STATISTICAL ANALYSIS PLAN

An open label phase 1b study to characterise the pharmacokinetic/pharmacodynamic relationship and safety of MMV367 in healthy adult participants experimentally infected with blood stage *Plasmodium falciparum*

Protocol No.: MMV_MMV367_22_01

Product Code: MMV367

PREPARED FOR: Medicines for Malaria Venture (MMV)
ICC-Block G 3rd Floor
20, Route de Pré-Bois
1215 Geneva 15
Switzerland
Phone: +41 22 555 03 00

PREPARED BY: Southern Star Research
Level 1, 1 Merriwa St
Gordon, NSW, 2072
Australia

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AUTHOR: Locadiah Kuwanda

SAP APPROVAL

By my signature, I confirm that this SAP has been reviewed and has been approved for use on the MMV_MMV367_22_01 study:

Name	Title / Company	Signature	Date
Etienne Guirou	Clinical Scientist Medicines for Malaria Venture		
Locadiah Kuwanda	Senior Statistician Southern Star Research Pty Ltd.		

Table of contents

1. ABBREVIATIONS

ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
APR28	Adequate Parasitological Response Rate at Day 28
APTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the plasma Concentration Time Curve
AUC_{last}	Area under the curve from time 0 to last measurable concentration
AUC_{inf}	Area under the curve from time 0 to infinity
β-HCG	β-Human Chorionic Gonadotropin
BDI	Beck Depression Inventory
BIC	Bayesian Information Criteria
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CK	Creatine Kinase
CL/F	Apparent Oral Clearance
C_{max}	Maximum plasma concentration observed
COVID-19	Corona virus disease 2019
CRA	Clinical Research Associate
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of Variation
DBP	Diastolic Blood Pressure
DTS	Data Transfer Specification
EC50	Concentration at 50% of Maximum Effect
ECG	Electrocardiography
eCRF	Electronic Case Report Form
EDC	Electronic Data capture
EMAX	Maximum Effect
EOS	End of Study
FAS	Full Analysis Set
FSH	Follicle-Stimulating Hormone
G6PD	Glucose-6-phosphate dehydrogenase
GGT	Gamma Glutamyl Transferase
HBsAg	Hepatitis B Surface Antigen
HEENT	Head, Eyes, Ears, Nose, Throat
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IBSM	Induced Blood Stage Malaria
IIV	Inter Individual Variability
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
LOQ	Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
MMV	Medicines for Malaria Venture
MPC90	Minimal Parasiticidal Concentration
NCA	Non-Compartmental Analysis
ND	Non Detect
NLME	Nonlinear Mixed Effects

PC	Pharmacokinetics Concentration
PD	Pharmacodynamics
Pf iRBC	*P.falciparum* Infected Red Blood Cell
pfMGET	Male gametocyte-specific transcript
pfSBP-1	Ring-stage transcript
pfs25	Female gametocyte-specific transcript
PK	Pharmacokinetics
PKPD	Pharmacokinetic-pharmacodynamic
PN	Preferred Name
PRR_{48}	Parasite Reduction Ratio Over 48 hours
PT	Preferred Term
$PCt_{1/2}$	Parasite Clearance Half-Life
QIMRB	QIMR Berghofer Medical Research Institute
qPCR	Quantitative Polymerase Chain Reaction
qRT-PCR	Quantitative Reverse Transcriptase Polymerase Chain Reaction
QTcB	Corrected QT interval with Bazett's Formula
QTcF	Corrected QT interval with Fridericia's Formula
RAT	Rapid Antigen Test
SAE	Serious Adverse Event
SAEM	Stochastic Approximation Expectation Maximization
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SBQ	Swiss BioQuant Central
SD	Standard Deviation
SDRT	Safety Data Review Team
SDTM	Study Data Tabulation Model
SE	Standard Error
SOC	System Organ Class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
SSR	Southern Star Research
$t_{1/2}$	Elimination Half-Life
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to Reach Maximum Plasma Concentration
VIS	Volunteer Infection Study
Vss/F	Apparent Volume of Distribution at the Steady State After Single Dose
VPC	Visual Predictive Check
Vz/F	Apparent Volume of Distribution after Single Dose
WOCBP	Women of Child Bearing Potential
WHODrug	World Health Organization Drug Dictionary
λ_z	Lambda-z: Slope of the apparent elimination phase

2. INTRODUCTION

The following Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of the data from the MMV_MMV367_22_01 study. The SAP details the methods for statistical analysis of outcomes relating to safety, pharmacokinetics (PK), pharmacodynamics (PD), and population modelling of pharmacokinetic / pharmacodynamic (PK/PD) data arising from this clinical trial. This SAP has been developed and finalised prior to database lock and final analysis.

Planned analyses identified in this SAP may be included in the clinical study report (CSR), regulatory submissions, and future manuscripts. In addition, post hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR and in any publications.

Any significant changes from planned analyses will also be described in the final CSR.

3. PROJECT OVERVIEW

3.1 Study Design

This is an open-label, adaptive study that will utilise the *P. falciparum* induced blood stage malaria (IBSM) model to characterise the pharmacokinetic/pharmacodynamic (PK/PD) profile and safety of MMV367.

Up to 18 participants will be enrolled in cohorts of up to 6 participants each. The study will proceed as follows for all participants:

- Screening period of up to 28 days to recruit healthy adult participants.
- Day 0: Intravenous inoculation with approximately 2,800 viable *P. falciparum*-infected erythrocytes.
- Days 1-3: Daily follow up via phone call or text message.
- Days 4-7: Daily site visits for clinical evaluation and blood sampling to monitor malaria parasitaemia via quantitative polymerase chain reaction (qPCR).
- Day 7 PM: Start of confinement within the clinical trial unit.
- Day 8: Administration of a single oral dose of the investigational medicinal product (IMP) (MMV367). Different doses of MMV367 will be administered across and within cohorts in order to effectively characterise the PK/PD relationship.
- Days 8-11: Regular clinical evaluation and blood sampling to monitor malaria parasitaemia and measure MMV367 plasma concentration.
- Day 11 AM: End of confinement within clinical trial unit.
- Days 12-23: Outpatient follow-up for clinical evaluation and blood sampling.
- Day 24: Initiation of compulsory definitive antimalarial treatment with Riamet® (artemether/lumefantrine) and/or other registered antimalarials if required. Treatment will be initiated earlier than Day 24 in the event of:
    - Insufficient parasite clearance following IMP dosing (parasitaemia not reduced ≥10-fold by Day 10 compared with peak parasitaemia on Day 8).
    - Parasite regrowth following IMP dosing (initial parasite clearance is followed by asexual parasite regrowth above 5000 parasites/mL).
    - Participant discontinuation/withdrawal
    - Investigator's discretion in the interest of participant safety.
- Day 27: End of study visit for final clinical evaluation and to ensure complete clearance of malaria parasitaemia (at least one negative malaria PCR result required).

MMV367 will be administered as a single oral dose on Day 8, with different doses to be tested across and within cohorts to effectively characterise the PK/PD relationship. Participants will be randomised to a dose group on the day of dosing. The highest dose of MMV367 administered in this study will be no more than 1500 mg.

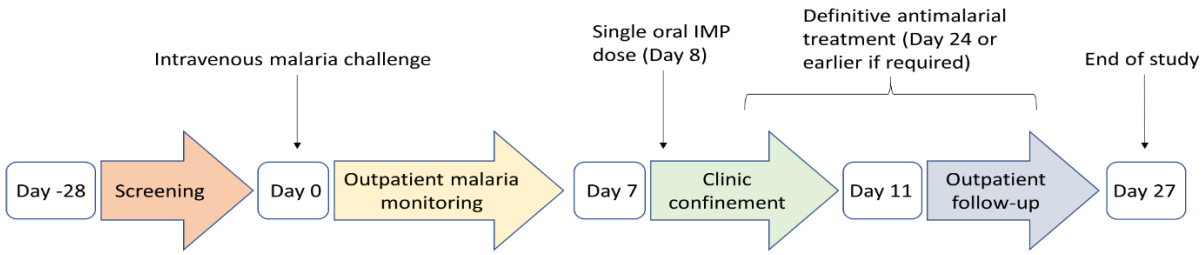
The doses to be tested in Cohort 1 will be as follows:

MMV367 dose	20 mg	90 mg	1500 mg
Number of participants	3	2	1

The Safety Data Review Team (SDRT) will meet following the completion of Cohort 1 to review all safety, PK, and PD data. Doses to be tested in Cohort 2 will be informed by the results obtained in Cohort 1 and will be designed to refine the PK/PD parameter estimates. It may be necessary to test a dose lower than 20 mg in Cohort 2 if PK/PD parameters such as the EC50 were not sufficiently well estimated in Cohort 1. It may also be necessary to obtain additional data at the dose levels tested in Cohort 1. The maximum dose in Cohort 2 will not exceed 1500 mg. Specific doses, and the number of participants per dose, to be tested in Cohort 2 will be decided by the SDRT based on PK/PD simulations.

The SDRT will meet following the completion of Cohort 2 to review all safety, PK, and PD data. If the SDRT deems sufficient data has been obtained to achieve the primary endpoint (i.e., the PK/PD relationship of MMV367 has been appropriately characterized), a third cohort of participants will not be enrolled. If the SDRT deems further data is necessary, doses for Cohort 3 will be selected as described above for Cohort 2.

3.2 Schema



3.3 Schedule of Activities

The below table summarises the activities and procedures to be conducted as per this protocol during screening, eligibility, malaria inoculation, out patient monitoring, IMP administration and clinic confinement, and at the end of study.

