CONFIDENTIAL

An Open Label Study to Assess the Efficacy, Safety, Tolerability and Pharmacokinetics of a Single Dose of MMV390048 in Adult Patients with Acute, Uncomplicated *Plasmodium vivax* or *falciparum* Malaria Monoinfection over a 35 Day Period

Working Title:

MMV390048 Phase IIa efficacy POC in *P. vivax* and *P. falciparum*

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Site Names:	**University of Gondar Hospital/Maksegnit Health Centre** **Gondar, Ethiopia** **Jimma University Referral Hospital/Agaro District Hospital** **Jimma, Ethiopia**
Sponsor:	**Medicines for Malaria Venture** **ICC, Route de Pré-Bois 20** **PO Box 1826** **1215 Geneva 15** **Switzerland**

PROTOCOL APPROVAL AND AUTHORISATION

SPONSOR'S APPROVAL

Name	Affiliation	Signature	Date
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PRINCIPAL INVESTIGATOR DECLARATION

An Open Label Study to Assess the Efficacy, Safety, Tolerability and Pharmacokinetics of a Single Dose of MMV390048 in Adult Patients with Acute, Uncomplicated *Plasmodium vivax* or *falciparum* Malaria Mono-Infection over a 35 Day Period

I have read and approve protocol MMV_MMV390048_16_02. I confirm that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

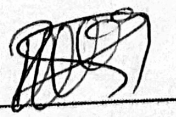
This protocol contains information that is confidential and proprietary to MMV and is to be used only for the purpose of the conduct of this study. I will therefore not disclose the contents of this protocol to any people other than the study personnel under my supervision, the Ethics Committees, or duly authorised representatives of regulatory agencies under the condition that they agree to keep this information confidential.

I may not use the information in this protocol for any other clinical study, nor provide the information to any person or entity not listed above, nor publish it without the prior written permission of MMV. If required to disclose any of this information to comply with regulations or regulatory requirements, I will notify MMV immediately.

I have read this protocol. I will conduct this study exactly as described in this protocol and agree that all details that I require to do so are provided in the protocol. I will provide copies of the protocol and access to all information furnished by MMV to the personnel under my supervision involved in the conduct of this study. I will present and discuss the protocol and all other necessary information with them and ensure that they are completely informed about the contents of the protocol, all requirements for conducting the study as per protocol, all relevant information about the drugs to be administered and all procedures to be conducted during this study.

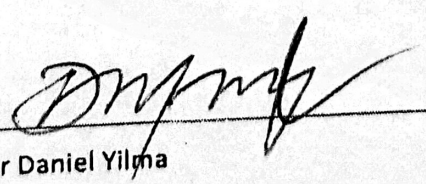
I understand that the study may be terminated or enrolment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interest of the patients. I will notify MMV immediately should such a situation arise.

I will conduct this study in accordance with all applicable regulations and ICH Guidelines for Good Clinical Practice (GCP).



Date: 30 Jan 2017

Dr Rezika Mohammed



Date: 30 Jan 2017

Dr Daniel Yilma

LIST OF ABBREVIATIONS

Ab	Antibody
ACT	Artemisinin-based combination therapies
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT / SGPT	Alanine aminotransferase
ALP	Alkaline phosphatase
ACPR	Adequate clinical and parasitological response
AST / SGOT	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
AUC_{0-t}	Area under the plasma concentration versus time curve from time zero to time of last quantifiable concentration
AUC_{0-inf}	Area under the plasma concentration versus time curve from time zero to infinity
BMI	Body mass index
BP	Blood pressure
CK	Creatine kinase
C_{max}	Maximum peak observed plasma concentration
CRF	Case report form
CRO	Clinical research organisation
CRU	Clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DBS	Dry blood spot
DRE	Disease-related event
ECG	Electrocardiogram
ED_{50}	The dose of a therapeutic agent that eradicates 90 per cent of the target pathogen
EDTA	Ethylene-diamine-tetra-acetic acid
EE	Efficacy evaluable
ETF	Early treatment failure
FCT	Fever clearance time
FIH	First in human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
G6PD	Glucose-6-phosphate dehydrogenase
HAV	Hepatitis A virus
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPLC-MS/MS	High performance liquid chromatography mass spectrometry
IBSM	Induced blood stage malaria
ICH	International Council for Harmonisation

IC_{50}	Plasma concentration required for 50% inhibition
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IMP	Investigational medicinal product
ITT	Intention to treat
LCF	Late clinical failure
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LPF	Late parasitological failure
MedDRA	Medical Dictionary for Regulatory Activities
MPC	Minimum parasiticidal concentration
MMV	Medicines for Malaria Venture
PC_{50}	Time to microscopic 50% reduction of asexual parasites
PC_{90}	Time to microscopic 90% reduction of asexual parasites
PC_{99}	Time to microscopic 99% reduction of asexual parasites
PC_{100}	Time to total microscopic clearance of asexual parasites
PCT	Parasite clearance time
PCR	Polymerase chain reaction
PD	Pharmacodynamic
P. falciparum	*Plasmodium falciparum*
PIB	Power in bottle
PK	Pharmacokinetic
POC	Proof of Concept
PRR	Parasite reduction rate
P. vivax	*Plasmodium vivax*
qPCR	Quantitative polymerase chain reaction
QTcF	QTc interval Fridericia's correction
RBC	Red blood cell
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SCID	Severe combined immunodeficiency
SOP	Standard operating procedure
SRT	Safety Review Team
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Time needed to decrease the drug concentration by half
t_{max}	Time to maximum peak observed plasma concentration
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WNCBP	Women of non-childbearing potential

LIST OF DEFINITIONS

Quantitative Polymerase Chain Reaction (qPCR):

A polymerase chain reaction procedure is used to quantify the amount of *P. falciparum*-specific DNA present and is transformed into number of parasites/µL.

Microscopy Parasite Clearance:

Microscopy parasite clearance is defined as at least two consecutive post-dose microscopy results that are negative for asexual parasites and obtained within an interval of 4 to 24 hours of each other.

Microscopy Parasite Clearance Time (PCT_{MIC}):

Microscopy parasite clearance time is defined as the time to the first of two consecutive post-dose microscopy results that are negative for asexual parasites and obtained within an interval of 4 to 24 hours of each other.

Minimum Parasiticidal Concentration (MPC):

The lowest plasma or blood concentration of a drug that produces the maximal antimalarial effect (White (2002) Trends in Parasitology)[1].

Parasite Reduction Rate (PRR):

The parasite reduction rate is calculated as the slope of the linear portion of the regression fit of natural log parasitemia (per microliter) versus time (in hours).

Fever Clearance:

Fever clearance is defined as at least two consecutive post-dose axillary temperature measurements <37.5°C obtained within an interval of 4 to 24 hours of each other.

Fever Clearance Time:

Fever clearance time is defined as the time from baseline to the first of two consecutive post-dose axillary temperature measurements <37.5°C obtained within an interval of 4 to 24 hours of each other.

Outcome Classification (by microscopy):

Treatment outcome will be classified in accordance with an MMV adaptation (to ensure safety of patients in early phase studies) of the standard WHO classification[2] of responses to treatment. Throughout these criteria, baseline parasitemia is defined as that determined from the slides performed 30 minutes pre-dose, and (unless otherwise stated) fever is defined as an axillary temperature ≥37.5°C.

Early Treatment Failure (ETF) is defined as one of the following:

- Development of any clinical complications (WHO definition of complicated/severe malaria, WHO [2012], Appendix 1)[3] on Days 1, 2 or 3 with parasitemia
- Parasitemia >100,000/µL on Days 0, 1, 2 or 3 with or without fever
- A ≥25% increase in parasitemia compared to baseline during the period up to 24 hours after dosing for *P. vivax* malaria or up to 12 hours after dosing for *P. falciparum* malaria, with or without fever, and together with any of the following:
  - clinical decline;
  - lack of clinical improvement; or
  - significant decrease in platelet count defined as:

- a >20% reduction from baseline for patients with a baseline platelet count between 50,000/mm^3 and 74,999/mm^3 (thrombocytopenia grade 2), or
- a drop in platelet count to <50,000/mm^3 for patients with a baseline platelet count ≥75,000/mm3

- Parasitemia >baseline with or without fever, between >24 and 48 hours after dosing for *P. vivax* and between >12 and 36 hours after dosing for *P. falciparum*;
- Any parasitemia with fever, or parasitemia >25% of baseline with or without fever, between >48 and 72 hours after dosing for *P. vivax* and between >36 and 60 hours after dosing for *P. falciparum*;
- Failure to clear all parasites by microscopy associated with axillary temperature ≥37.5°C or oral/rectal/tympanic temperature ≥38°C, between >72 and 96 hours for *P. vivax* and >60 and 96 hours for *P. falciparum*.

Late Clinical Failure (LCF) is defined as the presence of any of the following between Day 4 and 14 (or Day 28 for analysis of the secondary objectives) in a patient who did not previously meet any of the criteria of ETF:

- danger signs,
- severe malaria, or
- parasitemia with fever.

Late Parasitological Failure (LPF) is defined as the recurrence of parasitemia between Day 4 and 14 (or Day 28 for analysis of the secondary objectives) without fever in a patient who did not previously meet any of the criteria of ETF or LCF.

Adequate Clinical and Parasitological Response (ACPR) at Day 14 (or Day 28 for analysis of the secondary objectives) is defined as the absence of parasitemia on Day 14 (28), irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure.

Recurrence (*P. vivax* and *P. falciparum*):

Recurrence is defined as the appearance of asexual parasites after clearance of initial infection. The recurrence can be due to recrudescence, relapse (in case of *P. vivax*) or a new infection.

For *P. vivax* it will not be possible to differentiate between a recrudescence, relapse, and a new infection.

Recrudescence (*P. falciparum* only):

Recrudescence is defined as the appearance of asexual *P. falciparum* parasites after clearance of initial infection with a genotype identical to that of parasites present at baseline (at least one allele at each locus is common to both paired samples). Recrudescence must be confirmed by microscopy (positive blood smear) and PCR analyses. Confirmed recrudescence is regarded as a treatment failure. The methodology for differentiating between recrudescence and new infection will be in accordance with the most recent established techniques.[4]

New Infection (*P. falciparum* only):

New infection is defined as the appearance of asexual parasites after clearance of initial infection with a genotype different from those parasites present at baseline (all alleles from post dose sample are different from those in the pre-dose sample, for one or more loci tested). New infection must be confirmed by microscopy (positive blood smear) and PCR analyses. Confirmed new infection will not be regarded as treatment failure.

PCR-adjusted ACPR:

ACPR after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques.

Hy's Law:

A possible Hy's law case is defined as a patient with any value of ALT or AST above 3 × upper limit of normal (ULN) together with an increase in total bilirubin to a value higher than 2 × ULN (>35% conjugated) and NOT associated with an ALP value higher than 2 × ULN (Food and Drug Administration, 2009).[5] Specific procedures need to be followed-up in the event of a suspected case of Hy's law. Details of these procedures are documented in Appendix 6.

SYNOPSIS

Study Title	An Open Label Study to Assess the Efficacy, Safety, Tolerability and Pharmacokinetics of a Single Dose of MMV390048 in Adult Patients with Acute, Uncomplicated *Plasmodium vivax* or *falciparum* Malaria Monoinfection over a 35 Day Period
Working Title	MMV390048 Phase IIa efficacy POC in *P. vivax* and *P. falciparum*
Regulatory Status	Investigational – Phase IIa
Sponsor	Medicines for Malaria Venture ICC – Block G 3rd floor 20 route de Pré-Bois P O Box 1826 1215 Geneva 15 Switzerland
Study Sites	University of Gondar Hospital, Gondar, Ethiopia Maksegnit Health Centre, North Gondar zone, Gondar, Ethiopia Jimma University Referral Hospital, Jimma, Ethiopia Agaro District Hospital, Agaro, Jimma zone, Ethiopia
Principal Investigators	Dr Rezika Mohammed, University of Gondar Dr Daniel Yilma, Jimma University
Investigational Product	Single doses of MMV390048 administered as tablets for oral administration
Background	MMV390048 is a new antimalarial drug candidate which has undergone single ascending dose, food effect, and formulation bioavailability Phase I studies in healthy volunteers to demonstrate safety and tolerability and to describe the pharmacokinetic profile of different formulations of the compound. To date MMV390048 has been administered as a single dose up to 120 mg to healthy volunteers. Further dose escalation remains under consideration. Review of the safety data on the Phase I studies carried out to date revealed no obvious trends associated with exposure to MMV390048. The compound was well tolerated. The terminal half-life of the compound is sufficiently long (approximately 160 hours) to support a single low dose maintaining concentrations significantly above the minimum parasiticidal concentration (MPC). The dose calculated from efficacious concentrations in preclinical models to provide coverage above the MPC for >8 days is predicted to be approximately 20 mg. At the time of writing this protocol, the human Induced Blood Stage Malaria (IBSM) challenge study is ongoing and will inform efficacious concentration levels. The present proof-of-concept Phase IIa study aims to confirm, in patients, the observed activity of MMV390048 against *P. falciparum* in pre-clinical models and the human IBSM challenge model, and to determine the activity against *P. vivax* malaria in patients, both over 14 and 28 days. Additional aims are to characterise the safety of MMV390048 in patients. Patient safety will be monitored for up to 35 days post-dose including pharmacokinetic assessments. The study will investigate descending single doses of MMV390048 in response to results obtained in the first cohort/dose in each malaria sub-type. The results of this trial will identify active, well-tolerated doses for investigation in combination with a partner drug within a Phase IIb clinical trial.

