CLINICAL STUDY PROTOCOL

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

Short Study Title: First-in-Human Study to Assess the Safety, Tolerability and Pharmacokinetics of MMV367

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3.0	Non-substantial Amendment	08 Sep 2022
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Details of the amendment above can be found in Appendix 10.

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3 Synopsis

Sponsor:	**Drug Substance:**	**EudraCT No.:**
Medicines for Malaria Venture	MMV367	2022-000918-33

Title of Study:

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

Principal Investigator:

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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

Methodology:

Part 1: Single Ascending Dose Cohorts

Part 1 will be a double-blinded, randomised, placebo-controlled, single ascending dose (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 and will receive one of the following regimens according to the randomisation schedule:

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

[a] Predicted dose. 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.

The data obtained from each cohort (safety and PK) will undergo a formal review by the safety advisory committee (SAC). The SAC will determine if it is safe 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.

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 (Appendix 8), 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.

The following regimens will be administered according to the randomisation schedule:

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

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.

The following regimen(s) will be administered according to the randomisation schedule:

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

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

Parts 2 and 3 may be conducted before completion of Part 1 provided that this is justified by PK and safety data obtained from completed cohorts in Part 1. The total amount of active IMP administered as multiple doses in Part 3 will be no greater than the maximum safe and well tolerated dose in Part 1, dosed at a single dose level. Parts 2 and 3 may be conducted in parallel.

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 once daily regimen.

Study Design:

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.

Part 1: Single Ascending Dose Cohorts

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). Each cohort will follow the same study design.

Participants will also complete a written taste/palatability questionnaire individually and privately following administration of the IMP.

Part 2: Food Effect Cohort

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 discharge from the study on Day 14 (± 1 day).

Part 3: Multiple Dose Cohort(s)

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). Each cohort will follow the same study design.

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 Investigator's Brochure, 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.

Number of Participants Planned:

In Part 1, 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 investigational medicinal product (IMP).

In Part 2, it is planned to enrol 8 healthy male and female participants to ensure data in a minimum of 6 participants.

In Part 3, it is planned to enrol 8 healthy male and female participants per cohort (if optional cohorts are utilised) to ensure data in a minimum of 4 participants (per cohort) on active IMP.

Participants withdrawn due to an IMP-related adverse event (AE) will not be replaced. Participants who are withdrawn for other reasons may be replaced as required by agreement between the investigator and the sponsor to ensure sufficient evaluable participants.

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).

Duration of Study:

The estimated time from screening until the end of study visit is approximately 6 weeks for Parts 1, 2 and 3.

Main Inclusion Criteria:

Healthy males and healthy females aged 18 to 55 years inclusive at the time of signing informed consent.

Body mass index (BMI) of 18.0 to 32.0 kg/m^2 as measured at screening.

Investigational Medicinal Product, Dose and Mode of Administration:

The following IMP will be used in this clinical study.

IMP Name	Dose	Route of Administration
MMV367 Dispersible Granules, 250 mg/g (25% w/w)	Starting dose 100 mg[a]	Oral, Fasted (Parts 1, 2 and 3) or Oral, Fed (Part 2)
Placebo for MMV367 Dispersible Granules, 250 mg/g (25% w/w)	N/A	Oral, Fasted (Parts 1 and 3)

[a] Doses are not predicted to exceed the AUCcap set at 376 µg.h/mL, which is based on linear PK projections for a putative dose of 2000 mg or Cmaxcap set at 23.8 µg/mL, which is based on mean Cmax at the NOAEL in dog

The IMP will be dispersed in sterile water. Immediately after administration of the oral solution, the dosing vessel will be rinsed with water and participants will consume the rinse solution. During dosing, participants will consume up to a maximum total volume of 500 mL (including the dosing volume and volume of water used to rinse the dosing vessel) depending on the dose level. If required, additional water in 50 mL aliquots may be given with the test product.

Pharmacokinetic Assessments:

Blood samples for PK analysis will be collected at regular time intervals. The plasma concentration-time data for MMV367 will be analysed by Quotient Sciences using industry standard software (WinNonlin v8.3 or a more recent version, Certara USA, Inc., USA) and appropriate non-compartmental techniques to obtain estimates of the following parameters, where possible and appropriate:

Plasma Pharmacokinetic Parameters: Part 1 and 2

Parameter	Definition
Tmax	Time of maximum observed concentration
Cmax	Maximum observed concentration
AUC(0-24)	Area under the curve from time 0 to 24 h post-dose
AUC(0-48)	Area under the curve from time 0 to 48 h post-dose
AUC(0-last)	Area under the curve from time 0 to the time of last measurable concentration
AUC(0-inf)	Area under the curve from time 0 extrapolated to infinity
T1/2	Terminal elimination half-life
CL/F	Total body clearance calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown
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
Frel Cmax	Relative bioavailability based on Cmax (Part 2 fed dosing only)
Frel AUC(0-last)	Relative bioavailability based on AUC(0-last) (Part 2 fed dosing only)
Frel AUC(0-inf)	Relative bioavailability based on AUC(0-inf) (Part 2 fed dosing only)

Plasma Pharmacokinetic Parameters: Part 3

Parameter	Definition
Tmax	Time of maximum observed concentration
Cmax	Maximum observed concentration
AUC(0-tau)	Area under the curve for the defined interval between doses (tau)
T1/2	Terminal elimination half-life (Day 3 only)
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)
Vz/Ftau	Apparent volume of distribution based on the terminal phase calculated using AUC(0-tau) after repeated extravascular administration where F (fraction of dose bioavailable) is unknown (Day 3 only)
AR Cmax	Accumulation ratio based on Cmax repeated dose/Cmax single dose (Day 3 only)
AR AUC	Accumulation ratio based on AUC(0-tau) repeated dose/AUC(0-tau) single dose (Day 3 only)

Analysis of drug related QT/QTc interval changes relative to plasma PK concentrations will be conducted. This analysis will be performed on the analysis set for intensive cardiac assessment. Concentration/QTc modelling may be performed after completion of the CSR and will be reported separately.

In Part 1 Cohorts 1C and 1D, urine samples will be collected at regular time intervals provided a future bioanalytical method is available. Urine concentration data for MMV367 will be analysed by Quotient Sciences and reported in an addendum to the CSR or in a separate report. Estimates of the parameters of the following parameters in urine will be obtained where possible and appropriate:

Urine Pharmacokinetic Parameters: Part 1, Cohorts 1C and 1D only

Parameter	Definition
CLr	Renal clearance calculated using plasma AUC
Ae	Amount excreted
CumAe	Cumulative amount excreted
%Ae	Percentage of dose excreted
Cum%Ae	Cumulative percentage of dose excreted

Metabolite Profiling and Identification Assessment:

Metabolite profiling of MMV367 in plasma and urine will be performed using existing PK samples (pooled residual samples) collected in Part 1. Potential metabolites will be identified using liquid chromatography-mass spectrometry analysis. If results suggest that a major metabolite is present in plasma (e.g. greater than 10% of circulating MMV367 in plasma based on peak AUCs), metabolite quantification and PK analysis in plasma will be performed provided a future bioanalytical method is available. These results may be reported in an addendum to the CSR or in a separate report.

Taste/Palatability Questionnaire

Taste/palatability will be assessed in Part 1 using a questionnaire. The questionnaire will ask participants to rate the overall acceptability of palatability, with additional questions asked on specific palatability attributes (smell, sweetness, bitterness, flavour, mouth feel/texture, grittiness and aftertaste).

Safety Assessments:

The safety assessments to be conducted are:

- AE monitoring
- 12-lead ECGs
- Holter ECG monitoring
- Telemetry
- Vital signs
- Clinical laboratory tests (clinical chemistry, haematology, coagulation and urinalysis)
- Physical examinations

Statistical Methodology:

Assessment of Dose Proportionality

For Part 1, dose proportionality will be assessed using a power model approach using log-transformed Cmax, AUC(0-last) and AUC(0-inf) values, including data from up to 5 different dose levels, i.e. general linear model including log dose as a fixed effect and log PK parameter as the dependent variable. The estimate obtained for β together with its 90% confidence interval (CI) will be presented along with the number of participants and the geometric means. The resulting estimate slope (β) and 90% CI is a measure of dose proportionality; the relationship is considered dose proportional when β = 1.

Assessment of Taste Questionnaire Data

In Part 1, formal statistical analysis will be performed on the scores of each taste attribute and overall acceptability, in the comparison of each dose level of MMV367 to the pooled placebos, using non-parametric methods. Hodges-Lehmann estimation methods will be used to estimate the median difference between each dose level and the pooled placebos. The associated 95% CI will be calculated for the estimate. The p-value will be calculated from the Wilcoxon Rank Sum Test (Mann-Whitney-Wilcoxon Test) for the test of the null hypothesis that the difference between the medians of each dose level and

the pooled placebos is equal to zero, with the alternative hypothesis being that the difference is not equal to zero.

The number of participants and the median score for each treatment will be presented together with the Hodges-Lehmann estimate of the median difference and associated 90% CI. In addition, the p-value from the Wilcoxon Rank Sum Test will also be presented.

Assessment of Food Effect

In addition, for Part 2, formal statistical analysis will be performed, at a minimum, on the following PK parameters: Cmax, AUC(0-last) and AUC(0-inf) to assess for the effects of food. The PK parameters will undergo a natural logarithmic transformation and will be analysed using a mixed effect model with terms for fed/fasted status and period fitted as fixed effects and participant fitted as a random effect. The adjusted mean difference between the fed and fasted states, and the associated 90% CI obtained from the model are back transformed on the log scale to obtain the adjusted geometric mean ratio and 90% CI of the ratio. These will be presented together with the p-value from the fed/fasted comparison.

Sample Size and Power:

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.

In Parts 1 and 3, a participant will be considered evaluable if they have received study drug and completed safety and PK 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 study drug and completed safety and PK assessments up to 96 h post-dose in both periods.

4 List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
BDI-II	Beck Depression Inventory
BMI	body mass index
CI	confidence interval
CLcr	creatinine clearance
COVID-19	Coronavirus Disease 2019
CSPM	Clinical Sample Processing Manual
CV%	coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
DMP	data management plan
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
FIH	first-in-human
FSH	follicle stimulating hormone
GCP	good clinical practice
GLP	good laboratory practice
HBsAg	hepatitis B surface antigen
HCV Ab	hepatitis C virus antibody
HED	human equivalent dose
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	investigational medicinal product
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
NOAEL	No-Observed-Adverse-Effect Level
PBPK	physiological-based pharmacokinetic
PIS	Participant Information Sheet

PK	pharmacokinetic(s)
QA	quality assurance
QD	once daily
QTcB	Corrected QT interval by Bazett's formula
QTcF	Corrected QT interval by Fridericia's formula
RAP	Reporting and Analysis Plan
SAC	safety advisory committee
SAD	single ascending dose
SAE	serious adverse event
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoC	standard of care
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
WOCBP	woman of childbearing potential

The pharmacokinetic definitions used in this study are presented in Section 15.3.

5 Background Information

5.1 Introduction

MMV367 is a first in class, fast acting, orally bioavailable blood stage inhibitor of *Plasmodium falciparum*. It is highly active against different *Plasmodium falciparum* mutants and field panels exhibiting various resistance profiles, thus demonstrating absence of cross resistance to other antimalarial drugs. MMV367 is being developed primarily for the curative treatment of acute uncomplicated malaria, due to *Plasmodium falciparum* in adults and children, as a single dose regimen (best case) or up to a 3-day treatment, in a fixed-dose combination with another active and safe non-artemisinin antimalarial drug.

Malaria is a major infectious disease caused by *Plasmodium* parasites and transmitted by infected female *Anopheles* mosquitoes. Despite the fact that five different species can cause malaria in humans (*falciparum, vivax, malariae, ovale* and *knowlesi*), *Plasmodium falciparum* is by far the deadliest species and is responsible for the high mortality. In 2020, there were an estimated 241 million cases of malaria, an increase of approximately 14 million cases compared to 2019. Deaths reached 627000 compared to 558000 in the previous year. Most of the deaths occurred in the African region (94%) [1].

Historically, antimalarials have been designed to kill the intraerythrocytic stages of the parasite lifecycle that are directly responsible for the symptoms of the disease. Based on a high-throughput whole cell phenotypic screen, a new pyrrolidinamide class of antimalarials was selected for further research [2]. Within this novel antimalarial pyrrolidinamide series, MMV367 was identified as the most balanced compound; it is a compound able to kill parasite asexual blood stages.

None of the current clinical antimalarials share a similar mode of action and/or mechanism of resistance. It is anticipated that MMV367 exerts a novel antimalarial mechanism.

The clinical development programme will aim to evaluate the safety and efficacy of MMV367 in the treatment of acute uncomplicated malaria in adults and children. In this first-in-human (FIH) study, the safety, tolerability and pharmacokinetics (PK) of MMV367 will be assessed in healthy adult participants.

5.2 Investigational Medicinal Product

The investigational medicinal product (IMP) that will be used in this clinical study is presented in Table 1.