Screening and malaria challenge period

Study Day	**-28 to -1**	**-3 to -1**	**0**		**1**	**2**	**3**	**4**	**5**	**6**	**7 AM**
	Screening	**Eligibility confirmation**	**Pre-inoculation**	**Post-inoculation**	**Phone contact**			**Outpatient visits**			
Informed consent	X										
Beck Depression Inventory	X										
Cardiovascular risk	X										
Demography	X										
Medical history	X		X								
Prior medications	X		X								
Eligibility	X	X	X								
Urine drug screen	X		X								
Alcohol breath test	X		X								
Viral screen blood sample	X										
RBC alloantibody blood sample	X										
Coagulation profile blood sample	X										
COVID-19 rapid test			X								
COVID-19 PCR test		X								X	
G6PD test blood sample	X										
Serum pregnancy test blood sample	X[c]	X[d]									
Urine pregnancy test (WOCBP)			X								
FSH test (post-menopausal women)	X										
Urinalysis sample	X	X									
Adverse events				X	X	X	X	X	X	X	X
Concomitant medications				X	X	X	X	X	X	X	X
Safety serum retention			X								
Full physical exam	X[a]										
Abbreviated physical exam			X								
Symptom directed physical exam								X	X	X	X
Malaria clinical score			X					X	X	X	X
Vital signs	X[e]		X	X				X	X	X	X
Electrocardiograph (triplicate)	X		X								
Haematology blood sample	X	X									X

Study Day	-28 to -1	-3 to -1	0		1	2	3	4	5	6	7 AM
Biochemistry blood sample	X[b]	X									X
Diary card				X	X	X	X	X	X	X	X
Phone contact					X	X	X				
Malaria challenge agent administration				X							
Malaria PCR blood sample			X					X	X	X	X
Future malaria research blood sample (if participant consented)			X								

FSH: Follicle-stimulating hormone; G6PD: Glucose-6-phosphate dehydrogenase; PCR: Polymerase chain reaction; RBC: Red blood cell; WOCBP: Women of childbearing potential.
[a]Body height to be recorded at screening only.
[b]Lipids included at Screening for cardiovascular risk factor.
[c]Serum pregnancy test to be performed for all women at Screening.
[d]Serum pregnancy test to be performed for WOCBP at the eligibility confirmation visit.
[e]At screening, vital signs will be measured after the participant has rested in the supine position for 5 minutes. SBP and DBP will be measured again after the participant has transitioned to a standing position for 3 minutes to assess postural hypotension (see Section 5.2, exclusion criterion 10). At all other time-points vital signs will be measured after the participant has rested in the seated position for at least 5 min.

IMP administration and clinic confinement period

Study Day	7 PM	8										9			10			11
Hours post-IMP dose		Pre-dose	0	1	2	3	4	6	8	12	16	24	30	36	48	54	60	72
Urine drug screen	X																	
Alcohol breath test	X																	
COVID-19 rapid test	X																	
Urine pregnancy test (WOCBP)	X																	
Adverse events		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Abbreviated physical exam		X																
Symptom-directed physical exam				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Malaria clinical score		X						X		X		X	X	X	X	X	X	X
Vital signs		X						X		X		X	X	X	X	X	X	X
Electrocardiograph		X										X			X			X
Haematology blood sample		X										X						X
Biochemistry blood sample		X										X						X
Malaria PCR blood sample		X			X		X		X	X	X	X	X	X	X	X	X	X
Randomisation		X																
IMP administration			X															

IMP PK blood sample		X		X	X	X	X	X	X	X	X	X		X	X		X	X
Parasite *ex vivo* viability blood sample		X							X		X	X		X	X			X
Future malaria research blood sample (if participant consented)_		X																

IMP: Investigational medicinal product; PK: Pharmacokinetics; PCR: Polymerase chain reaction; WOCBP: Women of childbearing potential.

Outpatient follow-up period

Study Day	**12**	**13**	**15**	**17[d]**	**20[d]**	**22**	**24[d]**	**27 EOS[e]**
Hours (days) post-IMP dose	**96±4 (4)**	**120±12 (5)**	**168±24 (7)**	**216±24 (9)**	**288±24 (12)**	**336±24 (14)**	**384±24 (16)**	**456±24 (19)**
Viral screen blood sample								X
RBC alloantibody blood sample								X
Serum pregnancy test blood sample (WOCBP)								X
Urinalysis sample								X
Adverse events	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Safety serum retention blood sample								X
Full physical exam								X
Symptom directed physical exam	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X
Malaria clinical score	X	X	X	X	X	X	X	X
Electrocardiograph								X
Haematology blood sample			X			X		X
Biochemistry blood sample			X			X		X
Diary card	X	X	X	X	X	X	X	X
Malaria PCR blood sample	X	X	X	X	X	X	X	X
IMP PK blood sample	X	X	X	X	X			
Definitive antimalarial treatment							X[b]	
Parasite drug resistance blood sample				X[a]				
Parasite *ex vivo* growth blood sample	X			X[c]				
Future malaria research blood sample (if participant consented)	X		X					X

EOS: End of study; IMP: Investigational medicinal product; PK: Pharmacokinetics; PCR: Polymerase chain reaction; RBC: Red blood cell; WOCBP: Women of childbearing potential.
[a]One blood sample will be collected for parasite drug resistance assessment only in the event of parasite regrowth. This sample will be collected just prior to initiation of definitive antimalarial treatment.
[b]Definitive antimalarial treatment to be initiated on Day 24, or earlier in accordance with the criteria specified in section 4.1 of the protocol.
[c]One blood sample will be collected for parasite *ex vivo* growth only in the event of parasite regrowth. This sample will be collected just prior to initiation of definitive antimalarial treatment.
[d]Visit not required if participant has previously been administered definitive antimalarial treatment and returned at least one negative malaria PCR result.
[e]Participants who withdraw, or are withdrawn or discontinued from the trial, will be asked to attend an early termination visit with assessments equivalent to the Day 27 EOS visit.

3.4 Objectives

3.4.1 Primary Objective

- To characterise the PK/PD relationship of MMV367 in healthy participants experimentally infected with blood stage *P. falciparum.*

3.4.2 Secondary Objective(s)

- To evaluate the safety and tolerability of single oral doses of MMV367 in healthy participants experimentally infected with blood stage *P. falciparum*.
- To evaluate the safety and tolerability associated with blood-stage malaria infection in healthy malaria naïve participants.
- To characterise the pharmacokinetics of MMV367 following single oral dose administration in healthy participants experimentally infected with blood stage *P. falciparum*.
- To characterise the parasite clearance kinetics following single doses of MMV367 in healthy participants experimentally infected with blood-stage *P. falciparum*.

3.4.3 Exploratory Objective(s)

- To investigate potential resistance of *P. falciparum* to MMV367 in participants experiencing parasite regrowth after MMV367 administration.
- To characterise the effect of MMV367 on *P. falciparum* parasite viability.

3.5 Endpoints

3.5.1 Primary Endpoint (s)

- The PK/PD relationship between MMV367 plasma concentrations and blood stage asexual parasitaemia.

3.5.2 Secondary Endpoint (s)

3.5.2.1 Safety Parameters

- The incidence, severity and relationship to MMV367 of adverse events as determined by self-reported symptoms, clinical laboratory analysis, vital signs, physical examinations and ECG assessments.
- The incidence, severity and relationship to the malaria challenge agent of adverse events as determined by self-reported symptoms, clinical laboratory analysis, vital signs, physical examinations and ECG assessments. Additionally, the severity of the induced malaria infection in each participant graded by the malaria clinical score.

3.5.2.2 PK Parameters

- The pharmacokinetics of MMV367 calculated using non-compartmental methods.
  Parameters:
  C_{max}: Maximum plasma concentration observed
  t_{max}: Time to reach maximum plasma concentration
  AUC_{last}: Area under the curve from time 0 to last measurable concentration
  AUC_{inf}: Area under the curve from time 0 to infinity
  $t_{½}$: Half-life
  CL/F: Apparent Oral Clearance

V_z/F: Apparent volume of distribution
λ_z: Terminal rate constant

3.5.2.3 Parasite Clearance Kinetics

- The parasite clearance kinetics following dosing with MMV367 (parasite reduction ratio over a 48-hour period [PRR_{48}] and corresponding parasite clearance half-life [$PCt_{1/2}$]).

3.5.3 Exploratory Endpoint (s)

- Incidence and level of resistance to MMV367 in parasites determined using *in vitro* methods.
- The effect of MMV367 on parasite viability examined by *ex vivo* cultures.

3.6 Sample Size

A maximum sample size of up to 18 participants is expected to be sufficient to achieve the primary endpoint of the study, which is to determine the PK/PD parameters of MMV367. This sample size is not based on formal statistical calculations but rather is based on previous experience of characterising the PK/PD relationship of antimalarials using the IBSM model. The specific number of participants required will be dependent on the emerging results during the study; it is possible that less than 18 participants will be required. The SDRT will review the data after the completion of each cohort and decide when sufficient data has been obtained to complete the primary endpoint. No more than 18 participants will be administered IMP in this study.

3.7 Treatment Assignment and Randomisation

All participants will receive an identification number (screening number) as soon as they have signed the informed consent form. Participants who meet the eligibility criteria and are enrolled in the study will be assigned an enrolment number on Day 0 immediately prior to administration of the malaria challenge agent. Participants will be randomised within each cohort to a dose group on Day 8, immediately prior to administration of the IMP. A randomisation schedule will be prepared in advance and take in account potential participant withdrawals prior to scheduled dosing with IMP. The details of the randomisation procedure will be described in the randomisation plan. This is an open label study and therefore no blinding will be performed.

Replacement of Withdrawn/Discontinued Participants

Participants who withdraw, or are withdrawn or discontinued from the trial, may be replaced after mutual agreement between the Sponsor and the Principal Investigator. The decision regarding the replacement of participants will be documented.

All withdrawn participants must successfully complete the full course of definitive antimalarial treatment.

4. STATISTICAL CONSIDERATIONS

Data analysis will be performed according to the Sponsor's representative Standard Operating Procedures (SOPs).

The general analytical approach for all endpoints will be descriptive in nature. All summaries will present the data by dose group as well as by all participants combined.