Objectives	**Primary Objective:** To determine the 14-day efficacy of a single dose of MMV390048 for the treatment of uncomplicated *P. vivax* or *P. falciparum* malaria monoinfection. **Secondary Objectives:** • To assess the safety and tolerability of a single dose of MMV390048 in patients with *P. vivax* and *P. falciparum* malaria infection up to Day 35 • To assess the effect of a single dose of MMV390048 on signs and symptoms of *P. vivax* and *P. falciparum* malaria infection up to Day 28 • To assess the effect of a single dose of MMV390048 on treatment outcomes in patients with *P. vivax* and *P. falciparum* malaria infection: - Without PCR-adjustment at Day 14 (*P. falciparum* only) - Without PCR-adjustment at Day 28 (*P. vivax* and *P. falciparum*) - With PCR-adjustment at Day 28 (*P. falciparum* only) - Rates of recurrence (*P. vivax* and *P. falciparum),* recrudescence (*P. falciparum* only) and new infection (*P. falciparum* only) over 28 days • To describe parasite clearance kinetics after a single dose of MMV390048 in patients with *P. vivax* and *P. falciparum* malaria infection • To describe the pharmacokinetic characteristics of a single dose of MMV390048 in patients with *P. vivax* and *P. falciparum* malaria infection up to Day 35 **Exploratory Objectives:** • To describe the presence of gametocytemia after a single dose of MMV390048 in patients with *P. vivax* and *P. falciparum* malaria infection up to Day 28 • To investigate the relationship between microscopically determined and qPCR determined parasitemia • To explore the relationship between parasite genotypes of interest and parasite clearance kinetics/efficacy • To obtain pharmacogenetics samples from patients who specifically consent to this, for future exploratory analysis of genetic polymorphism (e.g. CYP_{2C8}, CYP_{2C19})
Study Population	Up to 102 adult patients (excluding replacements) with uncomplicated *P. vivax* or *P. falciparum* malaria monoinfection will be enrolled into a maximum of six cohorts (three *P. vivax* and three *P. falciparum*) of 17 patients each. Men and women of non-childbearing potential (WNCBP) will be enrolled. The sample size is considered adequate to gain preliminary efficacy and safety data in the target population. Patients must fulfill the following eligibility criteria for enrolment in the study. **Inclusion Criteria:** 1. Men or WNCBP between the ages of 18 and 55 years inclusive 2. Body weight between 40 kg and 90 kg inclusive 3. Presence of *P. vivax* or *P. falciparum* monoinfection confirmed by: - Fever, as defined by axillary temperature ≥37.5°C or oral/rectal/tympanic temperature ≥38°C, or history of fever in the previous 48 hours for *P. vivax* and 24 hours for *P. falciparum* and, - Microscopically confirmed parasite infection: 1,000 to 40,000 asexual parasite count/µL blood 4. Written informed consent provided by the patient in accordance with local practice. If the patient is unable to write, witnessed consent is permitted according to local ethical considerations. 5. Ability to swallow oral medication 6. The patient is able to understand and comply with protocol requirements, instructions and protocol-stated restrictions and is likely to complete the study as planned

7. Willing to be hospitalized for at least 72 hours or until malarial parasites are not detected by microscopy on 2 consecutive occasions (whichever is later) and return to clinic for all follow-up visits
8. Women must be of non-childbearing potential (WNCBP) as per one of the following definitions:
   - postmenopausal defined as having age-appropriate, natural (spontaneous) amenorrhea for at least 12 months prior to screening in the absence of an alternative medical cause for the amenorrhea, or
   - premenopausal with irreversible surgical sterilization by hysterectomy and/or bilateral oophorectomy or salpingectomy at least 6 months prior to screening (as determined by subject medical history)
9. Sexually active men must agree to comply with strict appropriate contraception rules (barrier contraception, e.g. condom) or complete abstinence when this is in line with the preferred and usual lifestyle of the patient. The contraception coverage in this situation should ensure full elimination of MMV390048, i.e. until 120 days after MMV390048 administration to the enrolled male patient (covering a full sperm cycle of 90 days starting after 5 x $t_{½}$ of the drug). Abstinent patients must agree to use the above-mentioned contraceptive methods if they start sexual relationships during the study, and to continue these methods until 120 days after study medication.

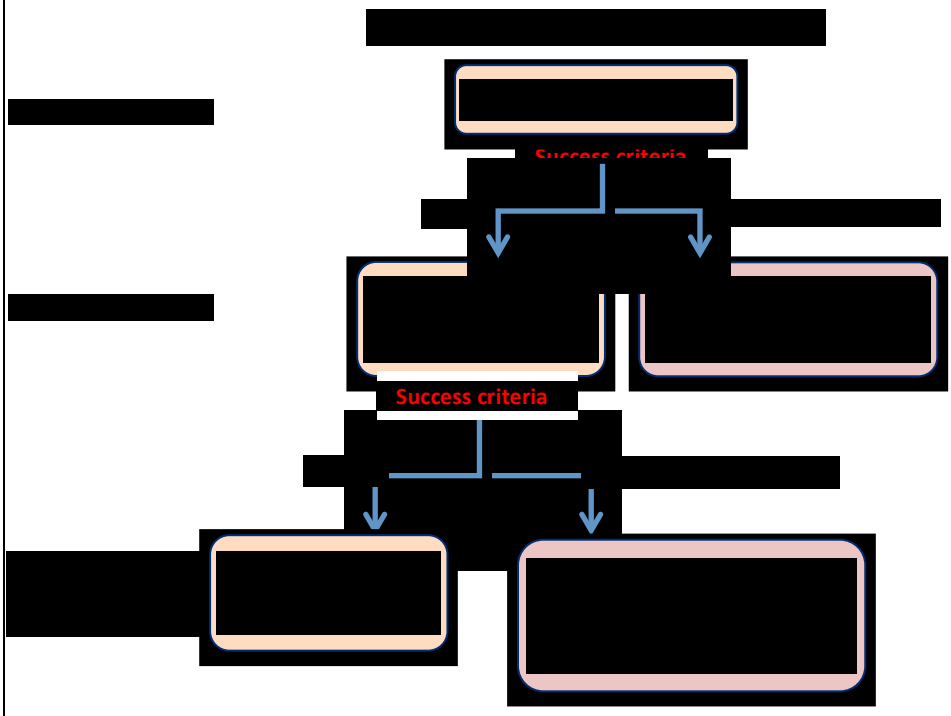
Exclusion Criteria:

1. Patients with signs and symptoms of severe / complicated malaria according to the World Health Organisation Criteria 2012[3]
2. Mixed *Plasmodium* infection
3. Vomiting more than three times in the 24 hours prior to inclusion in the study or inability to tolerate oral treatment, or diarrhea equivalent to 3 or more watery stools per day
4. Women who are nursing (lactating)
5. Presence of other serious or chronic clinical conditions requiring hospitalisation
6. Severe malnutrition (defined as a body mass index [BMI] of less than 16 kg/m^2 as per local guidelines)
7. Presence of concurrent febrile illness (e.g. typhoid fever)
8. Known history or evidence of clinically significant:
   - cardiovascular disease (including arrhythmia, QTcF interval >450 msec, personal or family history of long QT syndrome, PR interval >210msec; any relevant intra-ventricular heart block [QRS >120msec]),
   - respiratory conditions (including active tuberculosis),
   - history of jaundice or other hepatic dysfunction,
   - renal insufficiency,
   - gastrointestinal disorder, or any condition that may affect absorption of the study medication (e.g. vomiting or diarrhea),
   - immunological disorders (including known pre-existing HIV infection),
   - endocrine disorders (including any type of diabetes mellitus whether controlled or not, diabetes insipidus, uncontrolled hypo- or hyperthyroidism, endocrine reproductive disorders not requiring concurrent medication, disorders of adrenal function),
   - infectious conditions (other than minor skin or soft tissue infections or confirmed minor lower urinary tract infection),
   - malignancy,
   - psychiatric or neurological disorders (including a history of convulsions, major head trauma, focal neurological signs, psychosis, bipolar or major depressive disorder), or
   - any other disorder or condition that in the opinion of the investigator may

	render the patient unfit for participation in the trial, may limit his/her ability to provide informed consent, may interfere with protocol adherence or place the patient at increased risk through participation in the study. 9. Known to have any of the following markers of active hepatitis: - Hepatitis A IgM (HAV-IgM), - Hepatitis B surface antigen (HBsAg), or - Hepatitis C antibody (HCV Ab) and HCV RNA. 10. Have received any antimalarial treatment (alone or in combination) during the following periods before screening (list of prohibited medication is provided in Appendix 2): - Piperaquine, mefloquine, naphthoquine or sulphadoxine-pyrimethamine within 6 weeks prior to screening - Amodiaquine, chloroquine, pyronaridine or tafenoquine within 4 weeks prior to screening - Any artemisinin derivative (artesunate, artemether, arteether or dihydroartemisinin), quinine, halofantrine, lumefantrine and any other anti-malarial treatment or antibiotic with antimalarial activity (including cotrimoxazole, tetracyclines, quinolones and fluoroquinolones and azithromycin) within 14 days prior to screening - Any herbal products or traditional medicines during the 7 days prior to screening 11. Receipt of an investigational drug within 8 weeks or 5 half-lives (whichever is longer) prior to screening 12. Current participation in any other clinical trial, or previous participation in a clinical trial where MMV390048 was administered. 13. A history of regular abuse of alcohol, or use of drugs of abuse during the past 6 months, or any clinical signs of substance abuse 14. Neutrophil count <1,000/µL 15. Elevated liver function tests as follows: - AST/ALT >2 × the upper limit of normal (ULN), regardless of the level of total bilirubin - AST/ALT >1.5 and ≤2 × ULN and total bilirubin >ULN - AST/ALT >ULN and ≤1.5 x ULN • and total bilirubin >1.5 and ≤2 x ULN, • and conjugated bilirubin ≥35% of the total bilirubin - Total bilirubin >2 x ULN, regardless of the level of AST/ALT 16. Hb level <8g/dL 17. Serum creatinine levels >2 × ULN 18. Platelet level <50,000/mm^3
Trial Design	This will be a proof-of-concept/Phase IIa, adaptive, open label study to examine the efficacy of MMV390048 in uncomplicated *P. vivax* and *P. falciparum* blood-stage malaria monoinfection in adult patients. Patients will be recruited as per the diagram below into one of two arms: • Arm A: *P. vivax* malaria, or • Arm B: *P. falciparum* malaria The first *P. vivax* and *P. falciparum* cohorts will receive 120 mg of MMV390048. This dose may be adjusted in accordance with safety limits determined during ongoing Phase I studies, but based on data from the FIH study, this dose is expected to be well tolerated, safe and result in plasma concentrations that are within pre-defined exposure limits. In addition to this, preclinical data suggest that this dose will achieve parasite clearance and should meet the Day 14 primary efficacy endpoint. Four patients will be recruited into the *P. vivax* arm and followed until at least Day 14

post-dose prior to the recruitment of patients into the *P. falciparum* arm. Enrolment into the *P. falciparum* arm may follow, pending an acceptable review of safety and efficacy data (with or without available PK data) from the initial *P. vivax* patients by the SRT. Thereafter, enrolment into *P. vivax* and *P. falciparum* arms may occur in parallel. Patients will be followed for 28 days post-dose for efficacy, and until 35 days post-dose for safety and PK evaluations.

If the data from the first *P. vivax* (1A) and *P. falciparum* (1B) cohorts respectively meet the success criteria, lower doses may be explored or the same dose may be repeated in Cohort 2. If the data from the first cohorts do not meet the success criteria but are inconclusive, the same dose may be repeated. Within each treatment arm, progression to the subsequent dose cohort will be managed independently of the other treatment arm. For example, if data from the *P. vivax* cohort (1A) do not meet the success criteria and are not inconclusive, but data from the *P. falciparum* cohort (1B) do meet these criteria, then the *P. falciparum* arm may continue to explore varying doses according to the scheme (cohort 2B and 3B), while the *P. vivax* arm of the study will be terminated.



Patients will be admitted to the Clinical Research Unit (CRU) for screening. If they provide informed consent and fulfill the eligibility criteria, they will be recruited to the study. A single dose of oral MMV390048 will be administered to patients who will remain in a fasted state from 3 hours prior to dosing until at least 1.5 hours after dosing (water *ad libitum* permitted throughout). Following drug administration, patients will remain in the CRU for a minimum of 72 hours post-dose.

After drug administration, parasitemia will be determined microscopically (thick and thin blood films) and by qPCR every 4 hours until 24 hours post-dose, and then every 6 hours until 72 hours post-dose or until the time of parasite clearance if this is later. During this time, safety assessments (vital signs, hematology, clinical chemistry and 12-lead ECGs) will be performed and PK blood samples will be taken.

When patients have a complete clearance of microscopically detected parasitemia

	they may be discharged (a minimum of 72h after dosing). Upon discharge, the frequency of follow-up visits will depend on the availability of the results of qPCR assays as follows, and should consider the fact that visits should be scheduled to include Day 14 – a critical time point for evaluation of the primary endpoint: • In situations where qPCR assay results can be obtained within 24 hours: - If malarial parasites are detected on qPCR from either of the last two consecutive samples prior to discharge (66 and 72 hours post-dose or later), the patient will be required to return to the unit at least every 48 hours from the time of discharge until parasitemia is undetectable on qPCR. - If malarial parasites are undetectable on qPCR from both of the last two consecutive samples prior to discharge (66 and 72 hours post-dose or later) and there are no longer signs or symptoms of malaria, the patient will be required to be available every 3 to 4 days for blood sampling for microscopy and qPCR until the final efficacy assessment visit (Days 7, 10 or 11, 14, 17 or 18, 21, 24 or 25, and 28, as per Appendix 7). If qPCR levels become detectable during this time, patients will be re-hospitalised for observation and definitive malaria treatment. • In situations where qPCR results are not available within 24 hours of sampling: - Patients will be required to return to the unit at least every 48 hours after discharge until the final efficacy assessment visit (Days 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 and 28, as per Appendix 8). If microscopic parasitemia becomes evident during this time, patients will be re-hospitalised for observation and definitive malaria treatment. Definitive malaria treatment in accordance with local treatment guidelines will be given to all patients with *P. vivax* or *P. falciparum* malaria on Day 28 (end of study), or earlier if individual stopping criterion (section 3.2.2) are met or at the investigator's discretion. *P. vivax* patients who have had a normal G6PD test result, may also be given primaquine (currently not a standard of care in Ethiopia) at the time of the definitive antimalarial treatment administration. An end-of-study visit (including safety and PK assessments will be conducted on Day 35.
Endpoints	**Primary Endpoints:** • For *P. vivax:* Crude Adequate Clinical and Parasitological Response (ACPR) at Day 14 defined as the absence of parasitemia (thick smear) on Day 14, irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure • For *P. falciparum:* PCR-adjusted ACPR at Day 14 defined as the absence of parasitemia (thick smear) on Day 14, irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques <u>Success criterion:</u> Crude ACPR (*P. vivax*) or PCR-adjusted ACPR (*P. falciparum*) on Day 14 ≥80% (equivalent to ≤20% recurrence [*P. vivax*] or recrudescence [*P. falciparum*]). If PCR correction data are not available at the time of the *P. falciparum* interim analyses, crude ACPR may be used to inform decisions on cohort progression. **Secondary Endpoints:** <u>Secondary endpoints related to safety and tolerability up to Day 35</u> • Incidence, severity, drug-relatedness and seriousness of adverse events • Proportion of patients with clinically significant abnormal laboratory values including changes from baseline (biochemistry and hematology)