Table 1 Investigational Medicinal Product

IMP Name	Dose	Route of Administration
MMV367 Dispersible Granules, 250 mg/g (25% w/w)	Starting dose 100 mg[a]	Oral, Fasted (Parts 1, 2 and 3) or Oral, Fed (Part 2)
Placebo for MMV367 Dispersible Granules, 250 mg/g (25% w/w)	N/A	Oral, Fasted (Parts 1 and 3)

[a] Doses are not predicted to exceed the AUCcap set at 376 µg.h/mL, which is based on linear PK projections for a putative dose of 2000 mg or Cmaxcap set at 23.8 µg/mL, which is based on mean Cmax at the NOAEL in dog

The IMP is an un-licensed medicinal product for use only in the proposed clinical trial.

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

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

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

5.3 Previous Study Findings

Full details of previous non-clinical study findings can be found in the Investigator's Brochure (IB) [3]. A summary of the non-clinical findings is provided below. No clinical studies have been conducted with MMV367.

5.3.1 Non-clinical Findings

5.3.1.1 Primary Pharmacology

MMV367 exhibited potent in vitro activity against asexual stages of both sensitive and multi-drug resistant *Plasmodium falciparum* strains including fresh clinical isolates. Furthermore, MMV367 was active against other *Plasmodium* species (*knowlesi* and *vivax*) although with reduced potency compared to falciparum. The in vitro and in vivo parasite killing rates were high and comparable to artemisinins. The in vitro frequency of spontaneous resistance measured for MMV367 was low. In vivo, the compound demonstrated good oral efficacy in a *Plasmodium falciparum* murine model, with a potency comparable to or greater than marketed antimalarial drugs.

Preliminary target identification efforts conducted in order to characterise the mode of action of MMV367 suggest the involvement of the acyl CoA synthetase (ACS) pathway. This putative new mode of action could offer differentiation against all other antimalarials in clinical use or currently in development, which is of paramount importance in the development of de novo combination treatments, thereby ultimately avoiding the emergence of resistance. Model simulations predicted that a single human dose of 440 mg of MMV367 can potentially decrease 12 logs parasitaemia burden in acute uncomplicated malaria, generally parasite burden in acute uncomplicated malaria is lower than 12 logs and, therefore, predicted reduction by 12 logs indicates robust and potent antimalarial activity. The same efficacy can potentially be obtained with a dose of 100 mg once daily (QD) for two consecutive days or 30 mg QD for three consecutive days.

Results from activity measurements of MMV367 against parasite sexual stages suggested that MMV367 inhibits parasite development in the mosquito, but without affecting the functionality of mature gametocytes, thereby indicating lack of activity of MMV367 against mature gametocytes.

Activity against Plasmodium falciparum liver stages

The potential of MMV367 to inhibit intrahepatocytic parasite development was assessed in an infected primary human hepatocyte assay. Salivary gland sporozoites, isolated from mosquitoes infected with NF175 *Plasmodium falciparum* were used to infect cultured human hepatocytes. The percentage of infected hepatocytes was determined by immunofluorescence staining and automated high content imaging. MMV367 was tested in nine dilutions; 10 µM to 1 nM or 1 µM to 0.1 nM. MMV367 was found to inhibit liver stage parasites at relatively low concentrations (half maximal inhibitory concentration = 1.7 to 29.3 nM).

5.3.1.2 Pharmacokinetics

High oral bioavailability was observed in rats, and moderate oral bioavailability for mice and dogs. Minipigs showed a low bioavailability. Based on a physiological-based pharmacokinetic (PBPK) model, it has been predicted that MMV367 shows a high oral bioavailability, moderate volume of distribution and low blood clearance in humans, with a predicted human half-life of 19 h. Results from in vitro studies with human hepatocytes suggested that MMV367 is metabolised slowly in humans (predicted liver elimination of 1.60 mL/min/Kg). MMV367 has a low potential for drug-drug interactions based on in vitro findings. Results from a PK study in dogs suggested that concomitant food intake may increase systemic exposure to MMV367. Toxicokinetic data indicated that at high doses, elimination of MMV367 is limited by the solubility resulting in a prolonged apparent half-life.

Following intravenous administration of MMV367 to mice, rats dogs and minipigs, clearance values were low in mice and rats but high for dogs and minipigs. Associated mean terminal half-lives ranged between 0.6 h (dogs) and 2.1 h (mice).

5.3.1.3 Safety Pharmacology and Toxicology

In line with ICH M3 (R2) [11] and a previous FIH conducted with another malaria drug candidate in the US [4], standard safety pharmacology studies and 7-day oral toxicity studies in rats and dogs were conducted to support a short treatment course from single dose to 3 days against acute uncomplicated malaria. These studies demonstrated that MMV367 has a low oral toxicity. In rats, 100, 300 and 1000 mg/kg/day doses were administered. In male rats, 300 mg/kg/day was well tolerated and was the No-Observed-Adverse-Effect-Level (NOAEL); the NOAEL was 100 mg/kg/day in female rats. In dogs, 100, 300 and 1000 mg/kg/day doses were administered, and the NOAEL was assessed at 300 mg/kg/day in males and females.

Microscopic findings in the adrenal glands (cortical hypertrophy with vacuolation) and thymus (atrophy) have been observed in the 7-day toxicology study in rats. Overall, these observations, which were not detected in dogs, are compatible with a transient and reversible stress-induced cortical hypertrophy and changes in lipid composition. While no signal for the human targets interfering with lipid metabolism were observed with MMV367, positive staining for adipophilin and negative staining for LAMP-2 were observed in the rat adrenal glands, suggesting the vacuoles were likely to be neutral fat, which is supportive of a transient and reversible effect.

MMV367 was not mutagenic in the Ames test, showed no clastogenic potential in the in vivo rat model and no DNA damage potential in the in vivo Comet test. Standard reproductive toxicity studies have not been conducted. In an in vitro study using the rat whole embryo culture assay, MMV367 showed no teratogenic potential.

The effect of MMV367 on central nervous system function was assessed in rats in a GLP-study. Rats (N=6/group) were given single oral doses (gavage) of MMV367 at 0 (vehicle control), 100, 300 and 1000 mg/kg. MMV367 did not induce signs of CNS toxicity in the primary observation test over a 24-h recording period.

The effect of MMV367 on cardiovascular function was assessed in a GLP-study of beagle dogs. Each dog received single oral administrations (gavage) of 0 (vehicle), 100, 300 and 1000 mg/kg of MMV367 in a randomised crossover fashion. The washout period between treatments was at least 48 h. Telemetry recordings lasted for 24 h after each administration.

MMV367 caused a slight and transient increase in arterial blood pressure at 1000 mg/kg. The effect reached its maximum at 2 h post-dose (125 ± 2 mmHg for mean arterial blood pressure vs. 108 ± 5 mm Hg with vehicle, i.e. +16% from controls, $p < 0.01$). At 1000 mg/kg MMV367, a slight but prolonged increased mean heart rate was observed. The effect was observed from 2 to 20 h post-dose but reached statistical significance at 12 h (94 ± 3 vs. 69 ± 5 bpm with vehicle, i.e. +36% from controls, $p < 0.01$). Lower doses had no effect on arterial blood pressure or heart rate.

Irrespective of the dose level, MMV367 had no statistically significant effects on core temperature, QT and QTc intervals, no substantial effects on the QA interval, pulse pressure, and rate pressure product, and no effects on the PR and the QRS interval duration. No arrhythmia or other changes in the morphology of the electrocardiograms (ECGs) that could be attributed to MMV367 were observed over the test period in any of the dogs.

The effect of MMV367 on respiratory function was evaluated in rats in a GLP-study. The rats received single oral administrations (gavage) of 0 (vehicle), 100, 300 and 1000 mg/kg of MMV367. Measurements took place over 24 h following administration of MMV367 or vehicle. At the highest dose (1000 mg/kg), MMV367 decreased peak inspiratory (-48%) and expiratory flows (-48%), tidal volume (-36%) and minute volume (-40% at 12 h and -60% at 24 h) from 6 h post-dose. The effects reached statistical significance at 12 and 24 h for minute volume and at 24 h for the other parameters. Lower doses had no substantial effects effect on respiratory function over the 24-hour test period.

5.3.2 Clinical Findings

MMV367 has not been administered to humans previously. This study will be the first time MMV367 will be administered in humans (FIH).

6 Rationale

6.1 Study Rationale

The main purpose of this FIH study with MMV367 is to generate safety, tolerability and PK data when MMV367 is first administered to healthy men and women as escalating single ascending doses (Part 1) under fasted conditions. In addition, the potential effect of food consumption (high-fat meal) on the PK and safety at the selected dose level will be assessed (Part 2) and 3-day multiple doses (Part 3) will be investigated.

The rationale for taking MMV367 into further development is the expectation that this compound could be effective for the treatment of acute uncomplicated *Plasmodium falciparum* malaria with a therapeutic regimen that would ideally be given in a fixed dose

combination as a single dose regimen (single dose-single cure treatment) but could also be used in a standard fixed dose combination regimen of up to 3 days treatment (QD administration). Prior to initial testing in malaria patients, the safety and the PK characteristics of the drug in healthy participants must be investigated in order to provide sufficient data to proceed with the proof-of-concept study in the patient population. Preliminary information regarding the impact of food will also support further recommendations for the clinical development programme.

Parts 1 and 3 of this study will be placebo-controlled to establish the frequency and magnitude of changes in safety endpoints that may occur in the absence of active treatment. As Part 2 of this study will administer single doses of a single formulation in a crossover design to evaluate food effect, Part 2 will be open-label.

Randomisation will be used in all three study parts to minimise bias in the assignment of participants to treatment groups, to increase the likelihood that known and unknown participant attributes (e.g. demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of comparisons across dose groups. Blinded treatment will be used in Parts 1 and 3 to reduce potential bias during data collection and evaluation of clinical endpoints.

In Parts 1 and 3, to protect the safety of participants enrolled, a sentinel dosing design will be followed for all cohorts: 1 participant will receive active IMP and 1 participant will receive matching placebo initially. The remaining 6 participants (5 active, 1 placebo) will be dosed approximately 96 h post-dose (Part 1)/post-final dose (Part 3); the decision to dose the remaining participants will be made based on the available safety data. After review of the safety data up to 96 h post-dose (Part 1)/post-final dose (Part 3), the investigator, or medically qualified designees who are 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 (main group).

All approved standard of care treatments for acute uncomplicated malaria are administered for a maximum of 3 days duration. Therefore, in this study, MMV367 will be administered QD (morning dose) for a maximum of 3 days in Part 3. Considering its anticipated half-life of approximately 19 h, steady-state concentrations will not be achieved with a 3-day regimen. Although the pharmacological profile and PK properties of MMV367 are both expected to provide a single dose cure for acute uncomplicated malaria, the evaluation of a 3-day regimen will allow the assessment of tolerability and safety for an alternative therapeutic strategy in the target population. The assessment of up to a 3-day treatment regimen may be useful if a disconnect is observed in the predicted efficacy of the malaria human challenge model or malaria patients, such that MMV367 needs to be administered over 2 or 3 days to ensure a cure. Additionally, MMV367 will ultimately be administered/deployed in a fixed dose-combination regimen with an existing or novel antimalarial drug and dosing frequency will have to take the pharmacology of any proposed partner drug into account.

This study may also identify the genetic factors that affect the PK of MMV367 in humans through exploratory pharmacogenetic sampling. Such analysis will be triggered after study completion if specific safety and/or PK observations suggest that a genetic polymorphism could potentially account for variability in the study.

6.2 Dose Rationale

The recommendations of the following guidelines have been considered when setting the starting dose and escalation rules for this trial:

- Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1), 20 July 2017 [5]
- Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. July 2005 [6]

Part 1

The maximum recommended safe starting dose (MRSD) of 100 mg was calculated based on results from two GLP toxicology studies in rats (male/females) and dogs (male/females) supporting Phase I and in accordance with the 2005 FDA [6] and the 2017 [5] EMEA Guidances. The female rat was identified as the most sensitive species to set the starting dose according to the 2005 FDA guidance, whereas the dog was identified to be the most sensitive species with regards to the drug exposure, i.e. lower exposure at NOAEL, and was therefore selected to set the highest achievable human exposure.

To set the starting dose, the NOAEL of the most sensitive species was selected from the 7-day rat GLP toxicology study (NOAEL observed in female rats) and was 100 mg/kg/day. On the basis of body surface area, the corresponding extrapolated human equivalent dose (HED) for a human body weight of 60 kg was 960 mg. Applying a safety factor of 10, a starting dose of 100 mg can be supported from a toxicology perspective. This proposed starting dose is approximately 4 times below the predicted human efficacious single dose (440 mg) for treatment of acute uncomplicated malaria and is expected to be devoid of pharmacological activity in healthy participants.

Based on human PK predictions and assuming human bioavailability of approximately 90%, the proposed starting dose of 100 mg is associated with a safety margin of approximately 60-fold for AUC (i.e. compared with cumulative AUC(0-168) at the dog NOAEL) and 30-fold for Cmax.