Unless otherwise stated, the following statistical approaches will be taken:

Continuous variables:	Descriptive statistics will include the number of non-missing values, mean, standard deviation (SD), CV%, median, interquartile range, minimum, and maximum. The minimum and maximum values will be presented to the same number of decimal places as recorded in the raw data; mean and median will be presented to 1 decimal place more than raw data; and SD will be presented to two more decimal places than the raw data. The number of decimals for lab parameters may be reduced if the full presentation of the data includes more than 4 significant figures.
Categorical variables:	Descriptive statistics will include frequency counts and percentages per category. Percentages will be rounded to one decimal place, with the denominator being the number of patients in the relevant population.
Imputation:	No imputation will be performed for missing data.
Confidence intervals (CIs):	CIs will be two-sided and will use 95% confidence levels.
Unscheduled Visits	Unscheduled visits that do not have laboratory data on the same visit date will be excluded from summary tables.
Early termination visit	Assessments conducted at Early Termination will be excluded from visit-based summary tables unless otherwise indicated.

4.1 Data Capture

4.1.1 Database

The primary method of data collection is via the study database, developed within the chosen Electronic Data Capture (EDC) platform, IBM Clinical Development. The database has been designed based on the final protocol, the system/core configuration, electronic Case Report Form (eCRF) specifications and/or mock eCRF and consistency check specifications.

Data will be entered directly into the EDC system. Site-collected data will be entered directly from source notes at the site and will be verified by Clinical Research Associates (CRAs) to ensure data integrity.

Refer to the Data Management Plan for further details.

4.1.2. Third Party Data

4.1.2.1 Safety Laboratory

Central safety laboratory data will be received from Sullivan Nicolaides (SNP) Pathology Central Laboratory as specified in the Data Transfer Specification. At least one transfer will be delivered prior to database lock and reconciled against CRF data. Following successful reconciliation and resolution of any data issues, the data will be incorporated into the End of Study analysis.

No unit conversion of laboratory data will be performed.

4.1.2.2 PK Laboratory

PK samples will be analysed by Swiss BioQuant Central (SBQ) and PK parameters will be derived by PharmaKinetic. Final PK assay data will be transferred to SSR, as specified in the SBQ DTS, for incorporation into the PC SDTM.

4.1.2.3 PD Laboratory

All parasitaemia data will be generated by the Queensland Paediatric Infectious Diseases (QPID) laboratory and captured electronically using MARS (18S qPCR parasitaemia data). All parasite life-stage data (i.e. gametocytemia and ring-stage parasites) will be generated by the QPID laboratory and transferred electronically to the Queensland Institute of Medical Research (QIMR) Berghofer and this data will be used for PK/PD modelling. QIMR will provide the 'raw' PCR data 18S, the female gametocyte-specific transcript (pfs25), the male gametocyte-specific transcript (pfMGET) and the ring-stage transcript (pfSBP-1) to SSR as per DTS, and final PD parameters will be in the PRR report.

4.1.2.4 PK/PD Laboratory

PK/PD analysis will be performed by MMV, Pharmacometrics. SSR will be required to provide the PK concentration and parasitemia data, as well as any CRF datasets required to perform the PK/PD analyses (e.g. demographics, drug administration data).

4.2 Statistical Programming

4.2.1 Programming Specifications

4.2.1.1 Safety Analysis

Programming specifications will be prepared to detail the SAS programming of CDISC (SDTM and ADaM) datasets and listings, tables and figures.

4.2.1.2 PD Analysis

Data manipulation and data analyses for all PD data will be performed using R (version 4.1.0 or higher).

4.2.1.3 PK Analysis

The estimation of pharmacokinetic parameters by non-compartmental analysis (NCA) methods will be performed using Phoenix WinNonlin software (v8.3 or a more recent version, Certara USA, Inc., USA).

4.2.1.4 PKPD Analysis

All data processing, analysis, model setup and modeling result analysis including goodness-of-fit plots will be performed using R 3.6.3 or above and IQRtools package 1.8.0 or above.

NLME modelling will be performed with Monolix 2019R1 [MLX19] using Stochastic Approximation Expectation Maximization (SAEM) for parameter estimation. For PD modelling where typically the variance of random-effects cannot be estimated from the data, the IQRtools SysFit approach will be used to estimate typical and individual PD parameters.

4.2.2 Baseline

Baseline will be defined as:

Safety

- The last scheduled observation prior to the administration of the malaria challenge inoculum [Inoculation Baseline],
- The last scheduled observation prior to the first administration of IMP [Treatment Baseline].

For replicate measurements (e.g., ECG) at baseline, the mean of those replicates will be used as the baseline value.

PD

- The last observation prior to the administration of the IMP for PD data.

PK

- The last observation prior to the administration of the IMP for PK data.

4.2.3 Change from Baseline

Change from Baseline will be calculated as:

$$Change\ from\ baseline = (postbaseline\ value) - baseline\ value$$

4.2.3.1 Days relative to Inoculation

$$Days = (Assessment\ Date - Inoculation\ Administration\ Date) + 1$$

4.2.3.2 Days relative to IMP administration

$$Days = (Assessment\ Date - First\ Study\ Drug\ Administration\ Date) + 1$$

4.2.4 IMP Treatment Groups

Tabulations will summarise data by the IMP dose groups and these may vary for each cohort.

5. ANALYSIS SETS

The analysis sets to be used for the analyses will be: Full Analyses set (FAS), IMP set, PK set, PD set and PK/PD set.
The number of participants in each analysis set will be summarised, with a corresponding listing.

5.1 Analysis Set Descriptions

5.1.1 Full Analysis Set

The Full Analysis Set (FAS) will consist of all enrolled participants, i.e. participants that received the malaria challenge agent.

5.1.2 IMP Set

The IMP Set will include all enrolled participants administered with the IMP.

5.1.3 PK Analysis Set

The PK analysis set will include all participants who have sufficient plasma samples taken for at least one of the PK parameters to be calculated and who received any study treatment and experienced no protocol deviations with relevant impact on PK data. Should an adverse event, for example, vomiting within 4 hours of IMP dosing occur and be deemed detrimental to the data quality, additional subsets may be invoked, and those participants be omitted from the summary statistics. This will be confirmed by the sponsor if applicable.

5.1.4 PD Analysis Set

The PD analysis set will include all participants inoculated with the malaria challenge agent and who develop parasitaemia detectable by qPCR, received a dose of MMV367, and have no protocol deviations that would exclude them from the PD analysis due to their impact on the PD analysis.

5.1.5 PK/PD Analysis Set

The PK/PD analysis set will include all participants included in both the PK set and the PD set.

6. PROTOCOL DEVIATIONS

Analysis Set: FAS

All protocol deviations will be listed, grouped by participant and dose group.

The protocol deviation summary table will capture all deviations as minor and major.

The protocol deviation summary table will include:

- The total number of minor protocol deviations
- The total number of major protocol deviations
- The number of Participants who reported at least one minor protocol deviation
- The number of Participants who reported at least one major protocol deviation

7. PARTICIPANT DISPOSITION

Analysis Set: FAS

7.1 Disposition

A listing of participant disposition will present:

- Date of informed consent
- Date of inoculation
- Date of IMP administration
- Date of mandatory rescue medication administration
- Date of Primacin administration when applicable
- Did the participant complete the study?
- Date of completion / early withdrawal
- Primary reason for early withdrawal (including instances where early termination was related to COVID-19)

Detailed early withdrawal information will also be listed in a separate listing.
If there are any deaths reported, a separate death listing will be prepared.
The number and percentage of Participants entering and discontinuing the study will be summarised by dose group and overall along with the reason for discontinuation. The participant disposition summary table will include:

- Number of participants signed informed consent
- Number of participants who received IMP
- Number of participants who completed the full study
- Number of participants withdrawn from the study early
- Reason for early withdrawal

7.2 Analysis of Population Assignment

Analysis set data will be listed for all participants. A summary table will show the number of participants within each of the analysis sets.

8. DEMOGRAPHIC AND BASELINE INFORMATION

Analysis Set: FAS

8.1 Demographics

Demographic data will be listed for all enrolled participants and summarised by dose group and overall. Data includes:

Age
Sex
Women of Child-bearing potential
Post-menopausal women
Race
Ethnicity
Weight (kg)
Height (m)
BMI (kg/m^2)

8.2 Medical History

All medical history data will be listed, grouped by participant.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 24.1) and summarised by system organ class (SOC) and preferred term (PT).

8.3 Prior Medications

Prior medications are defined as any medication that is started before first inoculation with the malaria challenge agent, regardless of when it ended. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether it was taken before IMP or concomitantly, it will be considered as prior and concomitant. Medications will be coded using WHODrug Dictionary September 2021 release.

Prior medications will be listed.

8.4 Drug Screen

Drug screen data will be listed for all participants.

8.5 Alcohol Screen

Alcohol screening data will be listed for all participants.

8.6 SARS-CoV-2 Screening

Any positive SARS-CoV2 screening results will be listed.

8.7 Follicle Stimulating Hormone (FSH)

FSH results will be listed for Post-menopausal women only.

8.8 Beck Depression Inventory

Beck Depression Inventory (BDI-II) data will be listed for all participants, including answers to the individual questions as well as the total scores, which are auto-calculated within the CRF.

9. TREATMENT EXPOSURE

Analysis Set: FAS Set

Participant exposure to the protocol-specified treatments (IMP, malaria challenge agent, mandatory rescue medications - Riamet, Malarone, IV artesunate - and Primacin if also administered) will be listed and summarised by dose of IMP and overall.

10. PRIMARY ENDPOINT ANALYSIS (PK/PD ANALYSIS)

Analysis Set: PK/PD Analysis Set

The primary endpoint is the PK/PD relationship of MMV367.

10.1 Overview of methodology for PK/ PD Modelling

Two stage approach:

1. Estimate the PK parameters by fitting a PK model and relevant covariates to the individual PK concentrations
2. Estimate the PD parameters by fitting a PKPD model to the asexual parasitemia observations using the individual PK parameters as regressors

10.2 Sources of Data

The PK/PD dataset will contain the individual information on the inoculum volume, date and time of its administration; doses of MMV367 administered with date and time of administration; plasma PK concentrations of MMV367 with date and time of blood sampling; triplicate total parasitemia counts by 18S qPCR with date and time of blood sampling; gametocytemia counts by pfs25, pfMGET and pfSBP-1 if relevant; and typical covariates such as age, body weight, height, sex and race.