- Proportion of patients with clinically significant abnormal vital signs including changes from baseline
- Proportion of patients with a decrease in hemoglobin (Hb):
  - >2 g/dL from baseline
  - to an absolute value of <5 g/dL
- Proportion of patients with an absolute Neutrophil count <1,000/µL after baseline
- Proportion of patients meeting Hy's law criteria
- Proportion of patients with the following LFT changes:
  - Any ALT or AST ≥5 x ULN
  - Any AST or ALT ≥3 x ULN together with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (eosinophil percent or count above the ULN)
  - Persistent ALT ≥3 x ULN for a period of more than 4 weeks.
- Proportion of patients with ECG abnormalities and the association of these with clinically significant cardiac related symptoms
- Incidence of absolute QT- and QTcF-intervals as follows and the association of QT-prolongation with clinically significant cardiac related symptoms:
  - QT/QTcF < 450 ms
  - 450 ms ≤ QT/QTcF < 480 ms
  - 480 ms ≤ QT/QTcF < 500 ms
  - QT/QTcF ≥ 500 ms

  Incidence of change from baseline in QT- and QTcF-intervals as follows and the association of QT-prolongation with clinically significant cardiac related symptoms:
  - <30 ms increase from baseline
  - ≥30 ms and <60 ms increase from baseline
  - ≥60 ms increase from baseline
- Proportion of patients with clinical signs of possible cutaneous adverse reactions such as dermatitis, rash, erythematous rash, macular rash, papular rash, maculo-papular rash, pruritic rash, pustular rash, vesicular rash

<u>Secondary endpoints related to malaria signs and symptoms up to Day 28</u>

- Proportion of patients with symptoms or physical examination signs related to uncomplicated *P. vivax,* and *P. falciparum* malaria (fever, dizziness, headache, nausea, anorexia, vomiting, diarrhea, pruritus, urticaria, skin rash, abdominal pain, joint pain, muscle pain, palpitations, sleep disturbance, confusion, hearing disturbance, visual disturbance, fatigue)

<u>Secondary endpoints related to secondary treatment outcomes</u>

- Crude ACPR at Day 14 (*P. falciparum* only)
- Crude ACPR at Day 28 (*P. vivax* and *P. falciparum)*
- PCR-adjusted ACPR at Day 28 (*P. falciparum* only)
- Recurrence (*P. vivax* and *P. falciparum*), recrudescence (*P. falciparum)* and new infection (*P. falciparum)* up to Day 28

<u>Secondary endpoints related to parasite clearance kinetics by microscopy</u>

- Parasite clearance time (PCT)
- PRR (parasite reduction rate) and parasitemia half life
- Times to microscopic clearance of asexual parasites
  - Total reduction (PC100)
  - 99% reduction (PC99)
  - 90% reduction (PC90)
  - 50% reduction (PC50)
- Microscopically determined percentage reduction in asexual parasites from

	baseline at: - 24 hours after administration of study drug - 48 hours after administration of study drug - 72 hours after administration of study drug • Proportion of microscopically determined aparasitemic patients at: - 24 hours after administration of study drug - 48 hours after administration of study drug - 72 hours after administration of study drug Secondary endpoints related to PK parameters up to Day 35 AUC_{0-t}, AUC_{0-inf}, C_{max}, t_{max}, $t_{½}$ **Exploratory Endpoints:** • Microscopic determination of the percentage reduction in gametocytes (stratified by gametocyte status at inclusion) from baseline at: - 24 hours after administration of study drug - 72 hours after administration of study drug • Proportion of patients with gametocytes over 28 days • Area under the curve (AUC) of gametocyte density over time up to Day 14 and Day 28 respectively • qPCR determined ACPR at Day 14 and Day 28 and correlation of microscopic and qPCR quantitative parasite assessment • Correlation between parasite genotypes of interest and parasite clearance kinetics/efficacy • Prevalence of genetic polymorphisms (e.g. CYP_{2C8}, $CYP_{2C19)}$
Sample Size	Seventeen (17) patients will be enrolled in each cohort. A maximum of 102 subjects (excluding replacements) will be enrolled in the study. Each of the three cohorts in the *P. vivax* and *P. falciparum* malaria arms will be assessed separately for futility, unless data for a particular cohort(s) are regarded as inconclusive and the dose is repeated in a subsequent cohort(s). In this case, data from all cohorts in a particular arm receiving the same dose will be combined for the purpose of assessment of futility. The minimum Day 14 ACPR responder count to meet the cohort success criteria will be 14 out of 17 patients. Assuming a binomial distribution, the point estimate of the response rate with 14 out of 17 responders will be 82.4% with the lower margin of the 90% confidence interval (Clopper-Pearson method) greater than 60% (60.4% to 95.0%). A responder count of 11 to 13 out of 17 patients will be regarded as inconclusive and the dose may be repeated in a subsequent cohort. The maximum Day 14 ACPR responder count to declare futility of a dose level after one cohort will be 10 out of 17 patients (response rate of 58.8% or less) and will be associated with a risk of false conclusion of futility of less than 0.1% (alpha <0.001) assuming that the true population response is at least 90%. If a particular dose is repeated, the minimum combined Day 14 ACPR responder count across the two cohorts to meet the success criteria will be 28 out of 34 patients (82.4% response rate; 90% confidence interval of 68.1% to 92.0%). A responder count of 25 to 27 out of 34 patients will be regarded as inconclusive and the dose may be repeated in a third cohort. The maximum combined Day 14 ACPR responder count to declare futility of a dose level after two cohorts will be 24 out of 34 (response rate of 70.6% or less) and will be associated with a risk of false conclusion of futility of less than 0.2% (alpha <0.002) assuming that the true population response is at least 90%. If a particular dose is repeated across three cohorts, a combined Day 14 ACPR

	responder count across the three cohorts of at least 41 out of 51 patients (80.4% response rate; 90% confidence interval of 69.0% to 89.0%) will be required to meet the dose success criteria. An observed response rate across the three cohorts of 78.4% or less (at most 40 out of 51 patients) will be associated with a risk of false conclusion of futility of less than 2% (alpha <0.011) assuming that the true population response is at least 90%. The sample size is considered adequate to gain preliminary efficacy and safety data in the target population.
Duration of Patient Participation	Each patient will participate in the study for approximately 35 days, including a screening period of approximately 2 to 4 hours, administration of the investigational product on Day 0, and a follow-up period until Day 35 (±2). Patients will remain at the CRU for a minimum of 72 hours after MMV390048 dose administration.
Individual Stopping Criteria:	Patients meeting any of the following criteria will be treated with definitive antimalarial therapy as per local standard of care. 1. Development of any clinical complications (WHO definition of complicated/severe malaria, WHO [2012][3]) with parasitemia 2. Parasitemia >100,000/µL at any stage 3. A ≥25% increase in parasitemia compared to baseline, with or without fever, during the period up to 24 hours after dosing for *P. vivax* malaria or up to 12 hours after dosing for *P. falciparum* malaria together with any of the following: • Clinical decline; • Lack of clinical improvement • Significant decrease in platelet count defined as: - >20% reduction from baseline for patients with a platelet count at inclusion of between 50,000/mm^3 and 74,999/mm^3 (grade 2 thrombocytopenia), or - decline to <50,000/mm^3 for patients with a platelet count at inclusion of ≥75,000/mm^3. 4. Parasitemia > baseline (from the slides taken 30 min before start of treatment) with or without fever, between >24 and 48 hours after dosing for *P. vivax* and between >12 and 36 hours after dosing for *P. falciparum* 5. Any parasitemia with fever, or parasitemia >25% of the baseline parasitemia with or without fever, between >48 and 72 hours after dosing for *P. vivax* and between >36 and 60 hours after dosing for *P. falciparum* 6. Failure to clear all parasites by microscopy associated with axillary temperature ≥37.5°C or oral/rectal/tympanic temperature ≥38°C between >72 and 96 hours for *P. vivax* and >60 and 96 hours for *P. falciparum* 7. Danger signs or severe malaria or parasitemia with fever between Day 4 and 28 8. Recurrence of parasitemia between Day 4 and 28 without fever.
Study Drug	MMV390048 will be supplied by the sponsor in tablet form for oral administration. The product will be manufactured, tested for quality control purposes and shipped to the study site by Corealis Pharma (Canada) in accordance with good manufacturing practices (GMP) and local regulations. Each tablet will contain 20 mg of the active ingredient MMV390048 and the following excipients: tartaric acid powder, copovidone (Plasdone S-630), hypromellose acetate succinate (AquaSolve HPMC-AS MF), croscaramellose sodium (Solutab), microcrystalline cellulose type 102 (Avicel PH-102) and magnesium stearate (Ligamed MF-2-V). A detailed description of the physical, chemical and pharmaceutical properties of MMV390048 can be found in Section 3 of the Investigator's Brochure.

	MMV390048 tablets will be administered as a single dose in the semi-fasted state.
Efficacy, Safety and PK parameters	Efficacy evaluations will include microscopic and qPCR determined parasitemia in conjunction with clinical signs and symptoms of malaria. Parasite genotyping will also be performed at baseline and at the time of recurrence of parasitemia (if applicable) to differentiate between recrudescence and new infection in the case of *P. falciparum* malaria. Safety evaluations will include the following: adverse event evaluation, physical examination, physical measurements, vital signs, 12-lead ECGs and laboratory parameters (hematology and clinical chemistry). These will be performed at baseline and at various time points throughout the study to assess changes from baseline after administration of MMV390048. Blood sampling for PK analysis will be performed at scheduled time points from immediately before dosing with MMV390048 until 35 days post administration.
Statistical Analysis	Data will be analysed separately for each of the *P. vivax* and *P. falciparum* cohorts. Descriptive summaries of efficacy and safety data will be produced by cohort and overall, in the microbiological intent-to-treat and in the safety analysis sets, respectively. The proportion of responders will be reported for the primary ACPR and the secondary efficacy criteria with 90% confidence intervals using the Clopper-Pearson method. If several doses of MMV390048 are tested in the study, a dose-response logistic regression model of the responder rates may be performed, in order to predict the therapeutic dose range. Complete details will be available in the SAP prior to enrolment of the first patient.

1. INTRODUCTION

1.1 Background

Malaria is a parasitic disease that threatens half of the world's population. The World Health Organization (WHO) reported that since 2000, the number of malaria cases has fallen from a range of 205 to 316 million to an estimated 214 million new cases in 2013 out of 3.2 billion people at risk. In the same year, malaria caused 438,000 deaths; 90% of the mortality was in the African region. However, even in this region mortality rates have fallen by 66% in all groups and by 71% in children under 5 and overall, malaria deaths in children under 5 have decreased to 306,000 in 2015.[6]

The WHO has declared malaria control a global development priority and has changed its recommendation from control programs to eradication programs. New drugs are needed to make this possible. While global efforts have led to the significant progress in the prevention, diagnosis, and management of malaria, treatment of malarial infections in the face of emerging drug resistance among Plasmodium species continues to pose clinical challenges. In particular, the widespread resistance of *P. falciparum* has rendered conventional monotherapies such as chloroquine, amodiaquine, and sulfadoxine-pyrimethamine ineffective. To combat increasing levels of resistance, the WHO recommends artemisinin-based combination therapy (ACT) as the first-line therapy for the treatment of uncomplicated *P. falciparum* malaria.[7]

Artemisinin and its derivatives are currently the most potent and rapidly acting anti-malarial agents available.[8] Their antimalarial activities are characterized by high parasite kill rates and broad-stage activity that produce a faster clinical and parasitological response than other classes of anti-malarial agents. The peroxidic pharmacophore of artemisinins is believed to be the main source of their potent activity. However, artemisinin derivatives have been associated with high recrudescence rates when used as monotherapy if using the conventional 3 to 5 days of therapy.[9] Combination with other agents has allowed for shorter courses of ACT therapy, improved treatment outcomes, and enhanced patient compliance.

Combinations of artemisinin derivatives with long-acting antimalarials (ACTs) are currently the treatment of choice for *P. falciparum* infections (e.g. Coartem® (artemether-lumefantrine), Eurartesim® (dihydroartemisinin-piperaquine) or artesunate-mefloquine).

Plasmodial resistance to artemisinins is emerging[10] and the benefits afforded by their unique antiplasmodial properties will be lost. Mutations which may mediate resistance to artemisinin, delayed parasite clearance upon artemisinin treatment and treatment failures[11,12,13] suggest that artemisinin resistance may become a global issue in the coming years. In addition, emerging cases of resistance to piperaquine in combination with dihydroartemisinin in Cambodia (unpublished results) as well as undesired side effects of mefloquine underline the need for development of a novel long-acting antimalarial, preferably from a novel class.

Additionally, current falciparum malaria treatments have a relatively high pill burden and require at least a three-day dosing regimen that often reduces patient compliance, further contributing to the development of drug-resistance and inadequate cure rates.

1.2 MMV390048

MMV390048 is a new antimalarial drug candidate which has undergone single ascending dose, food effect, and formulation bioavailability Phase I studies in healthy volunteers to demonstrate safety and tolerability, and to describe the pharmacokinetic profiles of different formulations of the compound.

To date MMV390048 has been administered as a single dose up to 120 mg to healthy volunteers. Further dose escalation remains under consideration. The review of the safety data on the Phase I studies carried out to date revealed no obvious trends associated with exposure to MMV390048. The compound was well tolerated.

The terminal half-life of the compound is sufficiently long (approximately 160 hours) to support a single low dose maintaining concentrations significantly above the minimum parasiticidal concentration (MPC). The dose calculated from efficacious concentrations in preclinical models to provide coverage above the MPC for $\geq$8 days is predicted to be approximately 20 mg.

At the time of writing this protocol, the human Induced Blood Stage Malaria (IBSM) challenge study is ongoing and will inform efficacious concentration levels.

A detailed discussion of available preclinical and clinical data can be found in the Investigator's Brochure.[14]

1.2.1 Mechanism of Action and antiplasmodial activity

MMV390048 is a blood-stage schizonticide designed to achieve a single dose cure and have high prophylactic potential. The compound has also shown activity in gametocyte, ookinete, and liver infection assays suggesting a role beyond the asexual blood stage.

MMV390048 is a new antimalarial chemotype that selectively targets inhibition of plasmodial phosphatidylinositol-4-kinases (PIK4). The compound was tested against a range of human PI3 and PI4 kinases at the screening dose of 10 µM, a dose approximately 350-fold higher than the IC_{50} for inhibition of *P. falciparum* in a whole cell assay. Although there was no activity against most of the kinases, there was some significant inhibition of human PI3KCA and PI4KB (54 and 67% respectively) at the 10 µM level. IC_{50} values against these kinases were determined to be 8.8 and 9.7 µM respectively.[15,16,17]

MMV390048 kills the erythrocytic forms of *P. falciparum* with an in vitro potency (IC_{50}) of 28 nM. The compound has shown a steep inhibition curve with the IC_{50} and IC_{90} values less than a titration point apart.[18] Against a panel of resistant strains, cross resistance was not considered an issue, and MMV390048 was shown to have a low liability for cytotoxicity in L6 and hepG2 cells lines.[19]

MMV390048 has atovaquone-like parasite reduction kinetics in vitro, with a parasite clearance time of 100 hours. When tested in vivo, MMV390048 proved to be three-fold more potent than artemether in the four day Peters test with an ED_{90} of 1.1 mg/kg per os and gave a complete cure of *P. berghei*-infected mice at low oral doses (4 x 3 mg/kg or 1 x 30 mg/kg). MMV390048 also demonstrated good activity in the *P. falciparum* SCID mouse model with maximum effect against the parasites at 1 mg/kg/day and an intermediate parasite clearance rate similar to mefloquine (ED_{90} of 4.9 mg/kg).

