants
[l] See study protocol for single and triplicate 12-lead ECG time points. For triplicate ECGs, participants will be required to rest in the supine position with no external stimuli (e.g. music or television) for 15 min prior to the nominal time point where a triplicate ECG is scheduled.
[m] Continuous Holter monitoring will commence at least 1.5 h prior to dosing until at least 24 h post-dose. Participants will be required to rest in the supine position with no external stimuli (e.g. music or television) for 15 min prior to the nominal time point where an ECG extraction is scheduled. See study protocol for Holter extraction time points.
[n] Telemetry (continuous ECG monitoring) will commence at least 30 min before dosing until at least 12 h post-dose.
[o] Blood pressure, heart rate and respiratory rate at all time points. Oral temperature will be measured at screening and admission only. See study protocol for vital signs time points.
[p] See study protocol for PK sample time points.
[q] Sample will be taken prior to IMP administration (≤2 h before dosing).

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Appendix 3 Schedule of Assessments: Part 3 (Cohorts 3A to 3C)

Study Day	Screening	Admission	Resident In-clinic							Return Visit[b]	End of Study Visit[b]
	-28 to -2	-1	1	2	3	4	5	6	7[a]	9	17
General Assessments											
Informed Consent	X										
Medical History	X	X[c]									
Weight, Height and BMI	X	X[d]								X[d]	X[d]
Vein Assessment	X										
Carbon Monoxide Breath Test	X	X									
Drug Screen	X	X									
Alcohol Breath Test	X	X									
SARS-CoV-2 Antigen[e]	X	X									
Randomisation[f]			X								
IMP Administration[g]			X	X	X						
Safety Assessments											
BDI-II Questionnaire	X	X									
Physical Examination	X	X									
Targeted (symptom driven) Physical Examination[h]			X	X	X	X	X	X	X	X	X
Safety Labs[i]	X	X			X		X		X	X	X
Urinalysis[i]	X	X			X		X		X	X	X
Follicle-stimulating Hormone (FSH) Test[j]	X										
Serum Pregnancy Test[k]	X										
Urine Pregnancy Test[k]		X								X	X
Single 12-Lead ECGs[l]	X	X	X		X	X					X
Triplicate 12-Lead ECGs[l]				X		X	X	X	X	X	
Holter Periods[m]			X	X	X	X					
Vital Signs[n]	X	X	X	X	X	X	X	X	X	X	X
Orthostatic Vital Signs[n]	X		X	X	X	X				X	
Adverse Events	< ----------X---------- >										
Prior and Concomitant Medication	< ----------X---------- >										
PK/Pharmacogenetic Assessments											
Plasma Samples for MMV367[o]			X	X	X	X	X	X	X	X	
Blood Sample for CYP/UGT polymorphism[p]			X								

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Eligibility will be re-assessed at admission/pre-dose on Day 1.
[a] Discharge from clinical unit
[b] Participants will return for an outpatient visit on Day 9 and an end of study visit on Day 17 (± 1 day).
[c] Update only
[d] Weight only
[e] It is planned that testing will comprise an antigen test performed at screening and on Day -1 prior to admission to the clinical unit. The definition of the COVID-19 testing time points are participant 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.
[f] Participants will be randomised on the morning of Day 1 prior to dosing
[g] Participants will receive a dose of MMV367 or placebo in the morning on Days 1, 2 and 3
[h] Targeted (symptom driven) physical examination of the relevant body system(s) as clinically indicated, as per the investigator's judgement
[i] Haematology, coagulation, clinical chemistry and urinalysis at each time point, including virology and FSH (post-menopausal female participants only) at screening.
[j] Post-menopausal female participants only
[k] All female participants
[l] See study protocol for single and triplicate 12-lead ECG time points. For triplicate ECGs, participants will be required to rest in the supine position with no external stimuli (e.g. music or television) for 15 min prior to the nominal time point where a triplicate ECG is scheduled.
[m] Continuous Holter monitoring will commence at least 1.5 h prior to dosing until at least 24 h post-dose. Participants will be required to rest in the supine position with no external stimuli (e.g. music or television) for 15 min prior to the nominal time point where an ECG extraction is scheduled. See study protocol for Holter extraction time points.
[n] Blood pressure, heart rate and respiratory rate at all time points. Oral temperature will be measured at screening and admission only. See study protocol for vital signs and orthostatic vital signs time points.
[o] See study protocol for PK sample time points.
[p] Sample will be taken prior to IMP administration (≤2 h before dosing).