The PK/PD dataset will contain the data from the current VIS study MMV_MMV367_22_01 and from the past MMV_MMV367_21_01_FIH study.

The PK/PD dataset for MMV_MMV367_22_01 will be prepared by SSR in the MMV format from the database. The PK dataset for MMV_MMV367_21_01_FIH will be prepared by ClinBay.

10.3 Data Assembly

10.3.1 Master PK/PD dataset

Data from study MMV_MMV367_22_01_VIS will contain information on the individual MMV367 doses, MMV367 PK concentrations, the triplicated parasitemia levels, gametocyte data and typical covariates such as age, height, weight, sex and race. Data from study MMV_MMV367_21_01_FiH will be added to increase the number of individuals with PK profiles.

A master dataset will be assembled formatted according to the MMV dataset standard. (cf., "MS_IQdataset_V4 "). Plasma concentration will be in ug/mL, total parasite levels in counts/mL, and doses in mg. Gametocyte data is in copies/uL.

Parasite data after the first administration of rescue medication is flagged by setting the IGNORE column to "Rescued". The time in hours is relative to the (first) MMV367 administration time. Gametocyte data will be converted to parasite counts following the

instructions in "Analyzing RNA data by K.Collins Nov2017.docx". Total counts of parasites were flagged to be ignored (by setting the column IGNORE to "gametocytes") if counts of gametocytes exceeded 10% of total counts.

A general analysis dataset will then be created from the master dataset. The general dataset will contain the following observations: MMV367 plasma concentrations, total parasite count, as well as counts of gametocytes. In addition, dosing records for *P. falciparum* inoculation, MMV367 administration and rescue medication administration will be defined.

The following covariates will be included as additional columns in the general dataset.

- DOSELEVEL: the dose amount
- DOSEMULT: the number of doses
- WT0: body weight (kg)
- AGE: age (years)
- SEX: sex (male or female)
- Infection status (for all participants from MMV_MMV367_22_01_VIS infection status will be positive; For all participants from MMV_MMV367_21_01_FIH infection status will be negative.)
- PLbase: The model baseline parasitemia value – the geometric mean of parasite counts at time of first MMV367 dose.

10.3.2 PK modeling data set

Observations below the lower limit of quantification (LLOQ) will be censored by setting the CENS column for these observation records to 1 and setting the corresponding dependent variable (DV) column to the LLOQ (→ M4 method). Observation records with missing values and records with missing times will be ignored. Records flagged to be ignored will be removed from the dataset. Observations not analyzed in the PK modelling (i.e., all parasite count records) will be removed. Consequently, the PK modelling NLME dataset will contain only MMV367 dosing records and MMV367 plasma concentration records.

10.3.3 PD modeling data set

Observations below the LLOQ will be censored by setting the CENS column for these observation records to 1 and the corresponding DV value to the LLOQ, i.e., 10 p/mL (→ M3 method). Total and viable counts of parasites for which counts of gametocytes exceeded 10% of total counts are flagged to be ignored (by setting the column IGNORE to "gametocytes"). Observation records with missing values and records with missing times will be ignored. Records flagged to be ignored will be removed from the dataset. Observations not analysed in the PD modelling analysis (i.e., MMV367 plasma concentration records) will be removed. Consequently, the PD modeling NLME dataset will contain only MMV367 dosing records and total parasite counts.

Parasite counts will be log-transformed for the PD modelling and estimated individual PK model parameters will be added to the dataset as regressors.

10.4. Methods

10.4.1. General PKPD model building approach

Population models of the PK and PD will be developed in step-wise manner.

1. A population PK model will be developed to obtain individual PK parameter estimates based on which the individual PK profiles are well described.
2. A parasite growth model (parasite growth rate and deviation of parasitemia at inoculation from parasitemia at IMP administration) will be estimated from the total parasite counts before treatment administration. Estimation of typical and individual PD parameters will be performed with IQRtools SysFit. Other appropriate growth models, e.g. an oscillatory model, will be tested if advisable.
3. The PKPD model will be built using the individual PK parameter estimates and individual growth model parameter estimates as regression parameters. Estimation of typical and individual PD parameters will first be performed with IQRtools SysFit to investigate model identifiability and second with Monolix to additionally estimate IIV.

Estimations will be done using gradient-based SysFit algorithm in IQRtools or SAEM algorithm in Monolix. Other appropriate methods may be used if advisable.

Inter-individual variability (IIV) is implemented for normally distributed parameters using the following equation with Θ_0 as population average parameter, Θ_i as individual parameter, and η_i as random effect that is distributed normally around zero ($\eta_i \sim N(0, \omega^2)$).

$$\Theta_i = \Theta_0 + \eta_i$$

The following equation is used for log-normally distributed parameters.

$$\ln(\Theta_i) = \ln(\Theta_0) + \eta_i$$

Continuous covariates on log-normally distributed parameters will be implemented as follows.

$$\Theta_i = \Theta_0 \cdot \frac{COV_i}{COV_{median}}^{\beta} \cdot e^{\eta_i}$$

Θ_i represents the individual parameter, Θ_0 the population mean value, COV_i the individual covariate value, COV_{median}, the population median covariate value, β the covariate coefficient, and η_i the individual random effect.

Categorical covariates on log-normally distributed parameters will be implemented as follows.

$$\Theta_i = \Theta_0 \cdot \Sigma_j\left(e^{\beta_j \cdot COV_{ij}}\right) \cdot e^{\eta_i}$$

The individual covariate values COV_{ij} are 1 if participant i belongs to the j_{th} category of the covariate and 0 otherwise. $beta_j$ is the covariate value for the j_{th} category. For one category, i.e. the reference, $beta_j$ is 0.

For the NLME modeling with Monolix, the log-likelihood and the Fisher information matrix will be approximated by importance sampling and stochastic approximation respectively. The number of iterations in the burn-in and the accumulation phase will be 500 and 200 respectively, but might be adjusted if required based on inspection of parameter estimate and objective function traces along estimation iterations. Individual parameters will be determined as conditional modes.

For PD modelling with the IQRtools SysFit implementation, a non-linear fixed-effects modelling approach is employed. Typical and individual parameters are both treated as fixed effects. The parameterization of individual parameters and covariates is fully consistent with the NLME parameterization above. The variances ω^2 of NLME random effects are accounted for by quadratic priors, added to the log-likelihood function, where the values for ω^2 are fixed and the η parameters are estimated. The profile-likelihood method [4, 5] is used to compute confidence intervals of the parameters estimated with the SysFit approach.

10.4.1.1. Model evaluation

Assessment of model adequacy and decisions about increasing model complexity will be driven by the data and guided by goodness-of-fit criteria, including:

1. visual inspection of diagnostic scatter plots (observed vs. predicted concentration, residual/weighted residual vs. predicted concentration or time and histograms of individual random effects, for example),
2. successful convergence of the minimization routine with at least 2 significant digits in parameter estimates,
3. plausibility of parameter estimates,
4. precision of parameter estimates,
5. correlation between model parameter estimation errors<0.95, and
6. the Bayesian information criterion (BIC), given the minimum objective function value and number of estimated parameters.

For the nonlinear fixed effects models, additional diagnostic plots will be produced:

7. objective function values across multiple fits from randomised initial guesses, and
8. profile likelihood plots

All parameter estimates will be reported with a measure of estimation uncertainty, such as the relative standard error of the estimates. The individual PK fits will be used to evaluate the adequacy to use the individual PK parameter estimates as regression parameters for PD modeling.
The adequacy of simulation with the selected models will be evaluated by visual predictive checks (VPCs). VPCs for each dose level will be performed by simulation of the study 200 times taking parameter estimation uncertainty into account. 95%-confidence intervals for the 5th percentile, the median, and the 95th percentile will be derived and compared to the corresponding values based on the data.

10.4.2. Building a PK model

The PK of *MMV367* will be modeled using compartmental models describing the absorption after oral administration, distribution between central and peripheral compartments, and the elimination from the central compartment. The visual data analysis will guide the selection of models that will be tested (e.g., with respect to number of compartments, linear or saturable elimination, absorption kinetics and error model). Covariates will be included if appropriate. Estimations will be done using SAEM algorithm in Monolix. Other appropriate methods may be used if advisable.

FIH data from *MMV_MMV367_21_01_FIH* has previously indicated that *MMV367* PK is adequately described by a one-compartment model with first order absorption parameterized in terms of *CL/F, Vc/F* and *ka*. Therefore, this structural model will initially be used to model *MMV367* PK using the PK modeling dataset. If required to adequately describe *MMV367* PK, structural models with greater numbers of compartments and different absorption models (eg first-order rate, lag, transit compartments) will be fitted.

An exploratory investigation of covariate-parameter relationships will be undertaken during the PK modelling step. The covariate WT0 on the clearance and volume parameters will be included to allow predictions in children. Since the body weight distribution may be narrow, the exponents will be fixed to 0.75 and 1 respectively on clearances and volumes of distribution. Other covariates of interest may include AGE, SEX, Infection status and PLbase – however, depending on the population make-up of these covariates, some may not be included. In the event that the distributions of WT0 and AGE are very narrow, a reference value for the population may be used instead of individual participant covariates.

Covariate modeling will be undertaken in the following steps:

- Pre-defined covariate-parameter relationships will be identified based on exploratory analysis and mechanistic plausibility – in particular, WT0 on clearance and volume PK parameters (central and peripheral compartments, if appropriate).
- A full model will be constructed, avoiding simultaneous inclusion of covariates with correlation coefficients >0.5.
- Population parameters will be estimated (both fixed effects [covariate coefficients and structural model parameters] and random effects).
- An exploratory assessment of any remaining trends will be conducted by graphical inspection of all covariate effects (plots of MAP Bayes estimates of individual random effects and/or WRES from the full model vs. covariates).
- Inferences about clinical relevance of parameters will be based on the resulting parameter estimates of the full model and measures of estimation precision (asymptotic standard errors, bootstrap 95% confidence intervals or log-likelihood profile).
- No hypothesis testing will be conducted.
- This approach enables the direct assessment of clinical relevance of covariate effects and also provides some explanation for the apparent absence of a covariate effect (true lack of an effect vs. lack of information about that effect).