Part 2

Since MMV367 is a lipophilic molecule and considering the median bioavailability range of 13% to 94% in pre-clinical species, there is potential for increase in its bioavailability in the presence of high-fat food. In addition, a PK study in dogs showed that food consumption increases MMV367 exposure. The maximum exposure for a dose of 400 mg when administered with food (assuming close to 100% bioavailability) is expected to be less than a 750 mg single dose administered fasted considering predicted human bioavailability; therefore, Part 2 is planned to run after completion of safety and PK analysis of Cohort 1C data, in which a 750 mg dose is predicted for administration.

Part 3

The final selection of multiple doses to be administered in Part 3 will be confirmed based on preliminary PK results and safety data from the single ascending dose (SAD) cohorts

(Part 1). 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. It is proposed to administer a cumulative dose of 600 mg to participants in Part 3 (200 mg every 24 h for 3 days), but this will be confirmed on review of data from Part 1.

Estimated Human Minimal Efficacious Dose

Pre-clinical studies using a validated pre-clinical model for malaria (SCID mice inoculated with *Plasmodium falciparum*-infected red blood cells) were used to establish the minimal parasiticidal concentration (MPC) and the minimal inhibitory concentration (MIC) of MMV367. A human dose that could maintain blood concentrations above Minimal Parasiticidal Concentration (MPC) for 100 h (corresponding to 2 parasite erythrocyte cycles) was identified as a target minimal efficacious dose for the treatment of acute uncomplicated *Plasmodium falciparum* malaria. Using allometry methods and PBPK modelling for predicting human PK profile and a typical human body weight of 60 kg, the predicted efficacious human dose of MMV367 after single-dose administration was estimated to be 440 mg. This dose is projected to maintain blood concentrations above the MPC90 in humans for at least 4.5 days and to be sufficient to reduce parasitaemia by 12-log in 50% of the population, while 100 and 30 mg would have similar efficacy for a two- and three-day QD treatment respectively. The parasite rate reduction was measured at ≥8 and 5 within the in vitro and ex vivo assays, respectively, and therefore, the value of 5 was retained to estimate the killing rate Emax (0.26 h^{-1}). This is sufficient to reduce parasitaemia by 12-log in 4.5 days.

The 3-day regimen is proposed as it is in-line with the duration of treatment for the current standard of care (SoC) for uncomplicated malaria. Although a single dose cure for uncomplicated malaria is the ideal product profile, a QD regimen that is taken for 2 to 3 days would offer significant benefits over SoC in terms of efficacy and adherence if it overcomes the existing resistance to the current SoC (which has to be given multiple times a day). Furthermore, extended exposures will allow the assessment of tolerability and safety in the case of extended exposure in the patient population due to drug-drug interactions or co-morbidities, which is especially important due to the fact that the malaria burden disproportionately affect regions with fragile health systems where aftermarket drug monitoring may be less robust.

Rationale for Highest Proposed Dose

The rational for the highest proposed dose in Part 1 is based on:

1. The predicted human efficacious exposure (AUC(0-inf) = 80 µg.h/mL) for a single dose/single cure of acute uncomplicated malaria, which is anticipated to be achieved with a dose of approximately 440 mg
2. The need to document safety and tolerability of MMV367 at supratherapeutic exposures in humans in order to account for PK variability (intrinsic and extrinsic factors) in the target population
3. The toxicity profile of MMV367 observed in preclinical species, which showed monitorable toxicity and an absence of life-threatening events
4. The NOAEL in the two GLP species (rat and dog):
    - The cumulative exposure at NOAEL (100 mg/kg/day) in female rats was 4270 µg.h/mL
    - The cumulative exposure at NOAEL (300 mg/kg/day) in male rats was 3511 µg.h/mL

- The gender averaged cumulative exposure at NOAEL (300 mg/kg/day) in dogs was 1250 µg.h/mL (respectively, 1155 µg.h/mL in females and 1344 µg.h/mL in males)

Therefore, the exposure at NOAEL of the most sensitive species was identified from the 7-day GLP toxicology study in dogs as the highest acceptable human exposure. The corresponding exposure of 1250 µg.h/mL is the cumulative AUC(0-168) of the parent drug MMV367 observed in the 7-day GLP dog study (Average cumulative AUC(0-168) calculated as follows: (AUC on Day 1 [AUCD1] + AUC on Day 7 [AUCD7]) / 2*7)). This would correspond to a theoretical HED of 6500 mg, assuming a linear PK from 100 to 2000 mg.

Based on the predicted human efficacious exposure, the need to document a safety window above that exposure and the anticipated human dose levels, the human AUCcap identified for this FIH study (376 µg.h/mL) was calculated as the predicted exposure (AUC(0-inf), assuming dose linearity from 100 to 2000 mg) for a theoretical dose of 2000 mg. This proposed AUCcap is therefore 3-fold below the cumulative AUC identified at dog NOAEL (1250 ng.h/mL). Of note, based on the PBPK model, which suggests a less than dose-proportional increase in exposure, the highest dose of 2000 mg would result in a lower AUC(0-inf) of 208 µg.h/mL.

For the multiple-dose part (Part 3), a dose of 200 mg every 24 h for 3 days would result in an AUC(0-inf) of 114 µg.h/mL and a safety factor of 3 to the AUCcap and a margin of 11 to the cumulative AUC for the NOAEL from the dog study.

The simulated exposure in human along with exposure multiples compared to NOAEL exposure in the most sensitive species are presented in Table 2. Exposure multiples for AUC are presented using two different methods. The standard method compares AUCtau(24h),ss in animal to AUC(0-inf) in human. Given the current goal of developing a single dose combination regimen (single dose-single cure treatment) and/or a combination regimen of up to 3 days treatment (QD administration) and the fact that the steady-state will never be reached, the cumulative method comparing AUC(0-168) in animal to AUC(0-inf) was considered more relevant in this case. Therefore, the exposure multiple at the top dose of 2000 mg is at least 6 for AUC (using a cumulative method).

Additionally, the findings in animal toxicological species were non-adverse, monitorable and reversible [3]. Therefore, these increments are considered safe. Nevertheless, available PK data will be reviewed after each cohort to confirm that the observed AUC is comparable to the AUC simulated using the PBPK model and dose adjustments will be made, if required, before proceeding to the next cohort to ensure that the mean group exposure of the subsequent cohort will not exceed the highest achievable human exposure (AUCcap) of 376 µg.h/mL and/or the Cmaxcap of 23.8 µg/mL.

Selecting mean group values for human AUC(0-inf)cap and Cmaxcap in this FIH is considered acceptable due to the nature of the preclinical observations (GI toxicity, increased blood pressure/heart rate and decreased respiratory function) in the two GLP toxicology and safety pharmacology studies. These toxicities are not associated with steep dose-response relationship and are monitorable in humans.

Table 2 Margins between the Clinical Doses Predicted Plasma AUC(0-inf) and Cmax, and the Exposure at NOAEL in the Most Sensitive Species (Dog)

Proposed Dose (mg)	Prediction in Human based on PBPK model		Exposure multiple in dogs (NOAEL dose 300 mg/kg QD for 7 days)		
	Cmax (µg/mL)	AUC(0-inf) (µg.h/mL)	Cmax (23.8 µg/mL)[a]	AUC(0-168) (1250 µg.h/mL) Cumulative method[b,c]	AUCtau(24h)-ss (192 µg.h/mL) Standard method[d]
Single dose					
100 mg	0.7	18.8	34.0	66.5	10.2
300 mg	2.2	55.5	10.8	22.5	3.5
750 mg	5.0	127	4.8	9.8	1.5
1500 mg	7.7	193	3.1	6.5	1.0
2000 mg	8.2	208	2.9	6.0	0.9[c]
Multiple dose					
200 mg QD × 3	2.2	112	10.8	11.2	1.7

[a] Cmax after last dose in dogs
[b] Cumulative exposure method, AUC(0-168) / predicted AUC(0-inf) in humans. The average cumulative AUC(0-168) is calculated as follows: (AUCD1 + AUCD7) / 2*7.
[c] The approach calculating safety margin based on the cumulative method is considered more relevant in our setting because the steady-state will never be reached due to the maximum 3-day QD treatment duration with a 19 h half-life.
[d] Standard method: AUCtau(24h)-ss / predicted AUC(0-inf) in humans
Note: AUCcap = 376 µg.h/mL, calculated exposure at 2000 mg assuming dose linearity from 100 to 2000 mg.

6.3 Population Rationale

As this is a Phase I study assessing the PK, relative bioavailability and safety of MMV367, the most relevant population is healthy volunteers. Participants who are non-smokers without a history of alcohol or drug abuse or regular co-medication (except hormonal contraception and hormone replacement therapy [HRT]) are proposed to avoid interaction on drug metabolism and to avoid non-compliance.

Due to the target population in endemic areas with a substantial proportion of young women suffering from acute uncomplicated malaria, efforts will be made to enrol women of childbearing potential (WOCBP) in Phase I studies. In accordance with ICH M3 at this early stage of development, reproductive and developmental toxicity studies have not yet been conducted and, therefore, the risk of teratogenicity with MMV367 is currently unknown. Embryofoetal development studies will be completed before initiation of Phase II trials in African patients. Given the current lack of standard reproductive toxicity studies, WOCBP enrolled in Phase I studies with MMV367 must have a negative pregnancy test at screening and admission and are required to use a double method of contraception as described in Section 9.4.

As it is unknown whether MMV367 is found in semen and considering the current lack of fertility studies in animals, male study participants are also required to use highly effective contraception with their partner, if their partner is a WOCBP. Contraception requirements are detailed in Section 9.4.

Based on the above considerations and target population, healthy non-pregnant and non-lactating female participants and healthy male participants, aged 18 to 55 years are considered suitable for this study. In order to reflect the majority patient population, efforts will be made to ensure a gender balance and to recruit participants of Sub-Saharan origins (i.e. both parents are black and are of sub-Saharan African origin).

6.4 Risks and Benefits

6.4.1 Risks Associated with MMV367 Administration

There is currently no clinical experience with MMV367. Potential risks will be closely monitored as part of systematic safety evaluations being performed in this FIH study. Based on pre-clinical observations at toxicological doses in rats and dogs, potential risks associated with MMV367 administration are all monitorable in humans and consist of:

- Gastrointestinal toxicity with symptoms such as nausea and vomiting
- Cardiovascular effects with transient increased heart rate and blood pressure
- Decreased respiratory function

Gastrointestinal adverse reactions may manifest as epigastric/abdominal pain, nausea/vomiting, diarrhoea or constipation.

Heart rate and blood pressure will be closely monitored in this study and will also include orthostatic evaluations.

Effects on respiratory function may result in an increased resting respiratory rate.

Measures to minimise the risks to healthy participants will include:

- Selection of a starting dose below a dose level for which pharmacological effects are expected.
- Sentinel dosing in the SAD cohorts (Part 1) and the multiple dose cohort(s) (Part 3); one participant on IMP and one participant on placebo. If safety and tolerability is acceptable, the remaining participants in each cohort can be dosed with a minimum interval of 96 h post-dose (Part 1) or 96 h post-final dose (Part 3) in the sentinel participants.
- Progression to consecutive study parts or higher exposure dosing regimens only after evaluation of data from previous parts/cohorts and following approval from the safety advisory committee (SAC).
- Close and regular clinical, laboratory and ECG monitoring of study participants.
- Telemetry (Day 1 in Part 1 and Days 1 and Day 8 in Part 2) and Holter monitoring (up to 24 h post-dose on Day 1 in Part 1, up to 24 h post-dose on Days 1 and 8 in Part 2, and up to 24 h post-dose on Days 1 and 3 in Part 3) of each cohort/study part.
- Pre-defined stopping rules based on emerging human safety and PK data.

6.4.2 COVID-19 Related Risks and Risk Mitigation Measures

The following risks and risk mitigating measures apply to parts of the study in which the study is conducted during the Coronavirus Disease 2019 (COVID-19) pandemic.

6.4.2.1 IMP Related Risk

Against the background of the COVID-19 pandemic, the potential risk of a participant developing COVID-19 has been considered in terms of the risk-benefit evaluation. The mode of action of the IMP – as an inhibitor of acyl CoA synthetase in *Plasmodium* – has been considered alongside available pre-clinical and clinical data (including class effects) and it is considered that a participant would not be at increased risk of either becoming infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the virus that causes COVID-19) or experiencing a more severe illness. That is, the IMP has no known immunomodulatory effect that would confer an increased risk to healthy participants enrolled in the study.

6.4.2.2 General COVID-19 Related Risk Mitigation Measures

General risk mitigation against COVID-19 will be implemented in accordance with Quotient's monitoring and prevention control measures.

COVID-19 testing may be performed based on current infection rates and availability of tests. If required, it is planned that testing will comprise an antigen test performed at screening and on Day -1. Testing time points may be changed and additional time points may be added throughout the study as required. The decision on COVID-19 testing and the definition of the testing time points are subject to change based on the current risk mitigation in place and will be agreed by the study team and documented in the Investigator Site File (ISF) via the Clinical Kick-Off Meeting minutes.

The risk mitigation measures, where applicable, will be amended based on emerging government guidance.

6.4.2.3 COVID-19 Vaccine-Related Risk

Approved (including health authority conditional marketing authorisation) COVID-19 vaccines e.g. killed, inactivated, peptide, DNA and RNA vaccines will not be permitted during the study.