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Appendix 4 Part 1 (All Cohorts) Safety and Pharmacokinetic Assessment Time Points (Days 1 to 7)

Study Day	Time point	Plasma PK	Urine PK[a]	Safety Labs and Urinalysis	Holter Extractions	Vital Signs[b]	Orthostatic Vital Signs	Single 12-lead ECGs	Triplicate 12-lead ECGs
1	-1.5 h				X			X	
	-1 h				X			X	
	Pre-dose (-0.5 h)	X	X		X	X	X	X	
	0 h		0 to 6 h						
	0.5 h	X			X	X		X	
	1 h	X			X			X	
	2 h	X			X	X	X	X	
	3 h	X			X			X	
	4 h	X			X	X	X	X	
	5 h	X						X	
	6 h	X	6 to 12 h		X	X		X	
	8 h	X			X	X		X	
	10 h					X			
	12 h	X	12 to 24 h		X	X	X	X	
2	24 h	X	24 to 48 h	X	X	X	X	X	
3	48 h	X	48 to 72 h			X			X
4	72 h	X				X			X
5	96 h	X		X		X			X
7	144 h	X		X		X	X		X

a Part 1, Cohorts 1C and 1D only
[b] Blood pressure, heart rate and respiratory rate at all time points.

Allowable windows for PK blood sampling, vital signs assessments and ECGs can be found in: Section 13.1, 14.6 and 14.7 of the study protocol.

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Appendix 5 Part 2 Safety and Pharmacokinetic Assessment Time Points (Days 1 to 14)

Study Day	Time point	Plasma PK	Safety Labs and Urinalysis	Holter Extractions	Vital Signs[a]	Single 12-lead ECGs	Triplicate 12-lead ECGs
1	-1.5 h			X		X	
	-1 h			X		X	
	Pre-dose (-0.5 h)	X		X	X	X	
	0 h						
	0.5 h	X		X	X	X	
	1 h	X		X		X	
	2 h	X		X	X	X	
	3 h	X		X		X	
	4 h	X		X	X	X	
	5 h	X					
	6 h	X		X	X	X	
	7 h						
	8 h	X		X	X	X	
	10 h				X		
	12 h	X		X	X	X	
2	24 h	X	X	X	X	X	
3	48 h	X			X		X
4	72 h	X			X		X
5	96 h	X	X		X		X
7	144 h	X	X		X		X
8	-1.5 h			X		X	
	-1 h			X		X	
	Pre-dose (-0.5 h)	X		X	X	X	
	0 h						
	0.5 h	X		X	X	X	

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Study Day	Time point	Plasma PK	Safety Labs and Urinalysis	Holter Extractions	Vital Signs[a]	Single 12-lead ECGs	Triplicate 12-lead ECGs
	1 h	X		X		X	
	2 h	X		X	X	X	
	3 h	X		X		X	
	4 h	X		X	X	X	
	5 h	X					
	6 h	X		X	X	X	
	7 h						
	8 h	X		X	X	X	
	10 h				X		
	12 h	X		X	X	X	
9	24 h	X	X	X	X	X	
10	48 h	X			X		X
11	72 h	X			X		X
12	96 h	X	X		X		X
14	144 h	X	X		X		X

[a] Blood pressure, heart rate and respiratory rate at all time points.

Allowable windows for PK blood sampling, vital signs assessments and ECGs can be found in: Sections 13.1, 14.6 and 14.7 of the study protocol.