Based on diagnostics plot (if shrinkage is less than >30%) the estimation of random effect covariance matrix will be considered. Additionally, it will be attempted to estimate the full random effect covariance matrix. In order to assess the identifiability of the correlations between random effects, parameter estimations will be repeated from randomly chosen initial guesses for the fixed effect parameters that are estimated. All resulting parameters, including the correlation estimates for the random effects will be compared.

10.4.3. Building a PD model

PD model development will be done using gradient based algorithms in IQRTools SysFit. The selected model will then be estimated with SAEM in Monolix to attempt to estimate IIV. Other appropriate methods may be used if advisable. As a general concept the changes in living parasite P are modeled as the effect of a net exponential growth rate GR and a killing or clearance rate $Kill$ due to *MMV367*. The initial parasitemia P_{base} at time t_0 will be derived from the mean parasitemia which was observed at treatment administration and a parameter $PLerr$ to allow for population and individual deviations. The equations are expressed in the log-scale such as:

$$\begin{aligned} \frac{dPL}{dt} &= GR - Kill \\ PL(t_0) &= PL_{base} + PLerr \end{aligned}$$

where $PL = \ln(P)$ is the log-transformed parasite counts.
Different models describing the relationship of *MMV367* plasma concentration on the killing rate may be tested.

10.5. PK/PD Endpoints

- PK/PD equations comprising the final structural model
- Primary PK and PD parameters that make up the final structural model: estimated typical values with 90% confidence interval

10.6. Presentation of Results

A statistical and graphical analysis of the data (based on the general analysis dataset) will be included.

The analysis results will be reported in the main body of the CSR and technical details will be reported as an appendix (referred to here as the 'technical appendix'). The technical appendix will include the clinical data used in the analysis, data assembly, modelling methods, all results, discussions, and conclusions.

Key results will include description and interpretation of the selected model, parameter estimates, diagnostic plots of goodness-of-fit and will be included in the main text. Limitations of the model prediction will be discussed in the Discussion section of the technical appendix and mentioned in the main text of the CSR.

11. SECONDARY ENDPOINTS ANALYSIS

11.1 PD Analysis

Analysis Set: PD Analysis Set
PD endpoint: The parasite clearance kinetics following dosing with MMV367.

11.1.1 Data Handling

Handling of replicates
The data will be recorded as triplicate parasitaemia values for each participant at each time point. The replicate data will be summarised by calculating the geometric mean of the parasitaemia values per participant and time point and will be log10 transformed for statistical analyses.

Handling of missing data
Missing parasitaemia data will not be imputed. For any replicates that were non-detects (ND), the value will be substituted with 1 parasite/mL prior to calculating the geometric mean for parasitemia quantified from qPCR.

11.1.2 Parasite clearance kinetics

The Parasite Reduction Ratio (PRR) and corresponding parasite clearance half-life ($PCt_{1/2}$) of asexual parasites is derived from the clearance rate of parasitaemia after administration of MMV367 treatment. The analysis of PD response to investigational antimalarial therapy consists of:

- calculating the optimal parasite clearance rate (slope coefficient from the log-linear decay regression of qPCR data) for each individual, then,
- estimating dose specific parasite clearance rate and 95% confidence interval (CI) by calculating the weighted average slope estimate and corresponding standard error (SE) using an inverse-variance method.

The data used for all model selection and fitting calculations is comprised of the $\log_{10}$ transformed geometric mean of parasitaemia per time point per participant up to the first time point all parasitaemia replicates are ND. If during initial parasite clearance there are no samples ND for a participant, the last time point included in the analyses will be three time points after the minimum observed parasitemia value. All subsequent time points are set to 'missing' regardless of whether parasitaemia values increased afterwards due to potential

recrudescence. Sensitivity analyses may be performed using other thresholds to determine parasite clearance, for example, but not limited to, the lower limit of quantification (LOQ) (i.e. the lower limit of the reportable range) of 32 parasites/mL or limit of detection of 111 parasites/mL [1], to assess robustness of PRR estimates.
The PRR per 48 hours, PRR_{48}, for asexual parasite will be estimated using the slope of the optimal fit of the log-linear relationship of the parasitaemia decay over time from MMV367 administration for each individual, as detailed in CTM QIMR SOP 41 and Marquart et al. [2]

Table 1: Symbols and definitions of terms used in parasite clearance analysis (Part 1)

Symbol	Definition
$PRR_{48,i}$	Individual specific Parasite Reduction Ratio per 48 h
$PRR_{48,D}$	Dose specific Parasite Reduction Ratio per 48 h
$\beta_{1,i}$	Slope coefficient of log10 parasitaemia vs. time profile for individual i
$SE_{\beta_{1,i}}$	SE corresponding to $\beta_{1,i}$ for individual i
$\bar{\beta}_{1,D}$	Dose specific average slope estimate
$SE(\bar{\beta}_{1,D})$	Weighted SE of dose specific average slope estimate
PCt½	Parasite clearance half-life

Regression Modelling to Determine Optimal Fit

A regression modelling approach to remove potential lag and/or tail phases of the parasitaemia decay profile will be used to determine the optimal log-linear decay regression. The algorithm considers removing parasitaemia data points in an iterative process from both ends of the parasitaemia curve, i.e. a combination of right censoring (removing values from the tail phase) and left censoring (removing values from the lag phase), and uses model selection techniques to find the optimal log-linear regression.
The algorithm to obtain the log-linear decay for each participant is based on the log-linear regression detailed in Equation (1), where Time is the number of hours since administration of antimalarial treatment $(Time = 1, \dots, m)$, and β_0 and β_1 are the intercept and slope estimates, respectively.

$$\log_{10} Parasitemia = \beta_0 + \beta_1 Time \quad (1)$$

Based on the parasitaemia data for each participant, the iterative algorithm to determine the optimal log-linear decay for each participant is summarised in Table 2. The iterative algorithm is continued until a minimum of four observations are available.
The optimal log-linear regression model for a participant is deemed an appropriate fit if the overall model p-value < 0.001.

Table 2: Iteration process to determine the optimal log-linear decay curve.

Step 1: For each participant, fit the full model - fit a linear regression (as defined by Equation 1) to all m parasitaemia values of participant i
Step 2: Fit two models:
(a) Fit linear regression model to $m-1$ parasitaemia values, removing the first observation.
(b) Fit linear regression model to $m-1$ parasitaemia values, removing the last observation.
Step 3: Determine the best model of Step 2(a) and Step 2(b), defined as the model corresponding to the minimum overall model p-value.
Step 4: Of the best model defined in Step 3, repeat Step 2 and Step 3 in an iterative process until a minimum of four observations.
Step 5: Of the $m-3$ best models selected per iteration (including the full model (Step 1)), the optimal model was defined by the minimum overall model p-value.

Estimating Participant Specific PRR

The slope and corresponding SE estimate of the optimal linear regression model is used to calculate the participant specific PRR_{48} estimate and corresponding 95% confidence interval (95% CI), as shown in Equation (2) and (3), respectively.

$$PRR_{48,i} = 10^{-48\times\beta_{1,i}} \quad (2)$$

$$95\%\ CI:\ 10^{-48\left(\beta_{1,i}\pm 1.96\times SE(\beta_{1,i})\right)} \quad (3)$$

where $\beta_{1,i}$ and $SE_{\beta(1,i)}$ are the slope and corresponding standard error of the slope parameter of the optimal linear regression model, respectively.

Estimating Dose Specific PRR ($PRR_{48,D}$)

Of the participants with appropriate overall fit ($p<0.001$), the average PRR_{48} and corresponding 95% CI for each cohort is estimated by using the inverse variance method to calculate the weighted average linear regression slope ($\overline{\beta_1}$) and corresponding SE. The weighted average slope for s participants in the dose with appropriate overall fit is given by Equation (4):

$$\overline{\beta_1} = \frac{\sum_{i=1}^{s}(w_i\times\beta_{1,i})}{\sum_{i=1}^{n} w_i},\ i = 1,\dots,s \quad (4)$$

where the weight is the inverse of the squared standard error, $w_i = \frac{1}{SE(\beta_{1,i})^2}$. The standard error of $\overline{\beta_1}$ is estimated as, $SE(\overline{\beta_1}) = \sqrt{\frac{1}{\sum_{i=1}^{s} w_i}}$.

Therefore the dose specific PRR ($PRR_{48,D}$) and corresponding 95% confidence interval is estimated as shown in Equation (5) and (6), respectively:

$$PRR_{48,D} = 10^{-48\times\overline{\beta_1}} \quad (5)$$

$$95\%\ CI:\ 10^{-48\times\left(\overline{\beta_1}\pm 1.96\times SE(\overline{\beta_1})\right)} \quad (6)$$

PRR_{48} estimates will also be reported as $\log_{10}(PRR_{48})$.

Parasite Clearance Half Life

The parasite clearance half–life (PCt½) will be derived from the optimal decay rate, as shown in Equation (7):

$$\text{PC}t_{1/2} = \frac{\log_{10}(2)}{-\beta_1} \qquad (7)$$

The relationship between PRR_{48} and parasite clearance half-life ($PCt_{½}$) is a simple transformation of the PRR_{48} as shown in Equation (8):

$$PCt_{½} = log_{10}(2) \times \left(\frac{48\ hours}{log_{10}(PRR_{48,i})}\right) = \frac{\log_{10}(2)}{-\beta_{1,i}} \qquad (8)$$

where $PRR_{48,i}$ is the parasitaemia ratio estimated over a 48-hour interval that is subsequently transformed into a per hour clearance rate.