Additionally, MMV390048 has shown low nanomolar IC_{50} values against schizont and hypnozoite forms of *P. cynomolgi,* suggesting a potential to block parasite liver stages. When administered as a single dose of 20 mg/kg prophylactically 24 hours prior to infection in *P. cynomolgi* infected Rhesus monkeys, MMV390048 showed a high degree of protective effects for up to 100 days post-infection.[20]

1.2.2 Teratogenicity and Reproductive Toxicity Data

Testicular toxicity was observed in the rat following dosing for 7 days at 480 mg/kg/day or 90 mg/kg/day for 14 days. Determination of no effect levels are more appropriately based upon exposure rather than dose in these studies as exposures in the 14 day study were unexpected and

substantially higher than those seen at equivalent doses in the 7 day study, even although the same strain of rat was used. The testicular toxicity observed was consistent with an effect upon Sertoli cells. Germ cells were not directly affected. Recovery could not be established as the period for spermatogenesis in the rat is 54 days and the observed recovery period was only 14 days. The no effect dose of 30 mg/kg in the 14-day study was associated with a cumulative AUC_{0-336} of 1520 µg·h/ml. In the dog there were no effects on the testis at AUC_{0-24} exposures up to 380 µg·h/ml at steady state, and AUC_{0-336} up to 2244 µg·h/ml.

Definitive embryo-fetal development studies have not yet been completed. Consequently no conclusions concerning the preclinical assessment of reproductive toxicity to the developing fetus can be made. Dose finding studies in the pregnant rat and rabbit demonstrated maternal and fetal toxicity induction at high doses of MMV390048. In the rat, fetal alterations were seen at 60 mg/kg/day, a dose that also induced marked maternal toxicity. In the rabbit 10 mg/kg/day induced moderate maternal toxicity but no evidence of any fetal alteration.

1.2.3 Pharmacokinetics and Metabolism in Pre-Clinical Studies

Pre-clinical studies in rats, dogs, and monkeys were performed to characterise the pharmacokinetics and metabolism of MMV390048.

In mouse, rat, monkey and dog, the MMV390048 pharmacokinetic profile was characterized by low plasma clearance, moderate to high volumes of distribution and a long apparent elimination half-life (2.6 hours [mouse] to 61.1 hours [monkey]) in all four species.[21-27] Oral bioavailability from a simple aqueous suspension of MMV390048 was greater than 46% in all four species. Across multiple formulations, AUC values were consistently higher in fed dogs, with a corresponding decrease in the rate of absorption.

MMV390048 protein binding is moderate and is independent of concentration across species, ranging from 84.4% in the mouse to 86.1% in human. Average blood:plasma ratios range from 0.92 to 1 across all species, suggesting that MMV390048 is freely permeable across the red blood cell membrane.[28,29] In both liver microsomes and hepatocytes from mouse, rat, dog and human, MMV390048 was characterized by low clearance.[30-33] Two mono-oxidative metabolites, two direct glucuronides and one mixed oxidative/glucuronide metabolite were identified in plasma samples from rat, dog and monkey pharmacokinetic studies.[34] With the exception of one glucuronide which represented approximately 12% of the MMV390048 AUC in rat, all other metabolites were characterized as minor (<1%).

In human liver microsomes, MMV390048 did not inhibit CYP_{1A2}, CYP_{2C9}, CYP_{2C19}, CYP_{2D6} or CYP_{3A4} (testosterone), with IC_{50} >20 µM. Weak inhibition of $CYP_{3A4/5}$ was noted with terfenadine as the probe substrate (IC_{50} 13.5 µM).[35] In a preliminary CYP reaction phenotyping assay, data showed that MMV390048 is a substrate of CYP_{3A4}, and to a smaller extent of CYP_{2C8}.

1.2.4 Pharmacokinetics and Pharmacodynamics of MMV390048 in Humans

Pharmacokinetic data from the first in human (FIH) study revealed rapid absorption of MMV390048 after oral administration of the powder in bottle (PIB) formulation with t_{max} usually reached 1 to 3 hours after dosing. Individual C_{max} values observed in the trial ranged from 3.4 to 871.0 g/mL. Substantial variation was observed among C_{max} estimates for individuals from each dose group, except for the 20 mg dose group. This degree of variation was also observed in the AUC_{0-t} and AUC_{inf} estimates for individuals from all but the 5 mg and 20 mg dose groups. Absolute AUC_{inf} estimates from the trial ranged from 1.0 to 210.3 µg·h/ml.[36]

Approximately parallel elimination phase plasma concentration profiles were seen, indicative of a fixed elimination rate constant. As a consequence of the variable and extended absorption, estimates of $t_{½}$ were highly variable within each group and resulted in significant uncertainty regarding the true observed $t_{½}$ for MV390048.

Observed PK data from the first IBSM human challenge study were consistent with the high degree of inter-subject variability seen in both peak and total exposure in the FIH study.

Both new prototype formulations of MMV390048 (Formulations A and B) showed similar and reduced inter-subject variability after single dose administration of 40 mg as compared to the PIB formulation. Absorption of MMV390048 was rapid with higher C_{max} and AUC values, and much lower inter-subject variability for both formulations than seen with the PIB formulation.[37]

Formulation A was selected for further clinical development.

1.2.5 Clinical Summary

To date, MMV390048 has been administered to 55 healthy volunteers in the following studies:

1. Powder in bottle (PIB) formulation: A phase I double-blind, placebo-controlled, randomized single dose escalation study to evaluate the safety, tolerability and pharmacokinetic properties of MMV390048 in healthy human volunteers (FIH);
2. PIB formulation: A proof-of-concept, open label, phase I study using IBSM infection to characterize the activity of MMV390048 against early *P. falciparum* blood stage infection in healthy participants; and
3. New prototype tablet formulations: A Phase I, open label, single dose, parallel design exploratory study to evaluate the pharmacokinetics of selected oral formulations of MMV390048 administered in the fasted state to healthy volunteers.

The FIH study included a total of 40 male and female participants. MMV390048 was administered to 31 (26 male, 5 female) of these participants, five of whom were exposed to the product in both fasted and fed states to evaluate the effect of food intake on the pharmacokinetic (PK) profile of MMV390048 after oral administration. Participants in the fasted part of the study were exposed to five ascending doses: 5 mg, 20 mg, 40 mg, 80 mg and 120 mg. The fed cohort received a dose of 40 mg. Subjects were administered MMV390048 as a PIB formulation. Safety and tolerability assessments in this study were based on vital signs, ECG findings, safety laboratory data (clinical chemistry, hematology, coagulation, endocrinology, standard urinalysis tests) and adverse events. The study was stopped before full dose escalation could be achieved due to the large inter-subject variability in observed plasma concentrations of MMV390048.

The proof-of-concept, IBSM infection Phase I study was planned to include 3 cohorts. Eligible participants were inoculated on Day 0 with approximately 1,800 viable *P. falciparum*-infected human erythrocytes administered intravenously. Participants were monitored on an outpatient basis for adverse events and any unexpected early onset of symptoms, signs or parasitological evidence of malaria. On the day designated for commencement of treatment, as determined by qPCR results or clinical manifestation of malaria, participants were admitted to the study unit and confined for 72 hours for MMV390048 administration (PIB formulation), determination of parasite load and drug levels, and safety monitoring. If clinically well, participants were then discharged and monitored on an outpatient basis for safety, MMV390048 blood levels and the continued presence of malaria parasites via PCR. The effects of MMV390048 on parasitemia were observed for up to 16 days before initiating compulsory treatment with Riamet® (artemether-lumefantrine). As a safety measure, parasitemia continued to be monitored following the *Riamet* therapy and was assessed at the End of Study visit which took place approximately 28 days after the inoculation. Only one cohort (n=6) was dosed with a single dose of 20 mg MMV390048. Enrolment of additional subjects was

suspended pending reformulation of the investigational compound to address the high inter-subject variability seen in both this, and the FIH study.

A third, phase 1 exploratory study using two new prototype formulations was conducted in 18 subjects (two cohorts of nine subjects each) to identify a suitable formulation of MMV390048, capable of producing consistent, predictable and sustained pharmacokinetic exposures when administered as a single 40 mg dose. The safety, tolerability and pharmacokinetics of the new prototype formulations were assessed. Both formulations (designated as A and B) were associated with a reduction in inter-subject variability of plasma concentration profiles to within acceptable levels. Absorption of MMV390048 was rapid with median peak concentrations observed 3 hours post-dose for both formulations. Inter-individual variability in C_{max} was relatively low (18.0–22.3%) and similar in the two treatment groups. Inter-subject variability in $AUC_{0\text{-}inf}$ was moderate (48.6–53.5%) and again similar in the treatment groups. The safety findings from this study demonstrated that single oral doses of 40 mg of MMV390048 (both formulations A and B) were well tolerated by the study subjects. No SAEs nor severe AEs were reported during this study. Formulation A was selected for further development.

A combined single ascending dose and human challenge study using the reformulated compound is currently ongoing. Fifty (50) participants are planned to be enrolled in this study. To date, 40 mg and 80 mg doses of MMV390048 (Formulation A) have been tested in healthy volunteers, and the formulation has been confirmed to reduce the variability of the pharmacokinetic profiles. A dose proportional increase has been observed in C_{max}, and AUC. The next dose to be tested will be 120 mg, and exposures resulting from this dose are expected to be within the pre-defined AUC and C_{max} limits determined during pre-clinical studies. Subjects participating in the challenge part of the study will receive MMV390048 in the semi-fasted state. Preliminary data from the first seven subjects in the challenge part of the study indicate no difference in the safety nor pharmacokinetic profile compared to subjects participating in the escalating dose part of the study.

1.2.5.1 Human safety and tolerability data

Review of the safety data revealed no obvious trends associated with exposure to MMV390048 in any of the three studies conducted to date. No drug-related serious adverse events (SAEs) or unexpected adverse events were reported in either the IBSM or reformulation studies.

A total of 15 adverse drug reactions (ADRs) (neutropenia, urticaria, dizziness, dysgeusia, photophobia, malaise and diarrhea considered by the investigator to be related to the investigational product) were recorded in 13 participants during the FIH trial. These were evenly distributed amongst the treatment groups, with no clear relationship between dose and number of events. The 5 mg treatment group was the only treatment group without any reported ADRs.

The only ADRs that occurred in more than one treatment group were two counts of decreased neutrophil count (40 mg and 40 mg FED groups occurring in the same participant) and two counts of diarrhea (40 mg and 40 mg FED in different participants), all of which resolved completely and spontaneously. The subject that developed decreased neutrophil counts had mildly decreased counts at baseline prior to each dose administration. In terms of adverse events, the following were regarded as related by the investigator: neutropenia, urticaria, dizziness, dysgeusia, photophobia, malaise and diarrhea.

Analysis of safety laboratory, endocrinology, vital sign and ECG data from the FIH study revealed no significant or dose-dependent trends up to the highest dose tested (120 mg). One subject who received MMV390048 20 mg was noted to have PR-interval prolongation intermittently during the follow-up period from 48 hours post dose until the final study visit on Day 79. The onset of the finding and its erratic presence was not consistent with the observed peak plasma concentration of

MMV390048 and subsequent concentrations throughout the trial period. Analysis of QTcF-interval data (triplicate recordings) was unremarkable and no other ECG parameter anomalies were reported.

1.2.5.2 Serious Adverse Events

A single serious adverse event (SAE) was reported during the FIH trial in the 120 mg cohort. The participant experienced generalized myoclonus the day after IP administration and after voluntary sleep-deprivation the previous night. Clonazepam and valproic acid were administered to treat symptoms. Although the participant denied any history of fainting, fits, seizures or involuntary movement, further investigations revealed an undisclosed 7-year history of a pre-existing epilepsy syndrome with onset of generalised tonic clonic seizures and myoclonic seizures in mid-adolescence. The participant had been treated with phenytoin and later carbamazepine.

In the opinion of a neurologist consulted at the time of the event, MMV390048 could not be excluded as a possible factor resulting in a lowered seizure threshold in this participant. However, the participant's medical history alone strongly supported a diagnosis of Juvenile Myoclonic Epilepsy and the sleep deprivation he reported was considered sufficient to precipitate an episode of myoclonic status. The participant continued to report seizures after being discharged from the unit as part of an ongoing poorly controlled syndrome. Of note also, preclinical studies conducted in rodent suggest that MMV390048 does not cross the blood-brain barrier.

1.3 Study and Dose Rationale

The present Phase IIa study aims to confirm, in patients, the observed activity of MMV390048 against *P. falciparum* in pre-clinical models and the human IBSM human challenge model, and to determine the activity against *P. vivax* malaria in patients, both over 14 and 28 days. Additional aims are to characterise the safety of MMV390048 in patients. Patient safety will be monitored for up to 35 days post-dose including pharmacokinetic assessments. The study will investigate descending single doses of MMV390048 in response to results obtained in the first cohort/dose in each malaria sub-type.

The results of this trial will identify active, well tolerated doses for investigation in combination with a partner drug within a Phase IIb clinical trial.

Preclinical studies using SCID mice inoculated with *P. falciparum*-infected red blood cells link doses and exposures to the efficacy of MMV390048.[38] The active dose in the SCID model causing maximum effect (ED90) against the parasites is 1 mg/kg/day. The MPC derived from the SCID data was 39 ng/ml.[39] A human dose for the treatment of *P. falciparum* was sought that could maintain blood concentrations above 39 ng/ml (100 nM) for 8 days. Assuming linear pharmacokinetics and based on observed data from the Phase I exploratory formulation study in human volunteers, a dose of approximately 20 mg would be estimated to achieve the pharmacodynamic target drug concentration in humans based on the preclinical efficacy data generated in the SCID mice model. For new antimalarial drugs the translation of a predicted efficacious dose from the SCID mouse to the human challenge model and in turn to the treatment of acute, uncomplicated *P. vivax* or *P. falciparum* is unknown. To minimise the risk to patients and to ensure the highest probability of success, the maximum safe dose (as determined in healthy volunteers) that maintains a toxicokinetic safety margin to the repeat dose studies was selected for the first cohort in this study. This dose is expected to exceed the predicted MPC on Day 8 and provide significant target coverage at the site of action.