Based on the mechanism of action of the IMP, as an inhibitor of acyl CoA synthetase in *Plasmodium,* there is no perceived impact on the safety of the study participants or on the study objectives for participants who may receive these vaccines. It is also very unlikely that administration of the IMP would interfere with COVID-19 vaccination response; however, no specific pre-clinical or clinical investigations have been conducted at this point with MMV367.

The emerging safety and efficacy data from millions of vaccinated people indicate that these vaccines have an excellent safety and efficacy record. In the broader interests of society and to limit the extent of the global pandemic, it is important that participants should receive a vaccine when it is offered to them.

6.4.3 General Risks and Overall Risk-Benefit Assessment

Collecting a blood sample from a vein may cause pain, swelling, bruising, light-headedness, fainting, and very rarely, clot formation, nerve damage and/or infection at the site of the needle stick.

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

Electrocardiogram (ECG) and Holter stickers, and telemetry electrodes on the participants' chests and limbs may cause some local irritation and may be uncomfortable to remove but participants will be closely monitored to ensure any local irritation does not persist.

There is no benefit to the participants from taking part in this study. The development of a product to treat malaria or improve the treatment of malaria will be of benefit to patients with malaria.

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

7 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

8 Study Design

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.

8.1 Study Plan

8.1.1 Study Plan: Part 1 – Single Ascending Dose Cohorts

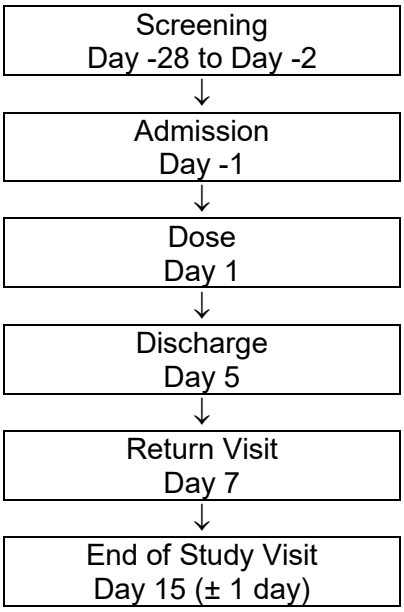
Part 1 will be a double-blinded, randomised, placebo-controlled, SAD study, which will comprise up to 5 fasted cohorts (Cohorts 1A to 1E; Cohort 1E will be optional), with 8 participants in each cohort. Participants will be randomly assigned to receive a single oral dose of either active IMP (6 participants) 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 and PK) will undergo a formal review by the SAC (see Section 8.2). The SAC will determine if it is safe 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. A participant will be considered evaluable if they have received study drug and completed safety and PK assessments up to 96 h post-dose.

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 3, according to the randomisation schedule.

Table 3 Description of Regimens: Part 1

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

[a] Predicted dose
Details of the IMPs are provided in Section 5.2.

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 8.2.

Participants will also complete a written taste/palatability questionnaire individually and privately following administration of the IMP (see Section 13.3). 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.

8.1.2 Study Plan: 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 (Appendix 8), and a single dose of MMV367 in the fasted state.

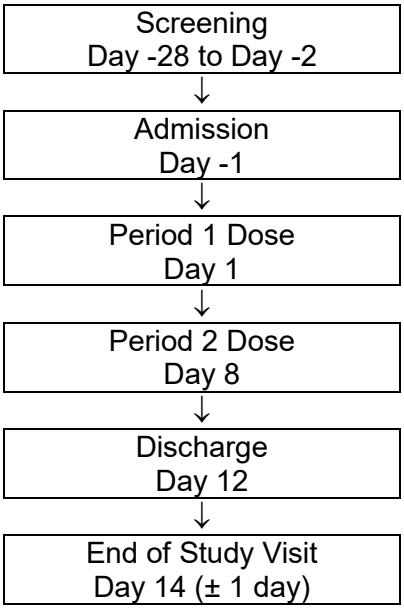
Each participant will receive 2 single doses of MMV367. In Period 1, participants will be randomised to 1 of 2 treatment sequences (Regimen 6/Regimen 7 or Regimen 7/Regimen 6). If a participant is randomised to receive MMV367 in the fasted state (Regimen 6) in Period 1, they will receive MMV367 in the 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. A participant will be considered evaluable if they have received study drug and completed safety and PK assessments up to 96 h post-dose in both periods.

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



Each participant will receive Regimens 6 and 7, presented in Table 4, according to the randomisation schedule.

Table 4 Description of Regimens: Part 2

Food Effect Cohort	Period	Regimen	IMP	Dosea	Route of Administration
2A	1 and 2 (randomised)	6	MMV367	XX mg	Oral, Fasted
		7	MMV367	XX mg	Oral, Fed

Details of the IMPs are provided in Section 5.2.
[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.

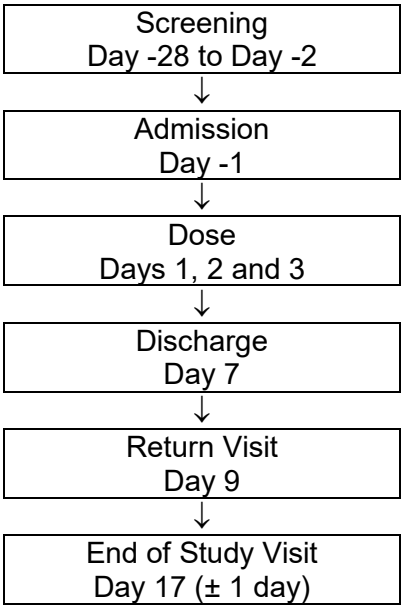
8.1.3 Study Plan: Part 3 – Multiple Dose Cohort(s)

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. A participant will be considered evaluable if they have received study drug and completed safety and PK assessments up to 96 h post-final dose.

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 5 according to the randomisation schedule.

Table 5 Description of Regimens: Part 3

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

Details of the IMPs are provided in Section 5.2.
[a] The dose(s) administered in Part 3 will be determined after review of the data from Part 1.

Parts 2 and 3 may be conducted before completion of Part 1 provided that this is justified by PK and safety data obtained from completed cohorts in Part 1. 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 in Part 1, dosed at a single dose level. Parts 2 and 3 may be conducted in parallel.

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.

8.2 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 a PK expert where appropriate.

8.2.1 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

8.2.2 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 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(0-last), 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
- The study will be halted (see Section 8.5) and thus a further dose decision will not be made if:
    - One or more participants experience an IMP-related serious adverse event (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 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 post-dose (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.

8.3 Participant Withdrawal

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

Early withdrawal is defined as the date of the decision to withdraw the participant from the study. Participant completion is defined as the date of the last procedure conducted or last contact (e.g. discharge from the study or unscheduled visit) for that participant.

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

Participants in Part 1 will receive a single dose in the study; therefore, after an individual participant has received a dose of IMP, withdrawal of that participant from further dosing is not possible. Participants will be monitored for the criteria listed below, which may require their withdrawal from some or all study procedures if continuation is not in their best interests, except when the withdrawal is a result of withdrawal of consent.

Participants in Parts 2 and 3 will be withdrawn from the study drug for the following reasons:

- Experiencing a serious or severe AE including but not limited to:
  - corrected QT interval by Fridericia's formula (QTcF) of >500 msec or increase in QTcF of >60 msec from baseline (confirmed following a repeat ECG)
  - alanine aminotransferase (ALT) concentration >3 × the upper limit of the reference range (confirmed following a repeat ALT blood test)
- Pregnancy (see Section 9.5)
- Termination of the study
- Upon the participant's request (withdrawal of consent)
- Significant deviation from the protocol
- Concurrent illness that would adversely affect participant safety or data integrity or requirement for prohibited medication
- At the discretion of the investigator

For the purpose of withdrawal criteria, baseline will be considered as the last available assessment prior to first dose.

For a participant who withdraws because of an IMP-related AE, every effort will be made to ensure the participant completes discharge procedures.

Early withdrawal for safety reasons will be distinguished from withdrawal of consent by the participant to participate in any further activities.

8.4 Participant Replacement

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.

8.5 Stopping Criteria

Cohort stopping rules

Dose escalation, as well as continued dosing within any given cohort, will be paused and may be halted based on full review of all available clinical safety data if any of the following occur:

- Two or more participants in the same cohort experience an AE assessed as severe
- Two or more participants with QTcF >500 msec and/or an increase in QTcF >60 msec considered related to IMP administration
- At least 2 participants in the same cohort with demonstrated recurrent or persistent post-dose orthostatic hypotension (i.e., either a drop of systolic blood pressure [SBP] ≥20mmHg or diastolic blood pressure [DBP] ≥10mmHg after 3 min standing) and/or symptomatic hypotension (lightheadedness, weakness, blurry vision, dizziness or fainting upon standing) requiring medical intervention

Overall study stopping rules

Enrolment into the study will be placed on hold and dosing will be halted if any of the following occur cumulatively across all of the cohorts

- At least one IMP-related SAE
- Two severe non-serious adverse reactions considered as, at least, possibly related to the IMP administration in two subjects in the same cohort, independent of within or not within the same system-organ-class are observed.
- The investigator and/or the study sponsor considers that the number and/or severity of AEs, abnormal safety monitoring test, or abnormal laboratory findings justify putting the study on hold.

Relatedness to IMP will be determined by the investigator.

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

8.6 Study Termination

After the start of protocol activities but prior to the commencement of dosing, the study may be terminated by the sponsor and investigator without consultation with the Medicines and Healthcare products Regulatory Agency (MHRA) and EC. Notification of early termination must be provided to the MHRA and EC immediately and at the latest within 15 days after the study is terminated, clearly explaining the reasons. A description of follow-up measures taken for safety reasons, if applicable, will also be provided.

If the study is abandoned prior to commencement of any protocol activities, the investigator or sponsor must notify the EC and MHRA by letter outlining the reasons for abandonment of the trial.

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

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

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

If it becomes necessary to consider termination of the study after dosing has begun, dosing may be suspended pending discussion between the investigator and sponsor. Dosing will be stopped immediately on safety grounds.

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

8.7 Lost to Follow-up

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

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

- The clinical unit must attempt to contact the participant and reschedule the missed visit as soon as possible.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (e.g. three telephone calls on

three separate occasions and, if necessary, an email or letter to the participant's last known email/postal address). These contact attempts should be documented in the participant's source.
- If the participant cannot be contacted, they will be considered lost to follow-up.

8.8 Treatment Assignment and Randomisation

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.

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 (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.

8.8.1 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).

Participant numbering by study part and cohort is provided in Table 6.

Table 6 Participant Numbers

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

8.8.2 Blinding

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.

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.

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

9 Selection of Participants

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

Before participants are admitted to the clinical unit, The Over Volunteering Prevention System will be checked to ensure that each participant has not been dosed in a study within 90 days of the planned first dosing date of this study.

9.1 Informed Consent

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

9.2 Inclusion Criteria

Informed Consent and Compliance

1. Must provide written informed consent
2. Must be willing and able to communicate and participate in the whole study

Demographics and Contraception

3. Aged 18 to 55 years inclusive at the time of signing informed consent
4. Must agree to adhere to the contraception requirements defined in Section 9.4

Baseline characteristics

5. Healthy males or non-pregnant, non-lactating healthy females.
6. Body mass index (BMI) of 18.0 to 32.0 kg/m^2 as measured at screening
7. Weight ≥50 kg at screening

Inclusion criterion 5 from the list above will be re-assessed at admission/pre-dose on Day 1.