Comparison of Dose Specific PRR_{48}
To determine whether there are differences between dose specific PRRs, an omnibus test for between group differences is used. The test is used to assess whether there are differences in the weighted mean slope of the J doses, using the test statistic shown in Equation (9),

$$Q_B = \sum_{j=1}^{J} w_{j\cdot}\left(\bar{\beta}_{j\cdot} - \bar{\beta}_{\cdot\cdot}\right)^2 \sim \chi^2_{j-1} \qquad j = 1, \ldots, J \qquad (9)$$

The weight for the j^{th} dose is denoted by $w_{j\cdot} = \sum_{i=1}^{s_j} w_{ij}$ for participant i with appropriate overall fit in dose j. The $\bar{\beta}_{j\cdot}$ is the weighted average slope for dose j as defined in Equation (10), and $\bar{\beta}_{\cdot\cdot}$ is the weighted grand mean given by:

$$\bar{\beta}_{\cdot\cdot} = \frac{\sum_{j=1}^{J} w_{j\cdot}\bar{\beta}_{j\cdot}}{\sum_{j=1}^{J} w_{j\cdot}} \qquad (10)$$

Post-hoc pair-wise comparisons can be calculated using the test statistic $Z_G = \frac{G}{\sqrt{v_G}}$, where G is the contrast ($G = c_1\bar{\beta}_{1\cdot} + \cdots + c_J\bar{\beta}_J$) and v_G is the variance of the contrast ($v_G = \frac{c_1^2}{w_{1\cdot}} + \ldots + \frac{c_J^2}{w_{J\cdot}}$). The p-value of the L pair-wise comparisons can be calculated using the Scheffe method, by comparing Z_G^2 to a chi-squared distribution with $L - 1$ degrees of freedom.

11.1.3 Presentation of Results

Parasitaemia data will be listed for all enrolled participants and summarised for the PD population. PD parameters will be presented for all participants included in the PD population.

Parasite life-stage data (pfs25, pfMGET and sbp1 qRT-PCR) will be listed by participant and timepoint.

A full report on the pharmacodynamic data analysis will be included in the appendices of the CSR. This report will include a listing of PD endpoints (PRR_{48}, $PC_{t1/2}$), a table for Summary of PD endpoints by dose group and a figure for individual log-parasitaemia regression fit.

List of planned tables, listings and figures are in Appendix, Table A.

11.2 PK Analysis

Analysis Set: PK Analysis Set

PK endpoint: The pharmacokinetics of MMV367 calculated using non-compartmental methods.

11.2.1 Data Handling

Imputation of Non-Numerical or Negative Values

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

- Pre-dose sample times will be entered as zero
- Values that are below the limit of quantification (BLQ) obtained prior to the C_{max} will be entered as zero
- Values that are BLQ after the C_{max} will be treated as missing.
- Should partial AUCs be required then values that are BLQ after C_{max} may be imputed as zero for these partial areas if lambda-z cannot be determined.
- Values that are quantifiable after at least 2 consecutive BLQ values after C_{max} will be treated as missing for the calculation of PK parameters.

Missing data

- Values that are reported as “No Result” or “No Sample” etc. will be treated as missing

11.2.2 Rules for Pharmacokinetic Parameter Estimation using WinNonlin

Plasma concentration vs time profiles of MMV367 will be generated for each participant to allow for PK analysis. Pharmacokinetic parameters will be estimated using standard Phoenix WinNonlin methods, details of which may be found in the documentation accompanying the WinNonlin software package. The following constraints will apply:

Parameter Estimation	Constraint
Trapezoidal Method	Linear trapezoidal linear/log interpolation method
Number of Points used for Lambda-z	At least 3, not including C_{max}
Minimum Requirements for AUC	At least 3 consecutive quantifiable concentrations
Dose	Actual dose
Sampling Times	Actual sampling times

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

The choice of data points for determination of lambda-z will be applied by the Phoenix software as a default method, the pharmacokineticist who may adjust the selection to provide a more appropriate fit and records of this will be documented in the software data.

11.2.3 Data Quality

The following flags/footnotes may be applied to the pharmacokinetic parameters:

Flag	Footnote
a	Rsq of regression was <0.8
b	Extrapolated portion of $AUC_{0\text{-inf}}$ >20%
c	Insufficient post-C_{max} data points for estimation of lambda-z
d	Entire profile BLQ, no pharmacokinetic parameters could be calculated
e	Regression could not be fitted

In the event that a reliable lambda-z cannot be determined, or the extrapolated portion of $AUC_{0\text{-inf}}$ is >20%, then the parameter estimates derived using lambda-z and/or $AUC_{0\text{-inf}}$ may be deemed unreliable and excluded from the summary statistics. Additional flags may be applied based on emerging data.

11.2.4 PK parameters

The following pharmacokinetic parameters for MMV367 in plasma will be estimated where possible and appropriate for each participant and dose group:

CDISC Term	Parameter	Definition	DP or SF	No. of DP/SF
TMAX	T_{max}	Time of maximum observed concentration	DP	2
CMAX	C_{max}	Maximum observed concentration	SF	3
AUCLST	AUC_{last}	Area under the curve from 0 time to the last measurable concentration	SF	3
AUCIFO	$AUC_{0\text{-inf}}$	Area under the curve from 0 time extrapolated to infinity	SF	3
LAMZHL	$t_{1/2}$	Apparent elimination half-life	DP	2
LAMZ	Lambda-z	Slope of the apparent elimination phase	DP	4
CLFO	CL/F	Total body clearance after extravascular administration	SF	3
VZFO	V_z/F	Apparent volume of distribution based on the terminal phase after extravascular administration	SF	3

DP=decimal places
SF=significant figures

11.2.5 Presentation of Results

All bioanalytical data will be listed and summarised according to the actual sampling timepoint.

If the actual sampling time is not within ± 20% of the scheduled sampling time, the concentration value at the sampling time point may be excluded from descriptive statistics and PK parameter estimation.

All pharmacokinetic parameters generated will be listed and summarised. Where pharmacokinetic data fails to meet the defined criteria in Section 11.2.3. (Data Quality) the affected results will be excluded from the descriptive statistics will be flagged as per exclusion reason.

11.2.5.1. Bioanalytical and PK Parameters Listings

All bioanalytical and pharmacokinetic data generated will be listed in individual tables according to the analyte and treatment.

11.2.5.2. Bioanalytical and Pharmacokinetic Summary Tables

Bioanalytical and PK parameters summary tables will be performed by SSR.

Summary statistics (i.e., mean, median, SD, CV%, minimum, maximum, n, geometric mean, geometric SD and geometric CV%) will be calculated for PK results for each time point, parameter and dose group.

All summary statistics (i.e., mean, median, SD, CV%, minimum, maximum and n) will be presented for all PK parameters by dose level. Also, geometric mean, geometric SD and geometric CV% will be presented for all PK parameters (except T_{max}) by dose group. The T_{max} summary statistics will be provided as n, minimum, median, and maximum only.

Additional summary tables might be produced if required and requested.

11.2.5.3. Bioanalytical and Pharmacokinetic Figures

All arithmetical mean plasma concentration vs. time curves will be produced by dose group on both linear/linear and log_{10}/linear scales.

All spaghetti plots of individual plasma concentrations against actual sampling times after dosing grouped by dose level will be produced on both a linear/linear and log_{10}/linear scale. Each participant's concentration profile will be represented on these plots with a different symbol and a legend will be included on the plots to define the symbols used.

List of summary tables, listings and figures are in Appendix, Table A.

11.3 Safety

Analysis Set: Safety data will use both FAS and IMP Sets

Endpoint: The incidence, severity and relationship to MMV367 and malaria challenge of adverse events.

Safety and tolerability will be assessed by clinical review of the following parameters:

- Adverse events (AEs)
- Vital signs
- 12-lead ECG
- Clinical Laboratory analysis
- Physical examination

11.3.1. Adverse Events

AEs will be reported according to the volunteer infection studies (VIS) plausible windows and reporting rules:

- Inoculum-emergent AEs (IEAEs)= AEs beginning any time from inoculation with the challenge agent until the end of study.

- Treatment-emergent AEs (TEAEs)= AEs beginning any time from administration of the IMP until the end of study.

Adverse Events of Special Interest (AESIs) may be serious or non-serious and are defined by the Sponsor as being of specific scientific and/or medical concern to the Sponsor's product or program. Evaluation on AESI will be based on both Safety Set and FAS depending on if it is treatment emergent or inoculum emergent adverse events.

Any abnormalities listed below should be reported as an AESI.

Hepatic:
- ALT or AST > 5× ULN
- ALP > 2 × ULN (in the absence of known bone pathology)
- Total bilirubin > 2× ULN (in the absence of known Gilbert syndrome)
- Any AST or ALT value > 2× ULN and total bilirubin > 1.5× ULN
- Any ALT or AST value > 2 × ULN and INR > 1.5
- Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and total bilirubin > 2× ULN [mainly conjugated fraction] without notable increase in ALP to > 2× ULN)
- Any clinical event of jaundice (or equivalent term)
- ALT or AST > 2× ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia (eosinophil percent or count above the ULN).

Cardiac:
- QTcF at any time >480 msec
- Bundle branch block (except right bundle branch block that was present prior to MMV367 administration)
- Any arrhythmia, except:
  - sinus bradycardia that is clinically asymptomatic and not associated with any other relevant ECG abnormalities
  - sinus tachycardia that is clinically asymptomatic, is associated with a body temperature >38.0°C, and not associated with any other relevant ECG abnormalities
  - respiratory sinus arrhythmia
  - wandering atrial pacemaker, or
  - isolated single premature atrial/ventricular complex (i.e., no bigeminy, trigeminy, couplets, triplets or salvos) that does not occur more than once in a particular ECG tracing.

Haematological:
- Haemoglobin drop >20.0 g/L from baseline (at eligibility visit)
- Absolute neutrophil count (ANC) <0.5 × 10^9/L.
- Platelet count <75 × 10^9/L.

Dermatological: *†

Clinical signs of possible cutaneous adverse reactions such as:

- Dermatitis
- Rash including
  - erythematous
  - macular
  - papular
  - maculopapular
  - pruritic
  - pustular
  - vesicular

*If one of these cutaneous reactions is observed, pictures of the lesions should be obtained when feasible.