2. STUDY OBJECTIVES

2.1 Primary Objective

To determine the 14-day efficacy of a single dose of MMV390048 for the treatment of uncomplicated *P. vivax* or *P. falciparum* malaria monoinfection.

2.2 Secondary Objectives

- To assess the safety and tolerability of a single dose of MMV390048 in patients with *P. vivax* and *P. falciparum* malaria infection up to Day 35
- To assess the effect of a single dose of MMV390048 on signs and symptoms of *P. vivax* and *P. falciparum* malaria infection up to Day 28
- To assess the effect of a single dose of MMV390048 on treatment outcomes in patients with *P. vivax* and *P. falciparum* malaria infection:
  - Without PCR-adjustment at Day 14 (*P. falciparum* only)
  - Without PCR-adjustment at Day 28 (*P. vivax* and *P. falciparum*)
  - With PCR-adjustment at Day 28 (*P. falciparum* only)
  - Rates of recurrence (*P. vivax* and *P. falciparum),* recrudescence (*P. falciparum* only) and new infection (*P. falciparum* only) over 28 days
- To describe parasite clearance kinetics after a single dose of MMV390048 in patients with *P. vivax* and *P. falciparum* malaria infection
- To describe the pharmacokinetic characteristics of a single dose of MMV390048 in patients with *P. vivax* and *P. falciparum* malaria infection up to Day 28

2.3 Exploratory Objectives

- To describe the presence of gametocytemia after a single dose of MMV390048 in patients with *P. vivax* and *P. falciparum* malaria infection up to Day 28
- To investigate the relationship between microscopically determined and qPCR determined parasitemia
- To explore the relationship between parasite genotypes of interest and parasite clearance kinetics/efficacy
- To obtain pharmacogenetics samples from patients who specifically consent to this, for future exploratory analysis of genetic polymorphism (e.g. CYP_{2C8}, CYP_{2C19})

Analysis of exploratory data may not be performed at the same time as the analysis of the primary and secondary endpoint data, and may be reported separately and not as part of the main clinical study report.

3. METHODS AND INVESTIGATIONAL PLAN

3.1 Study Design

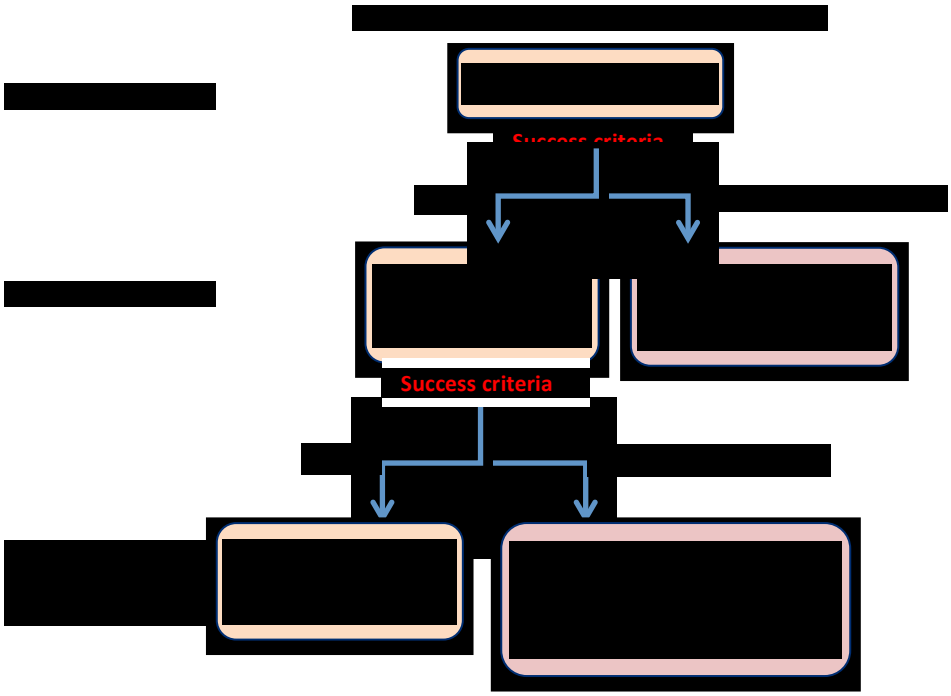
This will be a Proof-of-Concept/Phase IIa, adaptive, open label study to examine the efficacy of MMV390048 in uncomplicated *P. vivax and P. falciparum* blood-stage malaria monoinfection in adult patients. Patients will be recruited as per the diagram below into one of two arms:

1. Arm A: *P. vivax* malaria, or
2. Arm B: *P. falciparum* malaria

The first *P. vivax* and *P. falciparum* cohorts will receive 120 mg of MMV390048. This dose may be adjusted in accordance with safety limits determined during ongoing Phase I studies, but based on data from the FIH study, this dose is expected to be well-tolerated, safe and result in plasma concentrations that are within pre-defined exposure limits. In addition to this, preclinical data suggest that this dose will achieve parasite clearance and should meet the primary efficacy endpoint.

Four patients will be recruited into the *P. vivax* arm and followed until at least Day 14 post-dose prior to the recruitment of patients into the *P. falciparum* arm. Enrolment into the *P. falciparum* arm may follow, pending an acceptable review of safety and efficacy data (with or without available PK data) from the initial *P. vivax* patients by the Safety Review Team (SRT). Enrolment into the *P. vivax* arm will not pause during this SRT review. Thereafter, enrolment into the *P. vivax* and *P. falciparum* arms may occur in parallel. Patients will be followed for 35 days post-dose for safety, efficacy and PK evaluations.

If the data from the first *P. vivax* (1A) and *P. falciparum* (1B) cohorts respectively meet the success criteria, lower doses may be explored or the same dose may be repeated. If data from the first cohorts do not meet the success criteria, but are inconclusive, the same dose may be repeated. The same approach will be used for progress from cohorts 2 to 3, but with the addition of the option to re-escalate the dose in cohort 3 if success criteria are not met in cohort 2. Within each treatment arm, progression to the subsequent dose cohort will be managed independently of the other treatment arm. For example, if data from the *P. vivax* cohort (1A) do not meet the success criteria and are not inconclusive, but the data from the *P. falciparum* cohort (1B) do meet these criteria, then the *P. falciparum* arm may continue to explore varying doses according to the scheme (cohort 2B and 3B), while the *P. vivax* arm of the study will be terminated. The MMV390048 dose of cohorts 2 and 3 will be determined based on data from the preceding cohort(s) and the decision will be made independently for the *P. vivax* and *P. falciparum* arms.



3.2 Study Plan

3.2.1 General

Patients will be admitted to the Clinical Research Unit (CRU) for screening. If they provide informed consent for study participation and fulfill all of the eligibility criteria, they will be recruited to the study. A single dose of oral MMV390048 will be administered to patients who will remain in a fasted state from 3 hours prior to dosing until at least 1.5 hours after dosing (water *ad libitum* permitted throughout). Following drug administration, patients will remain in the CRU for a minimum of 72 hours post-dose.

After drug administration, parasitemia will be determined microscopically (thick and thin blood films) and by qPCR every 4 hours until 24 hours post-dose, and then every 6 hours until 72 hours post-dose or until the time of parasite clearance if this is later. During this time, safety assessments (vital signs, hematology, clinical chemistry and 12-lead ECGs) will be performed and PK blood samples will be taken.

When patients have complete clearance of microscopically detected parasitemia, they may be discharged (a minimum of 72 hours post-dose).

Upon discharge, the frequency of follow-up visits will depend on the availability of qPCR assay results as follows. and should consider the fact that visits should be scheduled to include Day 14 – a critical time point for evaluation of the primary endpoint:

- In situations where qPCR assay results can be obtained within 24 hours:
  - If malarial parasites are detected on qPCR from either of the last two consecutive samples prior to discharge (66 and 72 hours post-dose or later), the patient will be required to return to the unit at least every 48 hours from the time of discharge until parasitemia is undetectable on qPCR
  - If malarial parasites are undetectable on qPCR from both of the last two consecutive samples prior to discharge (66 and 72 hours post-dose or later) and there are no longer

signs or symptoms of malaria, the patient will be required to be available every 3 to 4 days for blood sampling for microscopy and qPCR until the final efficacy assessment visit (Days 7, 10 or 11, 14, 17 or 18, 21, 24 or 25, and 28, as per Appendix 7). If qPCR levels become detectable during this time, patients will be re-hospitalised and offered definitive malaria treatment as described beneath.

- In situations where qPCR assay results are not available within 24 hours of sampling:
  - Patients will be required to return to the unit at least every 48 hours from the time of discharge until the final efficacy assessment visit (Days 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 and 28, as per Appendix 8). If microscopic parasitemia becomes evident during this time, patients will be re-hospitalised for observation and definitive malaria treatment.

Decisions re observation, treatment and re-hospitalisation of patients who develop either microscopic or qPCR detected parasitemia after discharge will be made in accordance with the following guidelines, and in conjunction with the individual stopping criteria (Section 3.2.2):

- In situations where qPCR assay results are available within 24 hours of sampling:
  - Patients with qPCR determined parasitemia in the absence of microscopic parasitemia will be hospitalised for observation and receive treatment with definitive antimalarial therapy as soon as parasite levels are detected microscopically.
- In situations where qPCR assay results are not available within 24 hours of sampling:
  - Patients with microscopically detectable parasitemia will be re-hospitalised and treated with definitive antimalarial therapy.

Definitive antimalarial treatment will be administered on Day 28 (final efficacy assessment) to all patients enrolled in the study, or prior to this if individual stopping criteria are met (section 3.2.2) or otherwise at the Investigator's discretion. Patients will be given standard of care according to local treatment guidelines. *P. vivax* patients who have had a normal G6PD test result, may also be given primaquine (currently not a standard of care in Ethiopia) at the time of the definitive antimalarial treatment administration.

An end-of-study visit (including safety and PK assessments) will be conducted on Day 35.

A detailed description of time-point specific parasitological, safety and PK assessments during the study is presented in Section 5.

3.2.2 Individual Patient Stopping Criteria

Patients meeting any of the following criteria will be treated with definitive antimalarial therapy as per local standard of care:

- Development of any clinical complications (WHO definition of complicated/severe malaria, WHO [2012] [3]) together with parasitemia
- Parasitemia >100,000/µL at any stage
- A ≥25% increase in parasitemia compared to baseline, with or without fever, during the period up to 24 hours after dosing for *P. vivax* malaria or up to 12 hours after dosing for *P. falciparum* malaria together with any of the following:
  - Clinical decline;
  - Lack of clinical improvement; or
  - Significant decrease in platelet count defined as:
    - >20% reduction from baseline for patients with a platelet count at inclusion of between 50,000/mm^3 and 74,999/mm^3 (grade 2 thrombocytopenia), or
    - decline to <50,000/mm^3 for patients with a platelet count at inclusion of ≥75,000/mm^3

- Parasitemia > baseline (from the slides taken 30 min before start of treatment) with or without fever, between >24 and 48 hours after dosing for *P. vivax* and between >12 and 36 hours after dosing for *P. falciparum*
- Any parasitemia with fever, or parasitemia >25% of the baseline parasitemia with or without fever, between >48 and 72 hours after dosing for *P. vivax* and between >36 and 60 hours after dosing for *P. falciparum*
- Failure to clear all parasites by microscopy associated with axillary temperature ≥37.5°C or oral/rectal/tympanic temperature ≥38°C between >72 and 96 hours for *P. vivax* and >60 and 96 hours for *P. falciparum*
- Danger signs or severe malaria or parasitemia with fever between Day 4 and 28
- Recurrence of parasitemia between Day 4 and 28 without fever.

3.3 Study Endpoints

3.3.1 Primary Endpoints:

- For *P. vivax:* Crude Adequate Clinical and Parasitological Response (ACPR) at Day 14 defined as the absence of parasitemia (thick smear) on Day 14, irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure
- For *P. falciparum:* PCR-adjusted ACPR at Day 14 defined as the absence of parasitemia (thick smear) on Day 14, irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure, after adjustment for parasitemia due to new infections as determined by genotyping using PCR techniques

Success criterion:

Crude ACPR (*P. vivax*) or PCR-adjusted ACPR (*P. falciparum*) on Day 14 ≥80% (equivalent to ≤20% recurrence [*P. vivax*] or recrudescence [*P. falciparum*]). If PCR correction data are not available at the time of the *P. falciparum* interim analyses, crude ACPR may be used to inform decisions on cohort progression.

3.3.2 Secondary Endpoints:

3.3.2.1 Endpoints related to safety and tolerability of MMV390048 in patients up to Day 35

- Incidence, severity, drug-relatedness and seriousness of adverse events
- Proportion of patients with clinically significant abnormal laboratory values including changes from baseline (biochemistry and hematology)
- Proportion of patients with clinically significant abnormal vital signs including changes from baseline
- Proportion of patients with a decrease in hemoglobin (Hb):
  - >2 g/dL from baseline
  - to an absolute value of <5g/dL
- Proportion of patients with an absolute Neutrophil count <1,000/µL
- Proportion of patients meeting Hy's law criteria
- Proportion of patients with the following LFT changes:
  - Any ALT or AST ≥5 x ULN

  - Any AST or ALT ≥3 x ULN together with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (eosinophil percent or count above the ULN)
  - Persistent ALT ≥3 x ULN for a period of more than 4 weeks
- Proportion of patients with clinically significant ECG abnormalities and the association of these with clinically significant cardiac related symptoms
- Incidence of absolute QT- and QTcF-intervals as follows and the association of QT-prolongation with clinically significant cardiac related symptoms:
  - QT/QTcF < 450 ms
  - 450 ms ≤ QT/QTcF < 480 ms
  - 480 ms ≤ QT/QTcF < 500 ms
  - QT/QTcF ≥ 500 ms

  Incidence of change from baseline in QT- and QTcF-intervals as follows and the association of QT-prolongation with clinically significant cardiac related symptoms:
  - <30 ms increase from baseline
  - ≥30 ms and <60 ms increase from baseline
  - ≥60 ms increase from baseline
- Proportion of patients with clinical signs of possible cutaneous adverse reactions such as dermatitis, rash, erythematous rash, macular rash, papular rash, maculo-papular rash, pruritic rash, pustular rash, vesicular rash

3.3.2.2 Endpoint related to malaria signs and symptoms up to Day 28

- Proportion of patients with symptoms or physical examination signs related to uncomplicated *P. vivax* and *P. falciparum* malaria (fever, dizziness, headache, nausea, anorexia, vomiting, diarrhea, pruritus, urticaria, skin rash, abdominal pain, joint pain, muscle pain, palpitations, sleep disturbance, confusion, hearing disturbance, visual disturbance, fatigue)

3.3.2.3 Endpoints related to secondary treatment outcomes

- Crude ACPR at Day 14 (*P. falciparum* only)
- Crude ACPR at Day 28 (*P. vivax* and *P. falciparum)*
- PCR-adjusted ACPR at Day 28 (*P. falciparum* only)
- Recurrence (*P. vivax* and *P. falciparum*), recrudescence (*P. falciparum)* and new infection (*P. falciparum)* up to Day 28

3.3.2.4 Endpoints related to parasite clearance kinetics

- Parasite clearance time (PCT)
- PRR (Parasite reduction rate) and parasitemia half life
- Times to microscopic clearance of asexual parasites
  - Total reduction (PC100)
  - 99% reduction (PC99)
  - 90% reduction (PC90)
  - 50% reduction (PC50)
- Microscopically determined percentage reduction in asexual parasites from baseline at:
  - 24 hours after administration of study drug
  - 48 hours after administration of study drug
  - 72 hours after administration of study drug
- Proportion of microscopically determined aparasitemic patients at:

- 24 hours after administration of study drug
- 48 hours after administration of study drug
- 72 hours after administration of study drug

3.3.2.5 Endpoints related to PK parameters up to Day 35

AUC_{0-t}, AUC_{0-inf}, C_{max}, t_{max} and $t_{½}$.