9.3 Exclusion Criteria

Medical/Surgical History and Mental Health

1. Serious adverse reaction or serious hypersensitivity to any drug or the formulation excipients
2. Presence or history of clinically significant allergy requiring treatment, as judged by the investigator. Hay fever is allowed unless it is active
3. History of clinically significant cardiovascular, renal, hepatic, dermatological, chronic respiratory or gastrointestinal disease, neurological or psychiatric disorder, as judged by the investigator
4. Blood pressure (supine) at screening or admission outside the range of 90 to 140 mmHg systolic or 50 to 90 mmHg diastolic; and pulse rate outside the range of 45 to 100 bpm, unless deemed not clinically significant by the investigator
5. A decrease of SBP ≥20 mmHg after 3 min standing and/or a decrease of DBP ≥10 mmHg after 3 min standing, at screening (applies to Part 1 and Part 3 only)
6. History or presence of known structural cardiac abnormalities, family history of long QT syndrome, cardiac syncope or recurrent, idiopathic syncope, exercise related clinically significant cardiac events. Any clinically significant abnormalities in rhythm, conduction or morphology of resting ECG or clinically important abnormalities that may interfere with the interpretation of QT interval changes
7. Presence of sinus node dysfunction, clinically significant PR interval prolongation (>210 msec), intermittent second- or third-degree atrioventricular block, complete bundle branch block, sustained cardiac arrhythmias including (but not limited to) atrial fibrillation or supraventricular tachycardia; any symptomatic arrhythmia with the exception of isolated extra systoles, abnormal T wave morphology which may impact on the QT/QTc assessment, or QTcF >450 msec. Participants with borderline abnormalities may be included if the deviations do not pose a safety risk, and if agreed between the sponsor's medical monitor and the investigator
8. Participants with a history of cholecystectomy or gall stones
9. Participants with conditions that affect their ability to smell or taste (Part 1 only) including, but not limited to mouth ulcers, gum disease, nasal surgery and smell and/or taste disorders (e.g. dysosmia, dysgeusia, respiratory and/or sinus infection or cold)

Physical Examination

10. Participants who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator or delegate at screening

Diagnostic assessments

11. Evidence of current SARS-CoV-2 infection
12. Clinically significant abnormal clinical chemistry, haematology, coagulation or urinalysis as judged by the investigator (laboratory parameters are listed in Appendix 1). Participants with Gilbert's Syndrome are not allowed.
13. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) 1 and 2 antibody results
14. Females who are pregnant or lactating (all female participants must have a negative highly sensitive serum pregnancy test at screening and a negative urine pregnancy test at admission)

Prior Study Participation

15. Participants who have received any IMP in a clinical research study within the 90 days prior to Day 1, or less than 5 elimination half-lives prior to Day 1, whichever is longer
16. Participants who have previously been administered IMP in this study. Participants who have taken part in Part 1 are not permitted to take part in Parts 2 and 3 and participants who have taken part in Part 2 are not permitted to take part in Part 3
17. Donation of blood or plasma within the previous 3 months or loss of greater than 400 mL of blood

Prior and Concomitant Medication

18. Participants who are taking, or have taken, any prescribed or over-the-counter drug or herbal remedies (other than up to 4 g of paracetamol per day, hormonal contraception or HRT) in the 14 days before first IMP administration (see Section 11.4)
19. Participants who have received a COVID-19 vaccine within 7 days before first IMP administration

Lifestyle Characteristics

20. History of any drug or alcohol abuse in the past 2 years
21. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type)
22. A confirmed positive alcohol breath test at screening or admission
23. Current smokers and those who have smoked within the last 12 months. A confirmed breath carbon monoxide reading of greater than 10 ppm at screening or admission
24. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
25. Confirmed positive drugs of abuse test result (drugs of abuse tests are listed in Appendix 1)
26. Participant with a vegan or vegetarian diet (Part 2 only)

Other

27. Male participants with pregnant or lactating partners
28. A score of 20 or more on the Beck Depression Inventory (BDI-II), and/or a response of 1, 2 or 3 for item 9 of this inventory (related to suicidal ideation) [7]. Note, individuals with a BDI-II score of 17-19 may be enrolled, at the discretion of the investigator, if they do not have a medical history of psychiatric conditions and their mental state is not considered to pose additional risk to the health of the individual or to the execution of the trial and interpretation of the data
29. Participants who are, or are immediate family members of, a study site or sponsor employee
30. Failure to satisfy the investigator of fitness to participate for any other reason

Exclusion criteria 2, 4, 6, 7, 11, 12, 14, 15, 16, 18, 19, 22, 23, 25, 27, 28 and 30 from the list above will be re-assessed at admission/pre-dose on Day 1.

Healthy participants who do not meet the inclusion/exclusion criteria for the study will not be enrolled.

9.4 Contraception and Restrictions

Male Participants with Partners of Childbearing Potential

Male participants who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus an approved method of highly effective contraception from the time of informed consent until 94 days after the last IMP administration. This has been calculated based on 90 days (one cycle of spermatogenesis) plus 5 half-lives of the IMP. Five half-lives (based on predicted human half-life of 19 h) has been calculated as 4 days.

The following methods are acceptable:

- Partner's use of combined (oestrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Partner's use of progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable/implantable
  - intrauterine hormone-releasing system
- Partner's use of intrauterine device
- Vasectomised
- Partner's bilateral tubal occlusion

These contraception requirements are considered to be more conservative than the guidance issued by the Heads of Medicines Agency: Clinical Trials Facilitation Group [8].

Males with Partners of Non-childbearing Potential

There is a significant risk of drug exposure through the ejaculate (which also applies to vasectomised males) that might be harmful to sexual partners. Therefore, even if a male is sexually active with a partner of non-childbearing potential, they will be required to use a condom from first administration of IMP until after the end of study visit from the study.

Female Participants of Childbearing Potential

Female participants who are sexually active and of childbearing potential must use, with their partner, a double method of contraception, consisting of a highly effective method of birth control combined with a barrier contraceptive (condom) from the time of informed consent until 34 days after last IMP administration. This has been calculated based on 30 days (one female menstrual cycle) plus 5 half-lives of the IMP. Five half-lives has been calculated as 4 days.

The following highly effective methods are acceptable:

- Combined (oestrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation

  - oral
  - injectable/implantable
  - intrauterine hormone-releasing system
- Intrauterine device
- Vasectomised partner
- Bilateral tubal occlusion

Female Participants are not required to use any of the above contraceptive methods if their sexual partner is female.

These contraception requirements are considered to be more conservative than the guidance issued by the Heads of Medicines Agency: Clinical Trials Facilitation Group [7].

All Participants (Male and Female Participants of Childbearing Potential)

Alternatively, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

Females of Non-Childbearing Potential

Female participants who are not of childbearing potential do not need to use any methods of contraception. A woman is considered of childbearing potential unless postmenopausal or permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause and confirmed by a follicle-stimulating hormone (FSH) result of ≥40 IU/L.

9.4.1 Sperm Donation

Male participants should not donate sperm for the duration of the study and for 94 days after last IMP administration.

9.4.2 Egg Donation

Female participants should not participate in egg donation from dosing, for the duration of the study and for at least 34 days after last IMP administration.

9.5 Pregnancy

Participants will be instructed that if they/their partner becomes pregnant during the study or up to 3 months after final dose, this should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a participant/participant's partner is subsequently found to be pregnant after the participant is included in the study, then consent will be sought from the participant/partner and, if granted, any pregnancy will be followed and the status of mother and/or child(ren) will be reported to the sponsor after delivery. Any participant reporting a pregnancy during the study will be discontinued from the study treatment and every reasonable effort will be made by Quotient to follow up the pregnancy until delivery.

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

9.6 Additional Study Restrictions

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

1. Participants must abstain from alcohol during the 24 h prior to screening and the 24 h prior to admission until after the end of study visit
2. Participants must not drink liquids or eat food containing grapefruit, cranberry, caffeine or other xanthines from 24 h prior to admission until after the end of study visit
3. Participants should refrain from eating food containing poppy seeds for 48 h prior to screening and for 48 h prior to admission until after the end of study visit
4. Participants must not take part in any unaccustomed strenuous exercise from the 72 h before the screening visit and then from 72 h prior to admission until after the end of study visit
5. Must not donate blood or plasma (outside of this study), from clinical unit admission, throughout the study duration, and for at least 90 days following last dose of study medication

The additional restrictions above are not exclusion criteria; if non-compliance occurs, a protocol deviation will be completed.

10 Study Procedures

Study procedures will be performed as detailed in the study schedule of assessments in Appendix 2, Appendix 3 and Appendix 4, Appendix 5, Appendix 6 and Appendix 7, and in accordance with Quotient's SOPs unless otherwise stated in this protocol.

10.1 Screening

Within the 28 days preceding first dose, all participants will be required to undergo a screening visit. Screening procedures will be carried out in accordance with the schedule of assessments in Appendix 2, Appendix 3 and Appendix 4.

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

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

10.1.1 Participant Re-Screening

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

10.2 Admission and Pre-dose Procedures

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

In addition, the ongoing eligibility of participants will be re-assessed at admission/pre-dose, as described in Sections 9.2 and 9.3.

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

Reserve participants for the first dose occasion, in any group, will not require admission procedures to be repeated, if dosing is within 2 days.

If dosing is delayed, participants who have completed admission procedures do not need admission procedures to be repeated if dosing is within 2 days and the participants have remained resident in the clinical unit.

The participants will be admitted to the clinical unit on the morning before dosing (Day -1).

In addition, participants may be required to visit the clinical unit on Day -1 prior to admission to the clinical unit for SARS-CoV-2 antigen tests (if required; see Sections 6.4.2.2 and 14.5.8). Test results must be available prior to dosing.

The admission and pre-dose procedures are presented in Appendix 2, Appendix 3 and Appendix 4.

10.3 Study Day Procedures

10.3.1 Blood Volume

The number and timing of samples may be amended following any interim PK parameter estimations. However, in this case, the total blood volume for each participant will not exceed 550 mL in a 4-week period.

The first 0.5 mL of blood withdrawn via cannula will be discarded.

10.3.2 Timing of Procedures

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

- PK samples should take priority (i.e. taken at the nominal time point) over other procedures scheduled at the same time point
- Resting periods will be completed prior to ECGs and no other procedures will be performed within this time window
- ECGs should be taken prior to vital signs when both measurements are scheduled at the same time point
- Other assessments, e.g. physical examinations, will be performed within the required time windows

As guidance, where Holter resting periods coincide with other procedures i.e. vital signs and ECGs the order of procedures will be:

The Holter recording will be initiated before IMP dosing to allow for extraction of baseline ECGs. Then, before each PK time point, a rest period of approximately 15 min will be applied to ensure reasonable heart rate stability to allow extraction from the Holter recording or triplicate machine ECGs.

All safety assessments will be timed and performed relative to the start of dosing.

10.3.3 Discharge from the Clinical Unit

A participant will be allowed to leave the premises without additional investigator or sub-investigator review, following completion of study-specific procedures at 96 h post-dose (Part 1)/post-final dose (Parts 2 and 3), providing that:

- No AEs have been reported during the study visit
- The participant responds in the affirmative when asked if they are feeling well

If any of these conditions are not met, then the participant will only be allowed to leave the clinical unit with the authorisation of the investigator or sub-investigator.

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

10.3.4 Return Visits

Participants will be required to return to the clinical unit on Day 7 in Part 1 for the assessments described in Appendix 2 and on Day 9 in Part 3 for the assessments described in Appendix 4. The acceptable deviations for the return visit PK, vital signs and ECG assessments are described in Sections 13.1.1, 14.6 and 14.7, respectively.

10.3.5 End of Study Visits

Participants will be required to return to the clinical unit for end of study assessments on Day 15 (± 1 day) in Part 1 (as described in Appendix 2), on Day 14 (± 1 day) in Part 2 (as described in Appendix 3), and on Day 17 (± 1 day) in Part 3 (as described in Appendix 4). The acceptable deviations for the end of study visit PK, vital signs and ECG assessments are described in Sections 13.1.1, 14.6 and 14.7, respectively.

10.3.6 Medical Supervision

A physician will be responsible for the clinical aspects of the study and will be available at all times during the study. In accordance with the current Association of the British Pharmaceutical Industry guidelines [9], each participant will receive a card stating the telephone number of the investigator and the 24/7 contact details of the Quotient's on-call physician.

10.3.7 Follow-up

If a participant reports an SAE in the 30 days after the end of study visit, they may be required to attend the clinical unit for a further follow-up assessment (as an unscheduled visit). Completion of the last discharge assessment or unscheduled follow-up visit will be considered the end of the study.

11 Dosing of Participants

11.1 Food and Fluid Intake

Participants will be allowed water up to 1 h before the scheduled dosing time and will be provided with 240 mL of water at 1 h post-dose (to ensure adequate hydration), and thereafter, water will be allowed ad libitum. Decaffeinated fluids will be allowed ad libitum from lunch time on the day of dosing.

If, for technical reasons, dosing is delayed for more than 2 h beyond the expected dosing time, participants will receive 200 mL of an electrolyte drink (e.g. Lucozade Sport) at the originally scheduled dosing time, or earlier if possible.

Fed Dosing: Part 2, Fed Period

The calorie/fat content of breakfast will be controlled on the fed dosing day (refer to Appendix 8 for breakfast content). Participants will be provided with a standardised menu for all other meals.

For the fed regimen, a standard high-fat breakfast will be given 30 min before dosing.

Participants will be provided with a light snack the evening prior to dosing and will fast from all food and drink (except water) until the following morning, when they will be provided with a standard high-fat breakfast.

The breakfast should be consumed over a maximum period of 25 min, with dosing occurring 30 min after the start of breakfast. Participants should be encouraged to eat their meal evenly over the 25 min period. It is acknowledged that some participants will take less time to eat, but dosing should still occur 30 min after the start of breakfast. Participants must consume at least 90% of the pre-dose breakfast in order to eligible for dosing. The start and stop time and percentage of the breakfast consumed must be recorded in the source.

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

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

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

Fasted Dosing (Parts 1 and 3 and Part 2, Fasted Period)

The calorie/fat content of meals are not required to be controlled. Participants will be provided with a standardised menu.

Participants will be provided with a light snack the evening prior to dosing and then fast from all food and drink (except water) for a minimum of 8 h on the day prior to dosing until approximately 4 h post-dose, at which time lunch will be provided. An evening meal will be provided at approximately 10 h post-dose and an evening snack at approximately 14 h post-dose.

On subsequent non-dosing days, meals will be provided at appropriate times.