†Dermatological AEs need not be reported as AESIs if clearly unrelated to the malaria challenge agent or IMP (e.g. rash from cannula dressing or ECG dots).

11.3.1.1. ***Parameters***

Parameters to be included in the listings? will be:

- Event Term
- Dates, times and study days of onset and resolution
- Severity (CTCAE Grades 1 to 5)
- Outcome (Not Recovered / Not Resolved; Recovered / Resolved; Recovered / Resolved with Sequelae; Recovering / Resolving; Fatal; Unknown)
- Relationship of AE to IMP (Not Related/Not Suspected, Related/Suspected)
- Relationship of AE to rescue medication (Not Related/Not Suspected, Related/Suspected)
- Relationship of AE to malaria challenge agent (Not Related/Not Suspected, Related/Suspected)
- Relationship of AE to study procedures (Not Related/Not Suspected, Related/Suspected)
- Action taken with IMP (No action taken; Rescue medication administered instead of IMP)
- Other actions taken (including withdrawal from the study)
- Seriousness (and Serious Adverse Event (SAE) criteria)
- AESI status (Yes/No)
- Relatedness to COVID-19 (Yes/No)

Derived parameters:

- Duration in hours
- Time in days of onset relative to first IMP administration

11.3.1.2. ***Biostatistical Methods***

All pre-dose AEs occurring before inoculation will be reported as Medical History.

Adverse events (AE) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 – Sep 2021 and grouped by system organ class (SOC) and preferred terms (PT). Their severity will be graded according to NCI-CTCAE v5.0 27 Nov 2017.

11.3.1.2.1. Listings

All AE data will be listed for each participant, including severity, relationship to IMP, relationship to study procedures, relationship to rescue mediation, relationship to malaria

challenge agent, outcome and actions taken. In addition, listings of AEs leading to discontinuation of the study, SAEs and deaths, will be provided as applicable.

11.3.1.2.2. Tables

The number of events, as well as the number and percentage of participants experiencing an AE, will be summarised by, dose group and overall as follows:

Overall summary of IEAEs (FA set)
Overall summary of TEAEs (IMP set)

Summary of IEAEs by System Organ Class and Preferred Term - All Causalities (FA set)
Summary of TEAEs by System Organ Class and Preferred Term - All Causalities (IMP set)

Summary of IEAEs by System Organ Class, Preferred Term and Maximum Severity - All Causalities (FA set)
Summary of TEAEs by System Organ Class, Preferred Term and Maximum Severity - All Causalities (IMP set)

Summary of Malaria-Related IEAEs by System Organ Class and Preferred Term (FA set)
Summary of IMP-Related TEAEs by System Organ Class and Preferred Term (IMP set)

Summary of Malaria-Related IEAEs by System Organ Class, Preferred Term and Maximum Severity (FA set)
Summary of IMP-Related TEAEs by System Organ Class, Preferred Term and Maximum Severity (IMP set)

Summary of IE SAEs by System Organ Class and Preferred Term - All Causalities (FA set)
Summary of TE SAEs by System Organ Class and Preferred Term - All Causalities (IMP set)

Overall Summary of IE AESIs (FA set)
Overall Summary of TE AESIs (IMP set)

Summary of IE AESIs by System Organ Class and Preferred Term - All Causalities (FA set)
Summary of TE AESIs by System Organ Class and Preferred Term - All Causalities (IMP set

Summary of IEAEs Leading to Study Discontinuation by System Organ Class and Preferred Term - All Causalities (FA set)
Summary of TEAEs Leading to Study Discontinuation by System Organ Class and Preferred Term - All Causalities (IMP set)

For the summary tables, participants who experience the same AE (in terms of the MedDRA preferred term) more than once will only be counted once.

11.3.2. Concomitant Medication

Medications used in this study will be coded using WHODrug Global version B3 Sep 2021 – Added Context.

Concomitant medications are defined as medications continued or newly received at or after administration of the malaria challenge agent through to the End of Study visit.

If a medication has a missing or partial missing start/end date or time and it cannot be determined whether it was taken before initial treatment or concomitantly, it will be considered as prior and concomitant.

Concomitant medications will be summarised by ATC and PN. The summary tables will show the number and percentage of participants taking each medication by ATC and PN.

For the summaries of concomitant medications, participants who take the same medication (in terms of the ATC and PN) more than once will only be counted once for that medication.

Use of rescue medications will be analysed as part of the treatment exposure analysis (Section 9).

11.3.3. Laboratory

Parameters

Haematology

White cell count (WCC)
Neutrophils (NEUT)
Lymphocytes (LYM)
Monocytes (MON)
Eosinophils (EOS)
Basophils (BAS)
Mean cell volume (MCV)
Red cell count (RCC)
Haemoglobin (HGB)
Haematocrit (HCT)
Platelet count (PLAT)
Red cell distribution width (RDW)
Reticulocyte count (RETI)
Blood Group and Rh(D) tests (***Screening only***)

Biochemistry

Sodium (NA)
Potassium (K)
Chloride (CL)
Bicarbonate (BICARB)
Calcium (CA)
Corrected calcium (CCA)
Magnesium (MAG)
Glucose (GLUC)
Quantitative Glucose 6-Phosphate Dehydrogenase (G6PD) (***Screening only***)
Urea
Creatinine (CREAT)
Estimated glomerular filtration rate (eGFR) – CKD Epi calculation
Albumin (ALB)
Globulin
Total protein
Total bilirubin (BILI)
Direct (conjugated) bilirubin (BILDIR)
Alkaline phosphatase (ALP)
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Gamma-glutamyl transferase (GGT)
Lactate dehydrogenase (LDH)
Phosphate (PHOS)
C-Reactive Protein (CRP) ***(not required at Screening)***
Cholesterol (Chol) (***Screening only***)
Triglycerides (Trig) (***Screening only***)
High density lipoprotein (HDL) (***Screening only***)
Low density lipoprotein (LDL) (***Screening only***)

Pregnancy Test and FSH

β-Human Chorionic Gonadotropin (β-HCG) (women of child bearing potential only)

Follicular Stimulating Hormone (FSH) (post-menopausal women only)

Urinalysis

Glucose (GLUC)
Bilirubin (BILI)
Ketone (KETONES)
Specific gravity (SPGRAV)
Blood
pH
Protein (PROT)
Urobilinogen (UROBIL)
Nitrite
Leukocytes (WBC)
Microscopy, culture and sensitivity (***formal laboratory analysis if required***)

Coagulation

Prothrombin Time (PT)
Activated Partial Thromboplastin Time (APTT)
International Normalised Ratio (INR)

Viral Screen

HIV 1/2 (anti-HIV1 and anti-HIV2 Ab)
Hepatitis B (HBsAg, anti-HBc [IgG + IgM if IgG is positive])
Hepatitis C (anti-HCV)

Biostatistical methods

Listings

All laboratory parameters and change from treatment baseline values will be presented in data listings. Values outside the laboratory reference range will be listed with flags if considered low or high for values outside the reference ranges (where applicable) and if values considered to be clinically significant by the investigator.

Pregnancy test data will be listed only, for all women. FSH data will be listed only, for all post-menopausal women.

Coagulation data as well as qualitative and quantitative urinalysis data will also be listed only.

Tables

Haematology, biochemistry and continuous dipstick urinalysis laboratory data will be summarised for each scheduled visit, including observed values, absolute change from treatment baseline.

Categorical dipstick urinalysis results will be summarised for each scheduled visit using frequency tabulations.

Numbers of participants with treatment-emergent abnormalities will also be shown.

11.3.4 Vital Signs

Parameters

- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Heart Rate (beats/minute)
- Body Temperature (°C)
- Respiratory rate (beats/min)

Biostatistical methods

All vital signs data will be listed for all participants. Any values outside of the protocol defined normal ranges will be flagged, with clinical significance status presented for out-of-range results.

Table 1: Vital Signs Normal Ranges

Parameter	Range
Systolic blood pressure	90-140 mmHg
Diastolic blood pressure	50-90 mmHg
Heart rate	50-100 bpm
Temperature	35.0-37.5°C
Respiratory rate	10-25 breaths/min

Vital sign parameters will be summarised by presenting summary statistics for observed values and change from treatment baseline values for each scheduled visit.

11.3.5 Body Measurements

Definition of variables

- Height (Screening Only)
- Weight
- Body mass index (BMI)

Biostatistical methods

Body measurement data will be listed for all participants and visits, including height, weight and Body Mass Index (BMI) which is auto-calculated within the CRF.

Observed values, as well as changes from treatment baseline, will be summarised descriptively for weight and BMI by visit.

11.3.6. Physical Examination

Parameters

- Weight
- HEENT (Head, Eyes, Ears, Nose, Throat)
- Height (screening only)
- Chest / Lungs
- Abdomen
- Skin
- Neurological / Reflexes
- Heart / circulation
- Neck

Biostatistical methods

Physical examination findings will be listed for all participants and visits.

11.3.7. 12-lead ECG

Parameters

- PR interval (msec)
- QRS interval (msec)
- QTcF interval (msec)
- Overall ECG assessment (Normal, Abnormal)
- ECG abnormality (specify as appropriate)
- Clinical Significance

Biostatistical methods

ECG parameters will be listed for all participants and visits. Triplicate ECGs will be presented in listings for individual readings as well as the mean for each triplicate. The triplicate means will be used for the summary table. Any values outside of the protocol defined normal ranges (Table XX) will be flagged.

Table 2: ECG Normal Ranges

Parameter	Range
PR interval	≤210 msec
QRS	50–120 msec
QTcF	Males: ≤450 msec Females: ≤470 msec

Observed values, as well as changes from treatment baseline, will be summarised descriptively for all ECG parameters by visit. An addition table will present the frequencies of participants who fulfill the following prolongation (change from baseline) criteria, considering all scheduled and non-scheduled visit data:

- QTcF prolongation >30
- QTcF prolongation >60
- QTcF >450 msec for males
- QTcF >450 msec for females
- QTcF >470 msec for females

11.3.8. Malaria Clinical Score

Malaria clinical score data will be listed for all participants, including the individual scores for each of the 14 signs/symptoms as well as the total score.