3.3.3 Exploratory endpoints

- Microscopic determination of the percentage reduction in gametocytes from baseline at:
  - 24 hours after administration of study drug
  - 72 hours after administration of study drug
- Proportion of patients with gametocytes over 28 days
- Area under the curve (AUC) of gametocyte density over time up to Day 14 and Day 28 respectively
- qPCR determined ACPR at Day 14 and Day 28 and correlation of microscopic and qPCR quantitative parasite assessment
- Correlation of parasite genotypes of interest and parasite clearance kinetics/efficacy
- Prevalence of genetic polymorphism (e.g. CYP_{2C8}, CYP_{2C19})

3.4 Selection of Study Population

Patients will be provided with a written explanation of the study before any protocol specific procedures are carried out. A physician or nurse will explain to each patient the nature of the study, its purpose, expected duration and the benefits and risks involved in study participation. Patients will then be given the opportunity to ask questions and to discuss possible participation in the study with their family members and/or spouse. They will be reminded that participation in the study is voluntary, and that they may refuse to participate or withdraw from the study at any stage without prejudice. After this explanation and before entering the study, patients consenting to participation in the study will be required to do so in writing by signing the informed consent form in accordance with local practice. If the patient is unable to write, witnessed consent is permitted according to local ethical considerations.

Completion of all six cohorts will require 102 adult patients (excluding replacements) to be enrolled on the study (17 patients per cohort). Men and WNCBP will be enrolled in the study. It is anticipated that approximately 204 patients will be screened to achieve this. Enrolment is targeted to complete within one year. Patients who are withdrawn or drop out for reasons not related to lack of efficacy or safety concerns will be replaced at the discretion of the Sponsor in consultation with the Principal Investigator.

3.4.1 Inclusion Criteria

Patients must fulfill the following inclusion criteria to be eligible for enrolment in the study:

1. Men or WNCBP between the ages of 18 and 55 years, inclusive
2. Body weight between 40 kg and 90 kg inclusive
3. Presence of *P. vivax* or *P. falciparum* monoinfection confirmed by:
   - Fever, as defined by axillary temperature ≥37.5°C or oral/rectal/tympanic temperature ≥38°C, or history of fever in the previous 48 hours for *P. vivax* and 24 hours for *P. falciparum* and,

- Microscopically confirmed parasite infection: 1,000 to 40,000 asexual parasite count/µL blood

4. Written informed consent provided by the patient in accordance with local practice. If the patient is unable to write, witnessed consent is permitted according to local ethical considerations.
5. Ability to swallow oral medication
6. The patient is able to understand and comply with protocol requirements, instructions and protocol-stated restrictions and is likely to complete the study as planned
7. Willing to be hospitalized for at least 72 hours or until malarial parasites are not detected by microscopy on 2 consecutive occasions whichever comes later and return to clinic for all follow-up visits
8. Women must be of non-childbearing potential (WNCBP) as per one of the following definitions:
   - postmenopausal defined as having age-appropriate, natural (spontaneous) amenorrhea for at least 12 months prior to screening in the absence of an alternative medical cause for the amenorrhea, or
   - premenopausal with irreversible surgical sterilization by hysterectomy and/or bilateral oophorectomy or salpingectomy at least 6 months prior to screening (as determined by subject medical history)
9. Sexually active men must agree to comply with strict appropriate contraception rules (barrier contraception, e.g. condom) or complete abstinence when this is in line with the preferred and usual lifestyle of the patient. The contraception coverage in this situation should ensure full elimination of MMV390048, i.e. until 120 days after MMV390048 administration to the enrolled male patient (covering a full sperm cycle of 90 days starting after 5 x $t_{½}$ of the drug). Abstinent patients must agree to use the above-mentioned contraceptive methods if they start sexual relationships during the study, and to continue these methods until 120 days after study medication.

3.4.2 Exclusion Criteria

To be eligible for enrolment in the study, patients must NOT meet any of the following criteria:

1. Patients with signs and symptoms of severe / complicated malaria according to the World Health Organisation Criteria 2012[3]
2. Mixed *Plasmodium* infection
3. Vomiting more than three times in the 24 hours prior to inclusion in the study or inability to tolerate oral treatment, or diarrhea equivalent to three or more watery stools per day
4. Women who are nursing (lactating)
5. Presence of other serious or chronic clinical condition requiring hospitalisation
6. Severe malnutrition (defined as a body mass index [BMI] of less than 16 kg/m^2 as per local guidelines)
7. Presence of concurrent febrile illness (e.g. typhoid fever)
8. Known history or evidence of clinically significant:
   - cardiovascular disease (including arrhythmia, QTcF interval >450 msec, personal or family history of long QT syndrome, PR interval >210msec; any relevant intra-ventricular heart block [QRS >120msec]),
   - respiratory conditions (including active tuberculosis),
   - history of jaundice or other hepatic dysfunction,
   - renal insufficiency,
   - gastrointestinal disorder, or any condition that may affect absorption of the study medication (e.g. vomiting or diarrhea),

- immunological disorders (including known pre-existing HIV infection),
- endocrine disorders (including any type of diabetes mellitus whether controlled or not, diabetes insipidus, uncontrolled hypo- or hyperthyroidism, endocrine reproductive disorders not requiring concurrent medication, disorders of adrenal function),
- infectious conditions (other than minor skin or soft tissue infections or confirmed minor lower urinary tract infection),
- malignancy,
- psychiatric or neurological disorders (including a history of convulsions, major head trauma, focal neurological signs, psychosis, bipolar or major depressive disorder), or
- any other disorder or condition that in the opinion of the investigator may render the patient unfit for participation in the trial, may limit his/her ability to provide informed consent, may interfere with protocol adherence or place the patient at increased risk through participation in the study

9. Known to have any of the following markers of active hepatitis:
   - Hepatitis A IgM (HAV-IgM),
   - Hepatitis B surface antigen (HBsAg), or
   - Hepatitis C antibody (HCV Ab) and HCV RNA
10. Have received any antimalarial treatment (alone or in combination) during the following periods before screening (list of prohibited medication is provided in Appendix 2):
    - Piperaquine, mefloquine, naphthoquine or sulphadoxine-pyrimethamine within 6 weeks prior to screening
    - Amodiaquine, chloroquine, pyronaridine or tafenoquine within 4 weeks prior to screening
    - Any artemisinin derivative (artesunate, artemether, arteether or dihydroartemisinin), quinine, halofantrine, lumefantrine and any other anti-malarial treatment or antibiotic with antimalarial activity (including cotrimoxazole, tetracyclines, quinolones and fluoroquinolones and azithromycin) within 14 days prior to screening
    - Any herbal products or traditional medicines during the 7 days prior to screening
11. Receipt of an investigational drug within 8 weeks or 5 half-lives (whichever is longer) prior to screening
12. Current participation in any other clinical trial, or previous participation in a clinical trial where MMV390048 was administered
13. A history of regular abuse of alcohol, or use of drugs of abuse during the past 6 months, or any clinical signs of substance abuse
14. Neutrophil count <1,000/µL
15. Elevated liver function tests as follows:
    - AST/ALT >2 × the upper limit of normal (ULN), regardless of the level of total bilirubin
    - AST/ALT >1.5 and ≤2 × ULN and total bilirubin >ULN
    - AST/ALT >ULN and ≤1.5 x ULN
      - and total bilirubin >1.5 and ≤2 x ULN,
      - and conjugated bilirubin ≥35% of the total bilirubin
    - Total bilirubin >2 x ULN, regardless of the level of AST/ALT
16. Hb level <8g/dL
17. Serum creatinine levels >2 × ULN
18. Platelet level <50,000/mm^3.

3.4.3 Justification of the Eligibility Criteria

The inclusion and exclusion criteria have been selected to minimise risk to the well being of patients in this Phase IIa study and to ensure the inclusion of a study population that will facilitate the conduct of the study and the scientific evaluation of the study objectives. Since definitive embryo-fetal development studies have not yet been completed, women of child-bearing potential will not be included in the study.

If emerging safety signals during the study suggest that patients with specific medical conditions, signs or symptoms not currently mentioned as exclusion criteria may be subjected to unforseen risk through participation in the study, the eligibility criteria may be amended and additional screening examinations or procedures may be performed to exclude such patients from participation. In this event, the protocol will be amended and the Ethics Committee and Regulatory Authority notified of the emerging data and amended protocol.

3.5 Patient Restrictions

Patients enrolled in the study will be required to adhere to the following restrictions:

- Patient will remain in the clinic for a minimum of 72 hours post-dose (Day 3).
- Patients must attend all study visits at the CRU in accordance with the protocol up to the final end-of-study follow-up visit (Day 35).
- Patient should be able to remain fasting (except for water which will be permitted *ad libitum* from 3 hours prior to dosing until 1.5 hours post-dose).
- Patients must refrain from using prohibited concomitant antimalarial drugs (Appendix 2) for 14 days prior to enrolment in the study and during study participation.
- The use of drugs of abuse is prohibited during the study.
- No alcohol nor khat use will be permitted during the admission period. Patients are advised not to consume alcohol nor use khat for the duration of the study period, and excessive use of either during the follow-up period is prohibited.
- Male patients must adhere to contraception requirements (Inclusion Criterion 9).

3.6 Concomitant Medications

The following concomitant medications are permitted for symptomatic treatment of malaria and other adverse events as required:

- paracetamol (15 mg/kg, 4 hourly as required) for antipyretic and analgesic use,
- anti-emetics (except metoclopramide which may be associated with QT prolongation) for repeated vomiting
- penicillin-derivative antibiotics for the treatment of incidental bacterial infections; all other antibiotics, fluoroquinolones included, should be avoided.

Drugs with the potential to induce QT-interval prolongation (e.g. beta-adrenergic blocking agents) should be avoided during the study, and are not permitted during the admission period. Detailed information is provided at www.azcert.org (http://crediblemeds.org/).

Prohibited concomitant antimalarial drugs are listed in Appendix 2.

All previous and concomitant medication will be noted in the patient's case report form (CRF) for the period from 28 days prior to screening until the end-of-study assessments on Day 35.

3.7 Patient Withdrawal

Patients may be withdrawn from the study for any of the following reasons:

- at the request of the patient (withdrawal of informed consent), irrespective of the reason for this and without prejudice for further follow-up or treatment by the study site;
- at the discretion of the Investigator if he or she believes that continuation in the study would be detrimental to the patient's well-being in any way.

Any patient who vomits within 30 minutes of MMV390048 dose administration will be re-dosed with a full dose of the IMP. Details of the vomiting and second dose administration will be recorded on the CRF. Patients who vomit a second time within 30 minutes of the second dose administration will be withdrawn from the study and replaced.

Any patient that requires treatment with a drug with antimalarial activity (such as co-trimoxazole, tetracycline group drugs including minocycline and doxycycline, azithromycin and other macrolides, sulphonamides, fluoroquinolones etc.) for an infection other than malaria within 7 days of IMP administration, will no longer be followed up for efficacy assessments. They will be treated with definitive antimalarial therapy (as per local guidelines) and followed for safety, tolerability and PK assessments only as per the study schedule.

Patients who are withdrawn from the study will attend a withdrawal visit where assessments scheduled for Day 28 will be performed. They will be treated with definitive antimalarial treatment as described in Section 3.2 and will be requested to attend an end-of-study visit after the withdrawal visit where assessments scheduled for Day 35 will be performed. Every attempt should be made by the Investigator to ensure that patients enrolled in the study and who receive the IMP are followed up for 35 days post-dose if possible (equivalent to 5 half lives of MMV390048).

Patients withdrawn from the study (including those withdrawn from efficacy evaluations only) may be replaced at the discretion of the Sponsor and the Principal Investigator.

Patients who meeting stopping criteria for the study and are treated with definitive antimalarial therapy as per local standard of care prior to Day 28, will not be considered withdrawn from the study. They will continue to be followed for safety, tolerability and PK assessments as per the study schedule until Day 35.

4. INVESTIGATIONAL PRODUCTS

All investigational product supplies are to be used only in accordance with this protocol, and not for any other purpose.

4.1 Description of Products

4.1.1 Investigational Medicinal Product (IMP)

MMV390048 will be supplied by the sponsor in tablet form for oral administration. The product will be manufactured, tested for quality control purposes and shipped to the study site by Corealis Pharma (Canada) in accordance with good manufacturing practices (GMP) and local regulations. The packaging, labeling and release of the IMP will be performed in compliance with GMP (Annex 13) and all relevant regulations.

Each tablet will contain 20 mg of the active ingredient MMV390048 and the following excipients: tartaric acid powder, copovidone (Plasdone S-630), hypromellose acetate succinate (AquaSolve HPMC-AS MF), croscaramellose sodium (Solutab), microcrystalline cellulose type 102 (Avicel PH-102) and magnesium stearate (Ligamed MF-2-V).

A detailed description of the physical, chemical and pharmaceutical properties of MMV390048 can be found in Section 3 of the Investigator's Brochure.

Patients who meet all eligibility criteria will receive a single oral dose of MMV390048 tablets after being recruited sequentially to one of six cohorts:

- Cohort 1A – *P. vivax*: 6 tablets equivalent to 120 mg MMV390048 (or dose determined by safety limits identified during ongoing Phase I studies)
- Cohort 1B – *P. falciparum*: 6 tablets equivalent to 120 mg MMV390048 (or dose determined by safety limits identified during ongoing Phase I studies)
- Cohort 2A – *P. vivax*: MMV390048 dose to be determined
- Cohort 2B – *P. falciparum*: MMV390048 dose to be determined
- Cohort 3A – *P. vivax*: MMV390048 dose to be determined
- Cohort 3B – *P. falciparum*: MMV390048 dose to be determined

MMV390048 will be administered to patients after fasting for 3 hours (except for water which will be permitted *ad libitum*). The IMP will be administered by an appropriately qualified member of the study site designated by the Investigator. Administration will be directly observed and patients will remain fasted (except for water) for 1.5 hours thereafter. The exact time of dose administration will be noted on the CRF. The procedures to be followed for patients who vomit within 30 minutes of dosing are described in Section 3.7.