11.2 Administration of Test Preparations

Specific details of the IMP, and doses to be administered are provided in Section 5.2 and Section 8.1, respectively. In Parts 1 and 2, participants will be dosed on the morning of Day 1 of each study period, as applicable. In Part 3, participants will be dosed on the morning of Days 1, 2 and 3.

The exact time of dosing will be decided based on logistics and will be documented in the source. 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 (see also Section 8.8.2).

For Part 3, the acceptable deviation for dose administrations from the nominal time point is:

- Days 2 and 3 dose will be administered within ± 30 min of the nominal dosing time point, relative to the dosing time on Day 1

It is planned that each dose level (Parts 1 and 3) will be administered in a staggered 'sentinel' dose design. All groups will be split into two subcohorts; in Cohort Xa, one participant will receive active IMP and one participant will receive placebo; in Cohort Xb, five participants will receive active IMP, and one participant will receive placebo, where X indicates the number of the cohort.

Participants in Part 1 will receive a single dose of MMV367 or matching placebo. Participants in Part 2 will receive a single dose of MMV367 on 2 separate occasions: 1 in the fed state and 1 in the fasted state, in a crossover design. Participants in Part 3 will receive three doses of MMV367 or matching placebo QD over 3 consecutive days.

The IMP will be dispersed in sterile water. Immediately after administration of the oral solution, the dosing vessel will be rinsed with water and participants will consume the rinse solution. During dosing, participants will consume up to a maximum total volume of 500 mL (including the dosing volume and volume of water used to rinse the dosing vessel) depending on the dose level. If required, additional water may be given with the IMP in 50 mL aliquots and will be recorded in the source but will not be classed as a protocol deviation.

In Part 1 only, each participant will test the taste and palatability of the IMP (single dose on Day 1). The IMP will be held in the mouth and swirled for 10 to 15 sec before swallowing. The participant will subsequently complete a written palatability questionnaire individually and privately. Participants will receive training on admission (see Section 8.1.1) before the palatability test/dosing. Participants will be allowed to cleanse their palates using tap water (administered freely in 50 to 100 mL aliquots)

before tasting the IMP. During the taste test, participants will be observed by study staff to assure compliance.

11.3 Dosing Compliance

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

Mouth checks will be conducted after dosing to ensure the solution has been swallowed.

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

11.4 Prior and Concomitant Medications

No prescribed, over-the-counter medication or herbal remedies will be permitted from 14 days before IMP administration until after the end of study visit, except up to 4 g of paracetamol per day, hormonal contraception and HRT and those deemed necessary by the investigator to treat AEs (see also Section 9.3). Any medications used will be recorded in the source.

COVID-19 vaccines are not accepted concomitant medications. Participants will be excluded if they have received the vaccine within 7 days prior to first administration of IMP so that by the time of dosing any effects of the vaccine (e.g. pyrexia, fatigue, pain/stiffness at site of injection) are likely to have abated, and vaccines will be prohibited until discharge from the study.

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

12 Assessment of Efficacy

Not applicable for this Phase I study.

13 Assessment of Pharmacokinetics, Metabolite Identification and Pharmacodynamics

13.1 Assessment of Pharmacokinetics and Metabolite Identification

13.1.1 Blood Sampling for Pharmacokinetics and Metabolite Identification

Venous blood samples will be collected from the participants by a trained member of the clinical team. Consent will be collected from the participants for use of these samples for the purposes of the proposed study. Samples will be processed to isolate plasma and PK analysis and metabolite identification, where appropriate, will be carried out on plasma samples.

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

Venous blood samples will be withdrawn via an indwelling cannula or by venepuncture according to the time schedules presented in Appendix 5, Appendix 6 and Appendix 7.

All PK windows will be timed relative to the start of dosing and actual sampling times will be recorded.

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

- Day 1 in all parts and Day 8 in Part 2: The pre-dose samples will be taken ≤15 min before dosing
- On Days 2 and 3 (Part 3 only): The 24 h time point will coincide with the pre-dose sample; samples will be taken ≤10 min of the nominal time point
- 0 to 1 h post-dose samples will be taken within ± 2 min of the nominal post-dose sampling time
- 2 to 12 h post-dose samples will be taken within ± 10 min of the nominal post-dose sampling time
- 24 to 96 h post-dose samples will be taken within ± 30 min of the nominal post-dose sampling time if participants are resident in the clinical unit
- ≥144 h post-dose samples will be taken within ± 2 h of the nominal post-dose sampling time if participants are attending a return visit
- On Day 14 (Part 2 only): The End of Study sample will be taken within ± 1 day of the nominal post-dose sampling time point

The timing and number of the samples may be amended following any interim PK parameter estimations, including collection over a longer duration. Any changes to blood sampling time points would be documented in the interim dose decision report and retained in the ISF.

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

Samples will be shipped to Swiss BioQuant for the analysis of MMV367 and, where appropriate, metabolite(s).

13.1.2 Urine Sampling for Pharmacokinetics and Metabolite Identification

Urine samples will be collected in Part 1, Cohorts 1C and 1D, according to the time schedule presented in Appendix 5, provided a future bioanalytical method will be available.

The pre-dose urine sample will be taken in the 24 h period before dosing. Where a sample is not provided, this will not be considered a deviation. All individual urine voids will be collected and shipped to the bioanalytical laboratory for analysis, according to Quotient's SOPs, unless indicated otherwise by the sponsor.

Consent will be collected from the participants for use of these samples for the purposes of the proposed study. Samples will be collected into appropriate containers as specified by the bioanalytical laboratory. Details of sample containers and processing will be contained in the CSPM.

Urine samples will be sent for laboratory testing in linked anonymised form (participant number). This information is able to be linked directly to the volunteer by the Quotient research team and study monitor; however, not by the laboratory staff or sponsor.

Samples will be shipped to Swiss BioQuant for the analysis of MMV367 and metabolite(s).

13.2 Assessment of Pharmacodynamics

Not applicable for this Phase I study.

13.3 Taste/Palatability Evaluation

Taste/Palatability will be assessed in Part 1 using a questionnaire (example provided in Appendix 9) at the time points detailed in Appendix 2. 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.

14 Assessment of Safety

14.1 Definition and Classification of Adverse Events

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.

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

AEs will be monitored from the time the participant signs the ICF until the end of study visit. The severity of AEs should be assessed as follows:

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

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

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

14.2 Assessment of Assessment of Causality

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

Causality should be assessed using the following categories:

Unrelated:

An AE which cannot be reasonably explained by available facts (evidence) or arguments that the study drug caused the AE. For example, the occurrence of the AE can be explained by other causative factors, such as:

- Event attributed to concomitant medication.
- No reasonably temporal relationship associated with IMP administration
- Event is expected in the study indication and/or target population
- Negative de-challenge and/or negative re-challenge
- Other (must be specified)

Related:

An AE for which it can be reasonably explained that the study drug caused the AE by available facts (evidence) or arguments. For example, the occurrence of the AE cannot be explained by other causative factors, but can be explained by pharmacological effect of the study drug such as:

- Temporal relationship to IMP exposure
- Event is known to be associated with the IMP drug class
- Event improved on discontinuation or dose reduction of IMP
- Biological plausibility
- Other (must be specified on the source documents)

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

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

14.3 Recording Adverse Events

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

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

14.4 Serious Adverse Events

14.4.1 Definition of Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- An important medical event as recognised by the investigator

SAEs must be immediately reported to the sponsor.

Spontaneously reported SAEs will be collected until 30 days following the final study visit. SAEs experienced after this 30-day period will only be reported if the investigator suspects a causal relationship with the study drug.

14.4.2 Definition of Suspected Unexpected Serious Adverse Reactions

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

14.4.3 Expectedness (Reference Safety Information)

The Reference Safety Information is used for the assessment of the expectedness of all ‘suspected’ serious adverse reactions (SARs) that occur in clinical trials. The expectedness of a SAR is determined by the sponsor. The list of ‘expected SARs’ should be based on ‘suspected’ SARs that were previously observed and not on the basis of what might be anticipated from the pharmacological properties of a medicinal product or the compound class. An ‘expected’ SAR is therefore one that is listed in the Reference Safety Information. An adverse reaction, the nature of which is not consistent with the applicable reference safety information (in the IB for drugs in clinical development or SmPC for marketed drugs) is unexpected. Reports which add significant information on the specificity, increase in the occurrence or severity of a known and already documented SAR are unexpected events.

14.5 Laboratory Measurements

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

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

Safety laboratory tests and virology will be carried out on blood samples, and drugs of abuse tests and urinalysis will be carried out on urine samples. Blood samples will be collected for DNA analysis, as detailed in Section 14.5.9.

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

14.5.1 Haematology, Clinical Chemistry and Coagulation

Laboratory tests will be performed by The Doctors Laboratory according to the time schedules presented in Appendix 5, Appendix 6 and Appendix 7. Blood samples will be collected and processed as detailed in the CSPM. Scheduled blood samples will be taken following an 8 h fast.

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

- Post-dose/post-first dose blood samples will be taken ± 1 h from the nominal blood sampling time
- End of Study blood samples will be taken ± 1 day from the nominal blood sampling time

Creatinine clearance (CLcr) will be calculated at admission by The Doctors Laboratory using the Cockcroft-Gault equation [10] and body weight. Results of this assessment will be used for PK analysis and PK-PD modelling (reported separately).

14.5.2 Urinalysis

Urinalysis will be performed on-site using a dipstick according to the time schedules presented in Appendix 2, Appendix 3 and Appendix 4.

Urine samples will be collected and processed as detailed in the CSPM.

In Part 1, any urine used for urinalysis will be added back to the full sample for PK and metabolite identification analysis. If microscopy is required, a urine sample (approximately 20 mL) will be taken from the urine PK and metabolite collection, and sent to The Doctor's Laboratory, after the void has been weighed.

In Parts 2 and 3, if microscopy is required, a urine sample will be sent to The Doctor's Laboratory.

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

- On Day 3 (Part 3 only): the pre-dose urine sample will be taken ≤1 h before dosing.
- Post-dose urine samples will be taken ± 2 h from the nominal urine sampling time
- End of Study urine samples will be taken ± 1 day from the nominal urine sampling time

14.5.3 Pregnancy Test

Serum and urine highly sensitive pregnancy tests will be performed as detailed in Appendix 2, Appendix 3 and Appendix 4. The samples will be collected and processed as detailed in the CSPM.

14.5.4 Follicle-Stimulating Hormone Test

Serum FSH tests will be performed as detailed in Appendix 2, Appendix 3 and Appendix 4. The samples will be collected and processed as detailed in the CSPM.

14.5.5 Drug Screen

A urine drug screen will be performed on-site using a point of care testing method (e.g. Alere Drug Screen Test Cup) according to the time schedules presented in Appendix 2, Appendix 3 and Appendix 4. The sample will be collected and processed as detailed in the CSPM. Participants will be screened for the drugs of abuse listed in Appendix 1.

14.5.6 Alcohol Breath Test

An alcohol breath test will be performed according to the time schedules presented in Appendix 2, Appendix 3 and Appendix 4. A positive result will exclude the participant from dosing.

14.5.7 Carbon Monoxide Breath Test

A carbon monoxide breath test will be performed according to the time schedules presented in Appendix 2, Appendix 3 and Appendix 4. A result of greater than 10 ppm will exclude the participant from the study.

14.5.8 SARS-CoV-2 Tests

Testing for the SARS-CoV-2 virus will be performed at screening and admission and may be performed at other time points, if required, based on current infection rates and availability of tests. Tests will be performed according to the time schedules presented in Appendix 2, Appendix 3 and Appendix 4. The samples will be collected and processed as detailed in the Screening Sample Processing Manual and CSPM.

Testing time points may be changed and additional time points may be added throughout the study as required. The decision on COVID-19 testing and the definition of the testing time points are subject to change based on the current risk mitigation in place and will be agreed by the study team and documented in the ISF via the Clinical Kick-Off Meeting minutes.

14.5.9 Genetic Samples

In Part 1, Part 2 (Period 1 only) and Part 3, one mandatory blood sample per participant will be collected on Day 1 prior to IMP administration (≤2 h before dosing) to investigate allelic variants related to drug metabolism cytochrome P450 (CYP) enzymes and drug transporters that are potentially involved in the MMV367 absorption, distribution, metabolism and excretion. The blood sample and the extracted DNA will be kept until the end of study and will only be analysed under specific circumstances, including abnormal or unexpected PK or safety results. The decision to conduct the analysis will be taken once all data is available after last participant visit. The blood sample and extracted DNA will be destroyed either upon completion of analysis or when it is confirmed that they will not be required for analysis.

The sample will be collected and processed as detailed in the CSPM.

14.5.10 Abnormal Laboratory Findings

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

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

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

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

14.6 Vital Signs Measurements

Blood pressure and heart rate will be measured by an automated recorder after the participant has been in a supine position for a minimum of 5 min and oral temperature and respiratory rate will be measured according to the time schedules presented in Appendix 2Appendix 5, Appendix 6 and Appendix 7.