The number (and percentage) of participants scoring each symptom (0=absent; 1=mild; 2=moderate; 3=severe) will be tabulated per dose group and per protocol defined timepoint.

The highest score as well as the time(s) to the highest score observed will be tabulated.

11.3.9. Presentation of Safety Results

The table summary and listings of AEs and lab parameters will be presented for the CSR, and are provided in Appendix, Table B.

12. EXPLORATORY PARAMETERS

Analysis Set: PD Analysis Set

Endpoint: Incidence and level of resistance to MMV367 in parasites determined using *in vitro* methods.

Parasites will be genotyped and in vitro drug sensitivity testing will be performed.

Endpoint: Effect of MMV367 on parasite viability in ex vivo cultures.

Ex vivo growth is a measure of parasite viability. An estimate of the number of viable parasites following MMV367 treatment will be quantified using a limiting dilution assay by counting the number of wells with parasite growth using the following formula [8] :

$$Viable\ parasites = X^{n-1},$$

Where n is the number of wells with parasite growth and X is the dilution factor used in the assay. If no wells exhibit parasite growth (i.e. n=0) the number of viable parasites is estimated to be zero. Short term ex vivo cultures will be established from blood samples collected pre-MMV367 administration (Day 8), then at several time-points post-MMV367 administration. An estimate of the number of initial parasites will be established using the pre-MMV367 administration samples, which will be used to calculate a normalization factor for post-MMV367 administration samples. Limiting dilution assays will be run for participant samples in triplicate, with the estimate of the number of viable parasites described for each sample as a mean (SD) on the log-scale. Estimates of both the raw number of viable parasites and the normalized number of viable parasites will be presented. Estimates of viable parasites may also be summarized by MMV367 dose per study time-point, with dose comparisons assessed using ANOVA, Kruskal Wallis tests or equivalent, as appropriate. The results of parasite ex vivo growth analyses will be supportive to malaria 18S qPCR data in determining the kinetics of parasite clearance following MMV367 dosing (secondary endpoint).

13. CHANGES TO THE PLANNED ANALYSIS

There is no change to the planned analysis by the time this SAP was written.

14. INTERIM AND FINAL ANALYSIS

This study has no formal interim analyses other than review of safety, tolerability, parasitaemia and PK parameters by the SDRT between cohorts.

15. SOFTWARE

SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA) for Safety, demographic and baseline characteristics, participant disposition, protocol deviations, prior medications and treatment exposure analyses

All PK/PD analyses will be performed in R 4.1.3 and IQRtool package 1.10.0 [IQRtools]. NLME modelling will be performed with Monolix 2019R1 [MLX19] using Stochastic Approximation Expectation Maximization (SAEM) for parameter estimation. For PD modelling where typically the variance of random effects cannot be estimated

from the data, the IQRtools SysFit approach [KAS19] will be used to estimate typical and individual PD parameters.

Data manipulation and data analyses for all pharmacodynamic data will be performed using R (highest version available).

16. REFERENCES

1) Wang CYT, Ballard EL, Pava Z Marquart L, Gaydon J, Murphy SC, Whiley D, O'Rourke P, McCarthy JS (2021) Analytical validation of a real-time hydrolysis probe PCR assay for quantifying Plasmodium falciparum parasites in experimentally infected human adults, *Malaria Journal*, 20(181).

2) Marquart L, Baker M, O'Rourke P, McCarthy JS (2015) Evaluating the pharmacodynamic effect of antimalarial drugs in clinical trials by quantitative PCR, *Antimicrobrial Agents and Chemotherapy,*59, 4249–59.

3) **IQRtools** https://www.intiquan.com/iqr-tools/

4) **KAS19** Kaschek D, Mader W, Fehling-Kaschek M, Rosenblatt M, Timmer J. Dynamic Modeling, Parameter Estimation, and Uncertainty Analysis in R. J. Stat. Soft. 2019 Apr 30;88(10):1-32.

5) **RAU09** Raue A, Kreutz C, Maiwald T, Bachmann J, Schilling M, Klingmüller U, Timmer J. Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood. Bioinformatics. 2009 Jun 8;25(15):1923-9.

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8) Sanz LM, Crespo B, De-Cózar C, Ding XC, Llergo JL, Burrows JN, García-Bustos JF, Gamo FJ. P. falciparum in vitro killing rates allow to discriminate between different antimalarial mode-of-action. PLoS One. 2012;7(2):e30949. doi: 10.1371/journal.pone.0030949. Epub 2012 Feb 23. PMID: 22383983; PMCID: PMC3285618.

17. APPENDIX

Table A. PD and PK Planned Tables, Listings and Figures

Title	Analysis Set
PD Listings	
Pharmacodynamic –Parasitemia	PD
Pharmacodynamic –Parasite Life Cycle Stages	PD
PK Listings	
Pharmacokinetic Concentrations	PK
Pharmacokinetic Parameters	PK
PD Tables	
Summary of Malaria Parasitaemia (18S qPCR)	PD

Summary of Malaria Parasite Lifecycle Stage Data (pfs25. pfMGET and SBP-1 qRT-PCR)	PD
PK Tables	
Summary of Pharmacokinetic Concentration	PK
Summary of Pharmacokinetic Parameters	PK
PD Figures	
Individual qPCR 18s-time Profiles	PD
Individual RT-PCR pfs25-time Profiles	PD
Individual RT-PCR pfMGET-time Profiles	PD
Individual RT-PCR SBP-1-time Profiles	PD
PK Figures	
Arithmetic Mean (+SD) Pharmacokinetic Concentration-time Profiles by Dose Group	PK
Individual Pharmacokinetic Concentration-time Profiles	PK

Table B. Baseline Characteristics and Safety Analysis Tables and Listings

Title	Analysis Set
Listings	
Participant Disposition	FAS
Dose Group Assignment	FAS
Protocol Deviations	FAS
Analysis Population Assignment	FAS
Demographics	FAS
Medical History	FAS
Pregnancy Test	FAS
Follicle Stimulating Hormone (FSH)	FAS
Viral Screen	FAS
Urine Drug Screening	FAS
Alcohol Breath Test	FAS
Positive SARS-CoV-2	FAS
Prior Medications	
Concomitant Medications	FAS
Inoculum Administration	FAS
IMP Administration	FAS
Rescue Medication Administration	FAS
Inoculum-Emergent Adverse Events	FAS
Treatment-Emergent Adverse Events	IMP
Inoculum related Inoculum-Emergent Adverse Events	FAS
IMP related Treatment-Emergent Adverse Events	IMP
Inoculum Emergent Serious Adverse Events	FAS
Treatment Emergent Serious Adverse Events	IMP
Inoculum-Emergent Adverse Events Leading to Discontinuation	FAS
Treatment-Emergent Adverse Events Leading to Discontinuation	IMP
Inoculum-Emergent Adverse Events of Special Interest	FAS
Treatment-Emergent Adverse Events of Special Interest	IMP

Deaths	FAS
Individual Haematology Results	FAS
Individual Biochemistry Results	FAS
Coagulation Screening	FAS
Individual Urinalysis Results (dipstick)	FAS
Individual Urine Microscopy Results	FAS
Individual Vital Signs Results	FAS
Individual ECG Parameters Results	FAS
Physical Examination	FAS
Malaria Clinical Score Results	FAS
Tables	
Analysis Populations	FAS
Participant Disposition	FAS
Demographics and Baseline Characteristics	FAS
Summary of Prior Medications	FAS
Protocol Deviations	FAS
Overall Summary of Inoculum Emergent Adverse Events	FAS
Overall Summary of Treatment Emergent Adverse Events	IMP
Summary of Inoculum Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (All Causalities)	FAS
Summary of Treatment Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (All Causalities)	IMP
Summary of Inoculum Emergent Adverse Events by Maximum Severity (All Causalities)	FAS
Summary of Treatment Emergent Adverse Events by Maximum Severity (All Causalities)	IMP
Summary of Inoculum related Treatment Emergent Adverse Events by MedDRA System Organ Class, Preferred Term	FAS
Summary of IMP Related Treatment Emergent Adverse Events by MedDRA System Organ Class, Preferred Term	IMP
Summary of Inoculum Related IEAEs by System Organ Class, Preferred Term and Maximum Severity	FAS
Summary of IMP Related TEAEs by System Organ Class, Preferred Term and Maximum Severity	IMP
Inoculum Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term (All Causalities)	FAS
Treatment Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term (All Causalities)	IMP
Overall Summary of Inoculum Emergent Adverse Events of Special Interest (AESI)	FAS
Overall Summary of Treatment Emergent Adverse Events of Special Interest (AESI)	IMP
Inoculum Emergent Adverse Events of Special Interest (AESI) by MedDRA System Organ Class and Preferred Term (All Causalities)	FAS
Treatment Emergent Adverse Events of Special Interest (AESI) by MedDRA System Organ Class and Preferred Term (All Causalities)	IMP
Inoculum Emergent Adverse Events Leading to Study Discontinuation by MedDRA System Organ Class and Preferred Term (All Causalities)	FAS
Treatment Emergent Adverse Events Leading to Study Discontinuation by MedDRA System Organ Class and Preferred Term (All Causalities)	IMP
Summary of Concomitant Medications (FAS)	FAS
Summary of Concomitant Medications (IMP)	IMP
Haematology (Summary and Change from IMP Baseline)	FAS
Haematology (Categorical)	FAS
Biochemistry (Summary and Change from IMP Baseline)	FAS
Biochemistry (Categorical)	FAS
Urinalysis (Continuous) Results and Change from Baseline	FAS
Urinalysis (Categorical) Results	FAS

Vital Signs Results and Change from IMP Baseline	FAS
Abnormal Vital Signs Results	FAS
ECG Results and Change from IMP Baseline	FAS
ECG QTc Categorical Analyses	FAS
ECG Clinical Assessment	FAS
Malaria Clinical Score Summary by Question	FAS
Summary Peak Total Malaria Clinical Score and Time to Peak Total Malaria Clinical Score	FAS