4.1.2 Definitive Antimalarial Therapy

Definitive anti-malarial therapy for *P. vivax* or *P. falciparum* will be administered on Day 28 to all patients ongoing in the study, or prior to this if individual stopping criteria are met (Section 3.2.2). Treatment will be prescribed by the Investigator in accordance with National Ethiopian Guidelines. *P. vivax* patients who have a normal G6PD test result at this stage, may also be given primaquine (currently not a standard of care in Ethiopia) at the time of definitive antimalarial treatment administration, after confirmation of the patient's G6PD status.

4.2 Storage Conditions

The Principal Investigator is responsible for ensuring that the IMP is stored in accordance with instructions in a controlled facility.

MMV390048 is marginally light sensitive and should be stored at ambient room temperature protected from light, in a secure location with restricted access to unauthorised personnel. Storage conditions must be adequately monitored and appropriate temperature logs maintained throughout the study. Expiry dates will be provided to Investigators.

4.3 Product Accountability

Upon receipt of the IMP, the Principal Investigator or delegate will conduct an inventory of the product received. The date and time of receipt, as well as the condition of the product will be documented and acknowledged in writing to the Sponsor.

A drug accountability utilisation log will be maintained by the Investigator for all investigational product. This will include the date and time of administration and the quantity of investigational product administered to each patient. The log must be signed and dated by the Investigator or delegate.

At the end of the study, clinical trial material accountability will be checked by the Sponsor's designee, and the Sponsor and the Principal Investigator will retain copies of the complete logs. Unused supplies will be returned or destroyed locally in accordance with written instructions from the Sponsor.

5. VISIT SCHEDULE

5.1 Screening: Day 0 (approximately 2 to 4 hours prior to dosing)

Written, informed consent for study participation will be obtained prior to commencing any screening activities in accordance with local practice. If the patient is unable to write, witnessed consent is permitted according to local ethical considerations. Thereafter, patients will be assigned a screening number and undergo screening procedures to determine eligibility for the study in accordance with the study eligibility criteria.

The following information will be obtained and assessments performed during this time:

- Written informed consent
- Assignment of a screening number
- Demographic data
- Medical and surgical history and details of current medical conditions
- Social history (including previous and current use of alcohol, tobacco products and drugs of abuse [including khat])
- Previous and concomitant medications (medications used currently and in the 28 days prior to screening will be recorded in the patient's CRF)
- Use of herbal products
- Signs and symptoms of malaria
- Height and body weight
- A complete physical examination (excluding genitourinary unless indicated)
- Vital signs (blood pressure, pulse rate and axillary body temperature) after the patient has been resting in the supine position for 5 minutes
- Standard 12-lead ECG (single recording)
- Blood sampling for the following:
  - microscopy (thick and thin slides) for parasite and gametocyte counts and parasite species identification
  - qPCR determined parasitemia
  - hematology and chemistry safety laboratory tests
- Point-of-care whole blood/serum pregnancy test (females only)
- Review of eligibility criteria (including review of essential safety laboratory results as detailed in Section 6.4.7.1).

Patients who complete all screening assessments and satisfy all eligibility criteria will be eligible to participate in the study and will be allocated to the applicable treatment arm (*P. vivax* or *P. falciparum*). A screening log will be maintained of all patients who provided informed consent and will include the reasons for screening failure where applicable.

5.2 Baseline: Day 0 Pre-dose (-30 min)

Prior to dosing, the following information will be obtained and assessments performed (within 30 minutes of dosing):

- Update medical history as necessary
- Signs and symptoms of malaria
- Brief symptom-directed physical examination
- Vital signs (blood pressure, pulse rate and axillary body temperature) after the patient has been resting in the supine position for 5 minutes

- Standard 12-lead ECG (triplicate recording)
- Blood sampling for:
  - microscopy (thick and thin slides) for baseline parasite and gametocyte counts
  - baseline qPCR determined parasitemia
  - blood spot cards for parasite genotyping for later PCR correction (for *P. falciparum* only) and genotypic characterisation of drug-induced resistance (*P. vivax* and *P. falciparum*)
  - sample for retention for possible pharmacogenetic analyses (if consented to separately)
  - PK analysis
- Monitoring and recording of SAEs

5.3 Dose Administration: Day 0 (0 hours)

After a 3-hour fast (water permitted *ad libitum*, and to coincide with the period from start of screening to dosing), the IMP will be administered as described in Section 4.1.1.

Any patient who vomits within 30 minutes of MMV390048 dose administration will be re-dosed with a full dose of the IMP. Details of the vomiting and second dose administration will be recorded on the CRF. Patients who vomit a second time within 30 minutes of the second dose administration will be withdrawn from the study and replaced.

5.4 Compulsory Post-Dose Admission Period: Day 0 to Day 3 or longer as required (0 to 72+ hours post-dose)

During this time, patients will adhere to the restrictions with regard to intake (food and alcohol), confinement to the CRU and concomitant medication usage as detailed in Section 3.5. Patients will remain in the CRU until complete microscopic clearance of parasitemia (two consecutive negative samples) but for a minimum of 72 hours post-dose. The following assessments will be performed during this time:

- Signs and symptoms of malaria (2, 4, 8, 12, 16, 20 and 24 hours post-dose and every 6 hours thereafter until microscopy is negative for parasitemia on two consecutive occasions)
- Brief symptom-directed physical examination (2, 4, 8, 12, 16, 20 and 24 hours post-dose and every 6 hours thereafter until microscopy is negative for parasitemia on two consecutive occasions)
- Vital signs (blood pressure, pulse rate and axillary body temperature) after the patient has been resting in the supine position for 5 minutes (2, 4, 8, 12, 16, 20 and 24 hours post-dose and every 6 hours thereafter until microscopy is negative for parasitemia on two consecutive occasions)
- Standard 12-lead ECG (1, 2, 4, 6, 8, 24 and 72 hours post-dose, single recordings)
- Blood sampling for:
  - microscopy (thick and thin slides) for parasite and gametocyte counts (4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, 66 and 72 hours post-dose, and 6-hourly thereafter if parasitemia is still present until microscopy is negative for parasitemia on two consecutive occasions)
  - qPCR determined parasitemia (4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, 66 and 72 hours post-dose, and 6-hourly thereafter if parasitemia is still present until microscopy is negative for parasitemia on two consecutive occasions)
  - platelets (12 hours post-dose, *P. falciparum* only)
  - blood spot cards for parasite genotyping for later PCR correction (24 hours post-dose, *P. falciparum* only)
  - hematology and chemistry safety laboratory tests (24 and 48 hours post-dose, and then as per Section 5.5.1 if patient remains confined for an extended period)

  - PK analyses (0.5, 1, 2, 4, 6, 8, 12, 16, 24, 48 and 72 hours post-dose, and then as per Section 5.5.1 if patient remains confined for an extended period)
- Monitoring and recording of adverse events (including SAEs) and concomitant medications.

When patients have complete clearance of microscopically detected parasitemia, they may be discharged (a minimum of 72 hours post-dose).

Patients will be reminded of the following before leaving the CRU:

- The study restrictions as detailed in Section 3.5
- To return to the CRU for the subsequent scheduled visits
- To contact the CRU in the interim should they experience any symptoms of malaria, any other adverse events or require treatment with any concomitant medication.

Individual Stopping Criteria:

Patients meeting any of the individual stopping criteria (Section 3.2.2) during the admission period will be given definitive antimalarial treatment as per local standard of care and as described in Section 4.1.2. In addition to the scheduled assessments described above, the following will be performed in these patients prior to administration of the definitive antimalarial therapy:

- blood will be drawn for a G6PD enzyme test (*P. vivax* patients only)
- a 12-lead ECG (single recording) will be performed.

P. vivax patients with a normal G6PD enzyme test result may be given primaquine in addition to the local standard of care antimalarial therapy.

5.5 Outpatient Follow-Up Period: Day 4 to Day 27

After discharge (or during voluntary admission if the patients elects not be discharged), the frequency of follow-up visits (or assessments) will depend on the turn-around time of qPCR assay results as described in Section 3.2.1. and should consider the fact that visits should be scheduled to include Day 14 – a critical time point for evaluation of the primary endpoint.

Decisions on observation, re-hospitalisation and administration of definitive antimalarials to patients who develop either microscopic or qPCR detected parasitemia during this period will be made in accordance with the guidelines described in Section 3.2.1, and in conjunction with the individual stopping criteria (Section 3.2.2).

5.5.1 qPCR results not available within 24 hours: (Days 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 and 26)

At each follow-up visit, the following will be performed:

- Signs and symptoms of malaria (all visits)
- Brief symptom-directed physical examination (all visits)
- Vital signs (blood pressure, pulse rate and axillary body temperature) after the patient has been resting in the supine position for 5 minutes (all visits)
- Standard 12-lead ECG (single recording) only if individual stopping criteria are met, prior to administration of definitive antimalarial treatment
- Blood sampling for:
  - microscopy (thick and thin slides) for parasite and gametocyte counts (all visits)
  - qPCR for determination of parasitemia (all visits)
  - blood spot cards for parasite genotyping for PCR correction (*P. falciparum* only) and for genotypic characterisation of drug-induced resistance (*P. vivax* and *P. falciparum*);

samples to be taken at the time of first re-appearance of parasites if after Day 7, and prior to administering definitive antimalarial treatment
  - hematology and chemistry safety laboratory tests (Days 6, 10, 14 and 20)
  - G6PD enzyme test (*P. vivax* patients only); sample to be taken if individual stopping criteria are met, prior to administration of definitive antimalarial treatment
  - PK analyses (Days 6, 10, 14 and 20)
- Monitoring and recording of adverse events (including SAEs) and concomitant medications
- Patients will be reminded of:
  - the study restrictions as detailed in Section 3.5
  - to return to the CRU for the subsequent scheduled visit
  - to contact the CRU in the interim should they experience any symptoms of malaria, any other adverse events or require treatment with any concomitant medication.

5.5.2 qPCR results available within 24 hours: (Days 7, 10/11, 14, 17/18, 21 and 24/25)

Patients who have parasitemia detectable on qPCR from either of the last two consecutive samples prior to discharge (66 and 72 hours post-dose or later), will be required to return to the CRU at least every 48 hours from the time of discharge (i.e. will follow the schedule described in Section 5.5.1) until parasitemia is undetectable on qPCR when they can continue with a follow-up schedule described in this section.

Patients who have no parasitemia detectable on qPCR from either of the last two consecutive samples prior to discharge (66 and 72 hours post-dose or later), and who have no signs and symptoms of malaria, will adhere to the follow-up schedule described in this section.

At each follow-up visit, the following will be performed:

- Signs and symptoms of malaria (all visits)
- Brief symptom-directed physical examination (all visits)
- Vital signs (blood pressure, pulse rate and axillary body temperature) after the patient has been resting in the supine position for 5 minutes (all visits)
- Standard 12-lead ECG (single recording) only if individual stopping criteria are met, prior to administration of definitive antimalarial treatment
- Blood sampling for:
  - microscopy (thick and thin slides) for parasite and gametocyte counts (all visits)
  - qPCR for determination of parasitemia (all visits)
  - blood spot cards for parasite genotyping for PCR correction (for *P. falciparum* only) and for genotypic characterisation of drug-induced resistance (*P. vivax* and *P. falciparum*); sample to be taken at the time of first re-appearance of parasites if after Day 7, and prior to administering definitive antimalarial treatment
  - hematology and chemistry safety laboratory tests (Days 7, 10/11, 14 and 21)
  - G6PD enzyme test (*P. vivax* patients only); sample to be taken if individual stopping criteria are met, prior to administration of definitive antimalarial treatment
  - PK analyses (Days 7, 10/11, 14 and 21)
- Monitoring and recording of adverse events (including SAEs) and concomitant medications
- Patients will be reminded of:
  - the study restrictions as detailed in Section 3.5
  - to return to the CRU for the subsequent scheduled visit
  - to contact the CRU in the interim should they experience any symptoms of malaria, any other adverse events or require treatment with any concomitant medication.

5.6 Final Efficacy Assessments/Early Withdrawal Visit: Day 28 (±1)

Final efficacy assessments will be performed on Day 28. Assessments and procedures scheduled for this visit, including the administration of definitive antimalarial treatment as per local standard of care, should also be performed for any patients who are withdrawn from the study (as described in Section 3.7) at the time of withdrawal.

The following will be performed:

- Signs and symptoms of malaria
- A complete physical examination (excluding genitourinary unless indicated)
- Body weight
- Vital signs (blood pressure, pulse rate and axillary body temperature) after the patient has been resting in the supine position for 5 minutes
- Standard 12-lead ECG (single recording)
- Blood sampling for:
  - microscopy (thick and thin slides) for parasite and gametocyte counts
  - qPCR for determination of parasitemia
  - blood spot cards for parasite genotyping for PCR correction (for *P. falciparum* only) and for genotypic characterisation of drug-induced resistance (*P. vivax* and *P. falciparum*); sample to be taken if this is the time of first re-appearance of parasites)
  - hematology and chemistry safety laboratory tests
  - G6PD enzyme test (*P. vivax* patients only); sample to be taken if stopping criteria not previously met
  - PK analyses
- Monitoring and recording of adverse events (including SAEs) and concomitant medications
- Patients will be reminded of the following:
  - the study restrictions as detailed in Section 3.5
  - to return to the CRU for the end-of-study visit
  - to contact the CRU in the interim should they experience any symptoms of malaria, any other adverse events or require treatment with any concomitant medication.

<u>Definitive antimalarial treatment</u>

For all patients enrolled in the study who have not previously met individual stopping criteria, definitive antimalarial treatment will be administered on Day 28 after completion of the assessments described above. Patients will be given standard of care according to local treatment guidelines. Those with *P. vivax* infection who do not have a G6PD enzyme deficiency, may also receive primaquine (currently not standard of care for definitive malaria treatment in Ethiopia) at this stage.

5.7 End of Study Visit: Day 35 (±2)

The end-of-study follow-up visit will be conducted on Day 35. The following assessments will be performed:

- Signs and symptoms of malaria
- A complete physical examination (excluding genitourinary unless indicated)
- Body weight
- Vital signs (blood pressure, pulse rate and axillary body temperature) after the patient has been resting in the supine position for 5 minutes
- Standard 12-lead ECG (single recording)
- Blood sampling for:

  - hematology and chemistry safety laboratory tests
  - PK analysis
- Point-of-care urine pregnancy test (females only)
- Recording of adverse events (including SAEs) and concomitant medications.