Blood pressure and heart rate orthostatic measurements will also be taken according to the time schedules presented in Appendix 5, Appendix 6 and Appendix 7. Two measurements will be recorded; 1 supine and 1 standing. The first supine measurement will be performed after the participant has rested in a supine position for at least 5 min. The second blood pressure and heart rate measurements will be performed after the participant has been standing for at least 3 min but no more than 5 min. Orthostatic hypotension will be defined as either:

- A decrease of SBP ≥ 20 mmHg after 3 min standing, or
- A decrease of DBP ≥ 10 mmHg after 3min standing

The acceptable deviations from the nominal vital signs measurement time points are:

- Day 1 in all parts and Day 8 in Part 2: The pre-dose vital signs measurements will be taken ≤2 h before dosing
- On Days 2 and 3 (Part 3 only): the pre-dose vital signs measurements will be taken ≤1 h before dosing.
- Post-dose vital signs measurements will be taken ± 15 min from the nominal post-dose time point.
- For return visits, vital signs measurements will be taken ± 2 h from the nominal return visit time point.
- End of study visit vital signs measurements will be taken ± 1 day from the nominal time point.

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

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

14.7 ECG Measurements

Single 12-lead ECGs will be measured after the participant has been in the supine position for a minimum of 5 min according to the time schedules presented in Appendix 5, Appendix 6 and Appendix 7.

Triplicate 12-lead ECG measurements will be performed at least 2 min and no longer than 4 min apart after the participant has been 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 (Appendix 5, Appendix 6 and Appendix 7). No other procedures should be performed within the 15 min resting period.

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

- Post-dose triplicate ECG resting periods will be ended within ± 15 min of the nominal time point
- Day 1 only: The pre-dose ECG measurements will be taken ≤2 h before dosing
- On Days 2 and 3 (Part 3 only): the pre-dose ECG measurements will be taken ≤1 h before dosing.
- Post-dose ECG measurements will be taken ± 15 min from the nominal post-dose time point.
- For return visits, ECG measurements will be taken ± 2 h from the nominal return visit time point.
- End of study ECG measurements will be taken ± 1 day from the nominal time point.

The ECGs will be collected electronically and over-read by cardiologists at Banook. The Banook over-read will be used for cardiac safety evaluations during SAC data review.

For safety assessments, a mean value for the triplicate ECGs will be reviewed.

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

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

14.8 Holter (continuous ECG) Monitoring

All ECGs will be collected electronically using a Mortara H12+ Holter Recorder, and analysed by Banook. Specific procedures for ECG Holter recording and extractions will be provided to the investigator by Banook.

According to the time schedules presented in Appendix 5, Appendix 6 and Appendix 7, 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. This extraction will be taken by the third party Holter provider at the planned time and therefore no other procedures should be performed within the resting period.

Where one period of ECG rest runs into the rest period for the next ECG extraction, the minimum resting period before ECG extraction does not need to be started again except in cases where the rest is disturbed (e.g. participants has to get up for a comfort break after the preceding rest period).

Participants may move more freely outside of the primary ECG rest periods. Comfort breaks for hygienic purposes will be allowed each morning well in advance of the required supine/ECG extraction points.

Where any scheduled rest times are missed, where there is less than a 10 min rest period or where the final 5 min of a rest period is interrupted (for example, by participant movement or loss of leads) a protocol deviation will be recorded and the Holter provider informed.

Loss of leads or interruption of the recording outside of the scheduled rest times will not be considered a protocol deviation but should be recorded in the source.

The acceptable deviations for ECG rest periods from the nominal time point are:

- Pre-dose and post-dose ECG resting periods will be ended within ± 15 min of the nominal time point

See Section 10.3.2 for details on timing of Holter rest period/extractions in relation to other procedures and Appendix 7 for rest period/extraction time points.

The ECGs will be collected electronically and over-read by cardiologists at Banook. The Banook over-read will be used for cardiac safety evaluations during SAC data review.

14.9 Telemetry (Continuous ECG)

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.

14.10 Body Weight, Height and BMI

The participant's body weight and height will be measured and their BMI will be calculated according to the time schedules presented in Appendix 2, Appendix 3 and Appendix 4.

14.11 Physical Examination

Participants will undergo a physical examination according to the time schedules presented in Appendix 2, Appendix 3 and Appendix 4.

In the targeted (symptom driven) physical examination, a physician will assess the participant; if the participant reports feeling unwell or has ongoing AEs, then the physician will examine the appropriate body system(s) if required.

14.12 Beck Depression Inventory (BDI-II) Questionnaire

Each participant will undergo a BDI-II questionnaire [7], according to the time schedules presented in Appendix 2, Appendix 3 and Appendix 4. A participant will be excluded from the trial if they have a score of 20 or more on the BDI-II, and/or a response of 1, 2 or 3 for item 9 of this inventory (related to suicidal ideation).

Individuals with a BDI-II score of 17-19 may be enrolled, at the discretion of the investigator, if they do not have a medical history of psychiatric conditions and their mental state is not considered to pose additional risk to the health of the individual or to the execution of the trial and interpretation of the data.

14.13 Additional Safety Procedures

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

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

15 Statistics and Data Analysis

15.1 Sample Size Justification

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.

15.2 Data Management

Data management will be performed by Quotient.

Study data will be managed using a validated electronic case report form (eCRF) database system and will be subjected to data consistency and validation checks. Data queries will be raised within the study eCRF database by data management staff and resolved with the assistance of clinical staff.

AEs, medical histories and medications will be coded using the Medical Dictionary for Regulatory Activities (version to be specified in the Data Management Plan [DMP]) and the World Health Organization Drug Dictionary Global Drug Reference (version to be specified in the DPM), respectively. An independent coding review will also be performed within the Data Sciences department.

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

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

Further details are addressed in the DMP.

15.3 Pharmacokinetic Data Analysis

The plasma concentration data for MMV367 provided by Swiss BioQuant will be analysed by Quotient, using Phoenix WinNonlin v8.3 or a more recent version (Certara USA, Inc., USA).

PK analysis of the concentration time data obtained will be performed using appropriate non-compartmental techniques to obtain estimates of the PK parameters presented in Table 7 and Table 8, where possible and appropriate.

Table 7 Plasma Pharmacokinetic Parameters: Part 1 and 2

Parameter	Definition
Tmax	Time of maximum observed concentration
Cmax	Maximum observed concentration
AUC(0-24)	Area under the curve from time 0 to 24 h post-dose
AUC(0-48)	Area under the curve from time 0 to 48 h post-dose
AUC(0-last)	Area under the curve from time 0 to the time of last measurable concentration
AUC(0-inf)	Area under the curve from time 0 extrapolated to infinity
T1/2	Terminal elimination half-life
CL/F	Total body clearance calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown
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
Frel Cmax	Relative bioavailability based on Cmax (Part 2 fed dosing only)

Parameter	Definition
Frel AUC(0-last)	Relative bioavailability based on AUC(0-last) (Part 2 fed dosing only)
Frel AUC(0-inf)	Relative bioavailability based on AUC(0-inf) (Part 2 fed dosing only)

Table 8 Plasma Pharmacokinetic Parameters: Part 3

Parameter	Definition
Tmax	Time of maximum observed concentration
Cmax	Maximum observed concentration
AUC(0-tau)	Area under the curve for the defined interval between doses (tau)
T1/2	Terminal elimination half-life (Day 3 only)
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)
Vz/Ftau	Apparent volume of distribution based on the terminal phase calculated using AUC(0-tau) after repeated extravascular administration where F (fraction of dose bioavailable) is unknown (Day 3 only)
AR Cmax	Accumulation ratio based on Cmax repeated dose/Cmax single dose (Day 3 only)
AR AUC	Accumulation ratio based on AUC(0 tau) repeated dose/AUC(0 tau) single dose (Day 3 only)

Analysis of drug related QT/QTc interval changes relative to plasma PK concentrations will be conducted. This analysis will be performed on the analysis set for intensive cardiac assessment. Concentration/QTc modelling may be performed after completion of the CSR and will be reported separately.

In Part 1 Cohorts 1C and 1D, provided a future bioanalytical method is available, urine concentration data for MMV367, provided by Swiss BioQuant, will be analysed by Quotient and reported in an addendum to the CSR or in a separate report. Estimates of the parameters presented in Table 9 in urine will be obtained where possible and appropriate.

Table 9 Urine Pharmacokinetic Parameters: Part 1, Cohorts 1C and 1D only

Parameter	Definition
CLr	Renal clearance calculated using plasma AUC
Ae	Amount excreted
CumAe	Cumulative amount excreted
%Ae	Percentage of dose excreted
Cum%Ae	Cumulative percentage of dose excreted

Interim PK parameter estimations will be provided as described in Section 8.2.

Further details of the PK data analysis will be included in the reporting and analysis plan (RAP).

15.4 Metabolite Profiling and Identification Assessment

Metabolite profiling of MMV367 in plasma and urine will be performed using existing PK samples (pooled residual samples) collected in Part 1. Potential metabolites will be identified using liquid chromatography-mass spectrometry analysis. If results suggest that a major metabolite is present in plasma (e.g. greater than 10% of circulating MMV367 in plasma based on peak AUCs), metabolite quantification and PK analysis in plasma will be performed provided a future bioanalytical method is available. These results may be reported in an addendum to the CSR or in a separate report.

15.5 Statistical Data Analysis

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

In general terms, categorical data (including treatment-emergent AEs) will be presented using counts and percentages, while continuous variables will be presented using the mean, median, standard deviation, minimum and maximum. Additional statistics will be provided for PK-related data including coefficient of variation (CV%), geometric mean and geometric CV%.

Descriptive summaries for all safety data (AEs, vital signs, ECGs and safety laboratory assessments) by regimen will be provided (including changes from baseline as required).

Descriptive summaries for all PK data by regimen will be provided.

All safety and PK data will be listed.

Assessment of Dose Proportionality

For Part 1, dose proportionality will be assessed using a power model approach using log-transformed Cmax, AUC(0-last) and AUC(0-inf) values, including data from up to 5 different dose levels, i.e., general linear model including log dose as a fixed effect and log PK parameter as the dependent variable. The estimate obtained for β together with its 90% confidence interval (CI) will be presented along with the number of participants and the geometric means. The resulting estimate slope (β) and 90% CI is a measure of dose proportionality; the relationship is considered dose proportional when β = 1.

Assessment of Taste Questionnaire Data

In Part 1, formal statistical analysis will be performed on the scores of each taste attribute and overall acceptability, in the comparison of each dose level of MMV367 to the pooled placebos, using non-parametric methods. Hodges-Lehmann estimation methods will be used to estimate the median difference between each dose level and the pooled placebos. The associated 95% CI will be calculated for the estimate. The p-value will be calculated from the Wilcoxon Rank Sum Test (Mann-Whitney-Wilcoxon Test) for the test of the null hypothesis that the difference between the medians of each dose level and the pooled placebos is equal to zero, with the alternative hypothesis being that the difference is not equal to zero.

The number of participants and the median score for each treatment will be presented together with the Hodges-Lehmann estimate of the median difference and associated 90% CI. In addition, the p-value from the Wilcoxon Rank Sum Test will also be presented.

Assessment of Food Effect

In addition, for Part 2, formal statistical analysis will be performed, at a minimum, on the following PK parameters: Cmax, AUC(0-last) and AUC(0-inf), to assess for the effects of food. The PK parameters will undergo a natural logarithmic transformation and will be analysed using a mixed effect model with terms for fed/fasted status and period fitted as fixed effects and participant fitted as a random effect. The adjusted mean difference between the fed and fasted states, and the associated 90% CI obtained from the model are back transformed on the log scale to obtain the adjusted geometric mean ratio and 90% CI of the ratio. These will be presented together with the p-value from the fed/fasted comparison.

A categorical analysis of QTcF data will be reported (Table 10).

Table 10 QTcF Categorical Analysis

Absolute QTcF prolongation	• QTcF >450 msec • QTcF >480 msec • QTcF >500 msec
Change from baseline in QTcF	• QTcF increases from baseline >30 msec • QTcF increases from baseline >60 msec

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

The safety population and safety analysis set will be defined after database lock but prior to study unblinding; all other populations and analysis sets will be defined after database lock and unblinding when the relevant data are available.

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

- Criteria to be used to define each of the population and analysis sets
- Additional detail covering the analyses and/or description of primary and secondary analyses and safety data
- Handling of missing data, unused or spurious data
- Handling of data from withdrawn participants
- Unblinding procedures and maintaining the blind

15.6 Interim Analysis

No formal interim analyses are planned for this study. Interim Data Reviews will be performed as detailed in Section 8.2.

16 Safety Reporting to Regulatory Authorities and Ethics Committees

16.1 Events Requiring Expedited Reporting

SUSARs (Section 14.4.2) are subject to expedited reporting to the appropriate regulatory authority and EC.

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

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

16.2 Urgent Safety Measures

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

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

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

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

The sponsor is responsible for informing the appropriate regulatory authorities, and the EC; the task of reporting urgent safety measures will be delegated to Quotient.

16.3 Reporting

16.3.1 Reporting Serious Adverse Events

The investigator is required to notify the study sponsor and pharmacovigilance provider within 24 h of becoming aware of the occurrence of an SAE or serious adverse reaction. A copy of the written report of the event should promptly be sent to the study sponsor for information purposes, in accordance with ICH guidelines for GCP [11].