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Appendix 6 Part 3 Safety and Pharmacokinetic Assessment Time Points (Days 1 to 9)

Study Day	Time point	Plasma PK	Safety Labs and Urinalysis	Holter Extractions	Vital Signs[a]	Orthostatic Vital Signs	Single 12-lead ECGs	Triplicate 12-lead ECGs
1	-1.5 h			X			X	
	-1 h			X			X	
	Pre-dose (-0.5 h)	X		X	X	X	X	
	0 h							
	0.5 h	X		X				
	1 h	X		X	X		X	
	2 h	X		X	X	X	X	
	3 h	X		X	X		X	
	4 h	X		X	X	X	X	
	5 h	X						
	6 h	X		X	X	X	X	
	8 h	X		X	X		X	
	10 h			X	X			
	11 h							
	12 h	X		X	X	X	X	
2	-1.5 h							X
	-1 h							X
	Pre-dose (-0.5 h)[b]	X		X (Day 1, 24 h)	X	X (Day 1, 24 h)		X
	0 h							
	1 h							
	2 h							
	3 h							
	4 h	X			X			X
	5 h							
	6 h	X			X			X
	7 h							
	8 h							

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Study Day	Time point	Plasma PK	Safety Labs and Urinalysis	Holter Extractions	Vital Signs[a]	Orthostatic Vital Signs	Single 12-lead ECGs	Triplicate 12-lead ECGs
	9 h							
	10 h				X			
	11 h							
	12 h	X			X			X
3	-1.5 h			X			X	
	-1 h			X			X	
	Pre-dose (-0.5 h)[c]	X	X (Day 1, 48 h)	X (Day 1, 48 h)	X	X	X	
	0 h							
	0.5 h	X		X	X		X	
	1 h	X		X	X		X	
	2 h	X		X	X	X	X	
	3 h	X		X	X		X	
	4 h	X		X	X	X	X	
	5 h	X						
	6 h	X		X	X	X	X	
	7 h							
	8 h	X		X	X		X	
	9 h							
	10 h			X	X			
	11 h			X				
	12 h	X		X	X	X	X	
4	24 h	X		X	X	X	X	
	36 h	X			X			X
5	48 h	X	X		X			X
6	72 h	X			X			X
7	96 h	X	X		X			X
9	144 h	X	X		X	X		X

a Blood pressure, heart rate and respiratory rate at all time points.
[b] 24 h post-dose Day 1 sample will be taken pre-dose on Day 2

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[c] 24 h post-dose Day 2 sample will be taken pre-dose on Day 3

Allowable windows for PK blood sampling, vital signs assessments and ECGs can be found in: Sections 13.1, 14.6, 14.7 of the study protocol.

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Appendix 7 Example Taste/Palatability Questionnaire

An example of the taste/palatability questionnaire can be found on the next page.

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Study Part: | **Test Product:** | **Participant Number:**

Participant Initials:

Start time:
(to be completed within 10 minutes of tasting)

Date:

Question 1
All aspects considered (smell, sweetness, bitterness, flavour, mouthfeel/texture, grittiness, and aftertaste), how would you rate your overall liking of this product:

NOTE: Tick 1 box below in blue or black pen

Dislike extremely	Dislike very much	Dislike moderately	Dislike slightly	Neither like nor dislike	Like slightly	Like moderately	Like very much	Like extremely

Question 2
We want to know how much you like certain aspects of the product: smell, sweetness, bitterness, flavour, mouthfeel/texture, grittiness, and aftertaste.
NOTE: Tick 1 box in the row for each aspect

	Dislike extremely	Dislike very much	Dislike moderately	Dislike slightly	Neither like nor dislike	Like slightly	Like moderately	Like very much	Like extremely	N/A
Smell										
Sweetness										
Bitterness										
Flavour										
Mouthfeel/texture										
Grittiness										
Aftertaste										

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Approved Date: 19 Dec 2022

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