16.3.2 Reporting of Suspected Unexpected Serious Adverse Reactions

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

16.3.3 Expedited Reporting of Events

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

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

Fatal or life-threatening SUSARs

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

The sponsor is required to notify the EC of any fatal or life-threatening SUSAR as soon as possible, but no later than 7 calendar days after they first became aware of the reaction. Any additional relevant information should be sent within 8 days of the report. The task of reporting fatal or life-threatening SUSARs may be delegated to the investigator.

Other SUSARs

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

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

16.3.4 Reporting of Urgent Safety Measures

Quotient is required to notify the MHRA and the EC of an urgent safety measure immediately by telephone and follow-up in writing within 3 calendar days from the date the measures are taken.

16.3.5 Reporting of COVID-19 Vaccine-Related Adverse Events

AEs considered by the investigator to be related to COVID-19 vaccines will be reported to the MHRA via the Yellow Card system.

16.4 Serious Breaches

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

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

17 Protocol Amendments and Deviations

17.1 Amendments

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

All substantial amendments will be submitted to the MHRA and/or EC for an opinion as required by current regulations.

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

17.2 Protocol Deviations

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

Protocol waivers are not acceptable.

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

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

18 Regulatory

18.1 Compliance

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

- ICH GCP Guidelines approved by the Committee for Medicinal Products for Human Use on 17 Jul 1996, which came into force on 17 Jan 1997, updated Jul 2002, Integrated Addendum E6 (R2) dated 09 Nov 2016 [11]
- The Medicines for Human Use (Clinical Trials) Regulations. Statutory Instruments 2004 No. 1031 [12]

- The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2006 No. 1928 [13]
- The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations. Statutory Instruments 2006 No. 2984 [14]
- The Medicines for Human Use (Clinical Trials) Amendment Regulations. Statutory Instruments 2008 No. 941 [15]
- The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations. Statutory Instruments 2019 No. 744 [16]

In addition, the study will be performed according to the ethical principles outlined in the World Medical Association Declaration of Helsinki and its amendments [17].

18.2 MHRA and Ethical Approval

Prior to the initiation of the study, the clinical trial of an investigational medicinal product (CTIMP) application, the protocol and associated documentation must be approved by the MHRA and given a favourable opinion by an EC. A copy of this written approval and any correspondence with the MHRA and EC will be available at the clinical site and will be provided to the sponsor.

18.3 Source Data

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

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

18.4 Declaration of the End of the Study

The end of the study is defined as the point at which the sponsor determines that any remaining optional groups are not required to meet the objectives of the trial i.e. signed dose decision document or the completion of the final end of study visit or unscheduled follow-up assessment for the final cohort dosed, whichever occurs later. If all optional groups are utilised, completion of the final end of study visit or unscheduled follow-up visit will be considered the end of the study. Any changes to this definition will be notified as a substantial amendment (see Section 17.1).

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

18.5 Document Storage and Archiving

All documentation and correspondence pertaining to the study (source data, raw data, letters etc) will be kept in accordance with the ICH guidelines for Good Clinical Practice 1996, updated 2002, Integrated Addendum E6 (R2) dated 09 Nov 2016 (ICH GCP Section 4.9.5) [11], The Medicines for Human Use (Clinical Trials) Regulations 2004 [12], The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 [13],[14] and The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations [16].

All study related documents will be retained for a minimum period of 15 years. After this time, the sponsor will be contacted to ascertain whether continued storage or destruction is required in accordance with current regulations.

18.6 Protection of Personal Data and Confidentiality

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

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

- Computers storing electronic personal data are protected by antivirus software and the network on which computers are linked are protected by industry grade firewalls
- Off-site personnel can only access networked computers through a virtual private network
- Electronic access of data is limited according to user roles
- All data are stored on password protected computers

Organisational arrangements are as follows:

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

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

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

18.7 Data Security Breach

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

19 Quality Control and Quality Assurance

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

19.1 Monitoring

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

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

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

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

20 Finance and Insurance

The sponsor (Medicines for Malaria Venture) has co-funded this study, in partnership with the pharmaceutical company GlaxoSmithKline. A no-fault clinical trials insurance has been obtained by the sponsor. The sponsor insurance will compensate participants in accordance with the Association of the British Pharmaceutical Industry Guidelines for Phase I Clinical Trials 2018 edition [9].

21 Publication

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

Quotient shall have the right to publish the results of the research, subject to the sponsor's prior written consent, which shall not be unreasonably withheld or delayed. Following the receipt of such consent, Quotient shall submit a copy of the proposed publication to the sponsor who shall have 30 days in which to request amendments thereto which, to the extent that such proposed amendments are reasonable, Quotient shall be obliged to incorporate prior to such publication.

The sponsor undertakes that, prior to publication of any information, article, paper, report or other material concerning the research, it will submit a copy of such publication to Quotient who shall have 30 days in which to request amendments thereto which, to the extent that such proposed amendment are reasonable, the sponsor shall be obliged to incorporate prior to such publication.

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

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

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

[16] The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations. Statutory Instruments 2019 No. 744.

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

Appendix 1 Clinical Laboratory Parameters

Haematology	Clinical Chemistry	Virology	Urinalysis	Drugs of Abuse
Haemoglobin	Sodium	Hepatitis B surface antigen	Bilirubin	Amphetamines
Haematocrit (HCT; packed cell volume [PCV])	Potassium	Hepatitis C virus antibody	Urobilinogen	Barbiturates
Red blood cell (RBC; erythrocyte) count	Chloride	HIV 1 & 2 antibodies	Ketones	Benzodiazepines
Mean corpuscular volume (MCV)	Bicarbonate		Glucose	Cocaine
Mean corpuscular haemoglobin (MCH)	Urea		Protein	Marijuana/cannabis
Mean corpuscular haemoglobin concentration (MCHC)	Creatinine (admission plasma creatinine value will be used to calculate CLcr)	SARS-CoV-2 antigen	Blood	Methadone
Platelet count	Bilirubin (total)		Nitrites	Methamphetamine/ ecstasy
White blood cell (WBC; leukocytes) count	Bilirubin (direct; only if total is elevated)		pH	Morphine/opiates
Neutrophils	Alkaline phosphatase		Specific gravity	Phencyclidine
Lymphocytes	Aspartate aminotransferase (AST)		Leukocytes	Tricyclic antidepressants
Monocytes	Alanine aminotransferase (ALT)		**At discretion of investigator based on urinalysis results**	
Eosinophils	Creatine kinase (CK)		Microbiology	
Basophils	Gamma glutamyl transferase (GGT)		Urine microscopy	
Coagulation Tests	Protein (Total)		**Urine Pregnancy**	
Prothrombin time	Albumin		hCG (all female participants)	
International normalised ratio (INR)	Calcium			
Activated partial thromboplastin time (APTT)	Glucose (fasting)			
	Glucose			
	Follicle stimulating hormone (FSH; post-menopausal female participants only)			
	Human chorionic gonadotropin (β-hCG) (in serum; all female participants)			

Appendix 2 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				

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 subject to change based on the current risk mitigation in place and will be agreed by the study team and documented in the ISF via the Clinical Kick-Off Meeting minutes.
[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 Appendix 5 for safety blood sample time points.
[j] Post-menopausal female participants only
[k] All female participants
[l] See Appendix 5 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 Appendix 5 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 Appendix 5 for vital signs and orthostatic vital signs time points.
[p] See Appendix 5 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 Appendix 9 for details.

Appendix 3 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---------- >														

			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]**
Prior and Concomitant Medication	< ----------X---------- >														
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 subject to change based on the current risk mitigation in place and will be agreed by the study team and documented in the ISF via the Clinical Kick-Off Meeting minutes.
[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 Appendix 6 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 Appendix 6 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 Appendix 6 for vital signs time points.
[p] See Appendix 6 for PK sample time points.
[q] Sample will be taken prior to IMP administration (≤2 h before dosing).

Appendix 4 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[j]	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	

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
Blood Sample for CYP/UGT polymorphism[p]			X								

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 subject to change based on the current risk mitigation in place and will be agreed by the study team and documented in the ISF via the Clinical Kick-Off Meeting minutes.
[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 Appendix 6 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 Appendix 6 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 Appendix 6 for vital signs and orthostatic vital signs time points.
[o] See Appendix 6 for PK sample time points.
[p] Sample will be taken prior to IMP administration (≤2 h before dosing).

Appendix 5 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: Sections 13.1, 14.6 and 14.7.

Appendix 6 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	
	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						

Study Day	Time point	Plasma PK	Safety Labs and Urinalysis	Holter Extractions	Vital Signs[a]	Single 12-lead ECGs	Triplicate 12-lead ECGs
	8 h	X		X	X	X	
	10 h				X		
	12 h	X		X	X	X	
9	24 h	X		X	X	X	
10	48 h	X	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.

Appendix 7 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							
	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	

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
	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
[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 and 14.7.

Appendix 8 Breakfast Content (Part 2 only)

Meal Description	Energy from Fat (%)	Composition
High-Fat Breakfast (FDA approved)[a]	57.90	1 (40 g) hash brown, 2 (80 g) smoked rindless streaky bacon, 1 medium (45 g) egg fried in 10 g of butter, 2 slices (95 g) of white sliced bread with 20 g of butter, 240 mL of full fat milk

Values/content are approximate. Every effort will be made to include the items described above; however, items may be replaced as long as they contain the equivalent nutritional content as the item it has replaced.

[a] For FDA high-fat breakfast, if a replacement item is required it will be of comparable volume and viscosity.

Appendix 9 Example Taste/Palatability Questionnaire

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

QSCXXXXXX (Sponsor Study Number) Taste Questionnaire

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										

Entered into eCRF by (initials): _____ Date: _____ QC checked by (initials): _____ Date: _____

Appendix 10 Protocol Amendment Summary of Changes

Version 3.0 dated 08 Sep 2022

Due to logistics within the Quotient screening facility, it would be difficult to ensure subjects attend their end of study visit and have all the procedures performed within the ± 1 h window, and would likely result in protocol deviations. Therefore, it was agreed to increase this window from ± 1 h to ± 1 day.

In addition, clarifications were made throughout the protocol regarding the collection of urine for PK assessments, to ensure it is specific to Part 1, Cohorts 1C and 1D.

Changes were also made to correct previous errors and inconsistencies. These changes include:

- The removal of a physical examination and Holter procedure from Part 2 and Part 3 appendices, respectively;
- The addition of an ECG measurement to the Part 1 appendix;
- The removal of an incorrect sentence from Section 14.7 ECG Measurements and 14.8 Holter (continuous ECG) Monitoring;
- The specification of which parts exclusion criterion 5 refers to;
- An update to the Sponsor's Clinical Lead/Contact details in the study contacts and sponsor signature page following a change in personnel;
- The shading of blank boxes in the appendices tables to improve readability.

In addition, minor typographical updates were made throughout.

As these changes do not significantly affect the scientific value of the trial, the safety or physical or mental integrity of the subjects of the trial, this amendment was considered to be non-substantial.

All relevant sections of the protocol were updated accordingly, including:

- Document History Page
- Section 3 Synopsis
- Section 8.1.1 Study Plan: Part 1 – Single Ascending Dose Cohorts
- Section 8.1.2 Study Plan: Part 2 – Food Effect Cohort
- Section 8.1.3 Study Plan: Part 3 – Multiple Dose Cohort(s)
- Section 9.3 Exclusion Criteria
- Section 10.3.5 End of Study Visits
- Section 13.1.1 Blood Sampling for Pharmacokinetics and Metabolite Identification
- Section 14.5.1 Haematology, Clinical Chemistry and Coagulation
- Section 14.5.2 Urinalysis
- Section 14.6 Vital Signs Measurements
- Section 14.7 ECG Measurements
- Section 14.8 Holter (continuous ECG) Monitoring
- Section 15.3 Pharmacokinetic Data Analysis
- Appendix 2 Schedule of Assessments: Part 1 (Cohorts 1A to 1E)
- Appendix 3 Schedule of Assessments: Part 2
- Appendix 4 Schedule of Assessments: Part 3 (Cohorts 3A to 3C)
- Appendix 5 Part 1 (All Cohorts) Safety and Pharmacokinetic Assessment Time Points (Days 1 to 7)

- Appendix 7 Part 3 Safety and Pharmacokinetic Assessments Time Points (Days 1 to 9)
- Signatures for Sponsor Page

Version 2.0 dated 01 Jun 2022

The following revision was made to the protocol in response to a Grounds for Non-Acceptance (GNA) request from the MHRA:

Section 8.5 (Overall Study Stopping Rules): The following stopping criterion, “At least three participants experience a similar AE assessed as severe and considered related to IMP” has been replaced with: “Two severe non-serious adverse reactions considered as, at least, possibly related to the IMP administration in two subjects in the same cohort, independent of within or not within the same system-organ-class are observed”.

Signatures for Quotient Sciences

CONFIDENTIALITY AND GCP COMPLIANCE STATEMENT

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

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

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

Nand Singh BSc, MD, DPM, MFPM Principal Investigator Senior Clinical Research Physician	See electronic signature at the end of the document Signature Date

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Document Approvals

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