Patients will be thanked for their participation in the study, and will be reminded:

- of the ongoing requirement for contraception use (male patients)
- to inform the CRU should they experience any serious medical events for a period of at least one month after completion of their participation.

5.8 Assessment and Visit Windows

The following time-related windows for microscopy, qPCR and PK sampling, vital signs, ECG, hematology and blood chemistry assessments will be acceptable based on logistical and operational considerations:

- All pre-dose observations within 30 minutes prior to dosing
- PK sampling:
  - ± 20 min from 0.5 to 2 hours post-dose (inclusive)
  - ± 60 min from 4 to 16 hours post-dose (inclusive)
  - ± 120 min from 24 to 72 hours post-dose (inclusive)
  - within visit window thereafter
- Vital signs (blood pressure, pulse rate and axillary body temperature), qPCR and microscopy
  - ± 30 min from 2 to 72 hours post-dose (inclusive)
  - within visit window thereafter
- Standard 12-lead ECG:
  - ± 20 min for 1 to 2 hours post-dose
  - ± 30 min from 4 to 8 hours post-dose (inclusive)
  - ± 60 min for 24 post-dose
  - ± 2 hours for 72 hours post-dose
  - within visit window thereafter
- Hematology and chemistry safety laboratory sampling:
  - taken at the same time as PK samples.

At all time points where multiple assessments are performed and blood samples are collected, vital signs measurements and ECG recordings will be performed before blood sampling.

For all time points, the actual time of each assessment or blood draw will be documented in the CRF. Any deviations from the above-mentioned permissible window periods will be documented as protocol non-compliances and will be evaluated for significance at the data review meeting prior to database lock.

6. ASSESSMENTS

All assessments will be performed at the time points detailed in Section 5 and in the Schedule of Events in Appendices 7 and 8.

Baseline evaluations will be regarded as those performed immediately prior to IMP dose administration on Day 0, or at the time of screening if the observations are not scheduled to be repeated prior to dosing.

The estimated total volume of blood that will be drawn from each patient in this study to facilitate the required assessments is presented in Appendix 5.

6.1 Demographic and Social History Data

Demographic data to be collected on all patients include: date of birth, age and gender. Data regarding self-reported race/predominant ethnicity will also be collected and may contribute to the analysis of adverse event data (specifically possible photosensitivity reactions).

Patients will be questioned with regard to alcohol and tobacco use, and any use of drugs of abuse.

6.2 Relevant Medical and Surgical History

Patients will provide a detailed medical, surgical and medication usage history during screening in order to assess the eligibility of the patient for participation in the study.

Any event or change in the patient's condition or health status prior to the administration of the IMP will be reported in the relevant medical history/current medical conditions section of the CRF and not as an adverse event.

6.3 Parasitological Assessments

Full details of slide preparation, method of counting parasites and quality control will be described in the Study Laboratory Procedures Manual including gametocyte counts.

6.3.1 Blood Films (Microscopy)

Thick and thin blood films for parasite count should be obtained and examined at screening to confirm inclusion/exclusion criteria. Within 30 minutes prior to dosing on Day 0, a thick film will be examined for microscopic quantification of parasitemia to serve as the baseline value. Thereafter, thick and thin blood films will be performed at the time points detailed in Section 5 and Appendices 7 and 8. In addition, films will be prepared at any unscheduled visits, and a thin blood smear will also be reserved for species determination in the event of recurrence of parasitemia.

Venous blood will be collected using a standardised technique, either via cannula (during the admission period) or by direct venipuncture, for all smears. Blood smear preparation, staining, examination and interpretation must be in accordance with the guidelines provided by the Sponsor and will be standard at both sites. All microscopists involved in the study will be trained in accordance with the Sponsor guidelines prior to study start. At each time point, the following four slides will be prepared:

- 2 slides with thick smears (one for local site reading and one for quality control) for parasitemia counts
- 1 slide with a thin smear for species identification
- 1 slide with combined thick/thin smears for back-up purposes.

Local quality control of thick blood films is to be assured by reading of slides by 2 different qualified microscopists who are blinded to each other's results and reporting independently. The mean of the two counts will be recorded in the patient's CRF. In the event of a discrepancy of ≥50% in the asexual parasite counts between the two readings, a third microscopist (the Quality Assurance reader) will review the slides. The final classification will be based on the two out of three readings that are in closest agreement. The same approach will be adopted with regard to gametocyte counts.

In addition to local analysis, samples may be sent for analysis and quality control purposes to a laboratory in Europe (Swiss Tropical and Public Health Institute, Basel).

6.3.2 Blood Samples for Quantitative PCR

Approximately 150 µL of venous blood will be collected into EDTA microtainer tubes for qPCR analysis at the time points specified in Section 5 and Appendices 7 and 8. Samples will be processed, stored and transported in accordance with the specifications in the laboratory manual.

6.3.3 Dry Blood Spot Samples for Parasite Genotyping (PCR Correction)

In *P. falciparum* patients only, samples of blood will be collected on dry blood spot (DBS) cards at the pre-dose time point. Additional samples of blood will be collected on DBS cards at 24 hours post-dose and at the time of the first recurrence of parasites if this is after Day 7. At all three time points, 2 cards will be taken with a minimum of 3 spots on each card. The cards will be retained for genotyping by PCR for ACPR adjustment and will be sent to a laboratory in Europe (Institute of Tropical Medicine Antwerp) for analysis and quality control. Results will be interpreted using standard methods to differentiate between recrudescence and new infection (as per the most recent established techniques).[4]

6.3.4 Gametocyte Detection

Gametocytemia will be detected and counted by microscopy at the same time as the parasitemia assessments from the thick blood films.

6.3.5 Genetic Assessments Related to Drug-Induced Resistance

Samples of blood will be collected on dry blood spot (DBS) cards at the pre-dose time point, and after Day 7, if there is recurrence of parasitemia after an initial clearance. At both time points, one card will be taken containing a minimum of at least 3 spots. These samples may be used for exploring genetic markers of drug resistance in the parasite genome and will be sent to a laboratory in Europe (Swiss Tropical and Public Health Institute, Basel) for analysis.

6.4 Safety and Clinical Assessments

6.4.1 Height and weight

Height in centimetres (cm) and body weight (to the nearest 0.1 kg in indoor clothing, but without shoes) will be measured. BMI will be calculated using the formula: BMI = weight (kg) / height $(m)^2$.

6.4.2 Physical Examination

Full or abbreviated, symptom-directed physical examinations will be performed throughout the study at time points specified in Section 5 and Appendices 7 and 8.

The full physical exam will include: general appearance, head and neck (including eyes, ears, nose and throat), chest and lungs, cardiovascular, abdomen, neurological, lymphatic, musculoskeletal and dermatological examinations. Genitourinary and rectal examinations will not be performed unless specifically indicated.

Abbreviated, symptom-directed physical examinations will focus on changes since the previous examination and specific malaria signs and symptoms, but will always include at least: general appearance, chest and lungs, cardiovascular, abdomen, brief neurological, and dermatological examinations.

Clinically significant changes in physical examination findings will be recorded as adverse events in the CRF.

6.4.3 Signs and symptoms of malaria

A full assessment of malaria signs and symptoms will be made in conjunction with the physical examination at all specified time points.

6.4.4 Vital Signs

Vital signs will be measured in accordance with Section 5 and the schedule of events in Appendices 7 and 8, and at any other stage during the study if clinically indicated.

Blood pressure and pulse rate will be measured after the patient has been supine for at least 5 minutes. Where possible, the same arm will be used in all blood pressure assessments for a particular patient.

Axillary measurements of body temperature are preferred throughout the study. If a different site of measurement is used (oral, rectal or tympanic), this should be used consistently throughout the study period for a particular patient. Patients with a history of fever prior to screening will be monitored closely for fever peaks.

Whenever study procedures coincide, vital signs should be measured before blood draws.

6.4.5 12-Lead ECGs

Standard 12 lead ECGs will be performed throughout the study for safety purposes as per the schedule of events described in Section 5 and Appendices 7 and 8. In addition to this, an ECG should be repeated at any stage if clinically indicated.

Patients will rest in a supine position for at least 10 minutes prior to the start of each recording and the same body position will be assumed by the patient for each recording. The clinical staff will ensure that patients are awake during the ECG recording. Whenever study procedures coincide, ECGs should be taken before blood draws.

All ECG recordings will be performed using a suitable device that is capable of providing a validated automated report and storing all data electronically for later analysis. At baseline (pre-dose), three serial recordings will be performed approximately 1 minute apart (triplicate). For each parameter, the mean of these three recordings will be used as the baseline value for all subsequent comparisons. All ECG tracings will be stored electronically as well as printed and labeled as per standard procedures at the CRU.

The Investigator will immediately review each ECG for the presence of noise or other artefacts that may necessitate repeating the assessment. The ECG recorder will provide an automated report (based on a validated algorithm) that can be used as a guide as to whether a further ECG would be

required. Clinical indications for further ECG recordings include obvious rhythm abnormalities, prolonged QTc-interval (>450 msec), any relevant intra-ventricular heart block (QRS >120msec), obvious changes from the previous ECG or cardiac-type symptoms experienced by the patient such as chest pain, palpitations, light-headedness, syncope or shortness of breath.

The automated report should not, however, be regarded as the definitive source of information as to whether an abnormality is present for reporting purposes. Real-time clinical interpretation of the tracings will be made on-site by the Investigator, and any significant abnormalities identified will be discussed with the Medical Monitor and reviewed by an independent cardiologist if required. All clinically significant findings will be documented as adverse events. The Investigator will sign and date each ECG as evidence of their review.

The following information will be recorded in the CRF for each ECG recording:

- RR-interval
- PR-interval
- QRS-duration
- QT- and QTcF-intervals, where Fridericia's correction is calculated as: $QTcF = QT / \sqrt[3]{RR}$
- T-wave morphology
- Any ECG abnormalities

All ECG recordings will be saved electronically for archiving and possible later analysis and reporting as necessary.

6.4.6 Pregnancy Tests

Point-of-care pregnancy tests will be performed at screening (whole blood/serum) and Day 35 (urine) for all female patients. The result of the screening pregnancy assessment must be available (and negative as confirmation of the patient's non-childbearing potential) prior to dosing.

6.4.7 Clinical Laboratory Assessments

Clinical laboratory (hematology and biochemistry) tests will be performed as indicated in Table 1 in accordance with the study schedules outlined in Section 5 and Appendices 7 and 8, as well as at other time points if clinically indicated.

Throughout the study, the Investigator will evaluate and document the clinical significance of all results falling outside of the normal reference ranges, and will grade these according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, 2010 (Appendix 4).[40] Generally, clinically significant abnormalities that represent a change from baseline and could be considered to be detrimental, are to be recorded as adverse events. It is anticipated that a fall in certain hematological parameters may occur during malaria treatment. In general a fall in hemoglobin of up to 2 g/dL need not be reported as an adverse event unless that fall is considered to be drug related and/or detrimental to the patient. Detrimental changes in differential white cell count (other than clinically significant falls in neutrophils) should only be reported as adverse events if the absolute value falls outside the normal range.

Table 1: Clinical Laboratory Tests

Hematology	Hemoglobin Hematocrit Erythrocyte count (RBC) Reticulocytes Platelet count Leukocyte count (WBC) including differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Clinical Chemistry	Sodium Potassium Creatinine Glucose Total and conjugated bilirubin[1] Alanine aminotransferase (ALT/SGPT) Aspartate aminotransferase (AST/SGOT) Alkaline phosphatase (ALP) Creatine kinase (CK) Haptoglobin[2]
Other	Quantitative G6PD enzyme test Hepatotoxicity panel (Appendix 6)[3]
Urine	Dipstick and/or urine microscopy only if clinically indicated

[1] Conjugated bilirubin results will only be reported if total bilirubin is elevated.
[2] Blood will be collected as part of the routine chemistry panel, but assays will only be performed from all time points in patients who experience a hemoglobin-related AESI at any stage during the study. The assay will be performed at a specialised central laboratory (International Clinical Laboratories, Addis Ababa).
[3] At a specialised central laboratory in any patient with an AESI related to hepatotoxicity (Section 7.7.1) in accordance with Appendix 6.

All clinical laboratory tests will be analysed locally in Ethiopia except for the hepatotoxicity panel in cases of AESIs related to hepatotoxicity, where samples may be exported to a laboratory outside of Ethiopia for analysis if local expertise or laboratory accreditation for the required assays is not available.

6.4.7.1 Screening laboratory results:

At a minimum, the results of the following tests must be available before the patient is enrolled:

- Hemoglobin
- Neutrophil count
- Platelets
- Potassium
- Rapid blood glucose

- ALT
- AST
- Creatinine
- Total bilirubin (and conjugated bilirubin if total bilirubin is elevated)

All efforts should be undertaken to ensure that the results of these laboratory assessments are reported in an expedited manner to minimise the delay between screening and enrolment of patients. If the results of screening hematology and chemistry laboratory evaluations fall outside of the normal range and are regarded as clinically significant by the Investigator, the potential participant may not be enrolled. Patients with out of range laboratory values at screening which are not regarded as clinically significant by the investigator and do not violate specific eligibility criteria, may be enrolled in consultation with the Sponsor's medical monitor.

6.4.8 Adverse events

Adverse events will be recorded from the time of IMP administration until the end-of-study visit on Day 35. SAEs will be recorded from the time of screening until the end of study, and additionally until 30 days after completion of the study should the Investigator be made aware of such an event. A description of the assessment, recording and reporting of adverse events is detailed in Section 7.7.

6.5 Pharmacokinetic Assessment

6.5.1 Blood Sample Collection and Processing

Blood samples will be collected either by direct venipuncture or via an indwelling cannula inserted in a forearm vein at the specific time points detailed in Section 5 and Appendices 7 and 8. Samples will also be collected at time of treatment failure (if applicable) and in the event of any AESI related to hepatotoxicity (Section 7.7.1) or drug-related SAE. The exact date and time of blood sampling will be recorded in the appropriate section of the CRF.

A sample of approximately 2 ml of whole blood will be collected into a K3EDTA tube at each time point. Immediately after collection, the tube will be inverted gently several times to ensure mixing of tube contents. Thereafter, samples will be processed, stored and shipped to the Division of Pharmacology, University of Cape Town, South Africa in accordance with the procedures in the laboratory manual.

6.5.2 Pharmacokinetic Analytical Methods

The parent drug in the plasma samples will be analysed using validated HPLC-MS/MS methods. Assays will be performed and the methodology will be detailed by the analytical laboratory at the Division of Pharmacology, University of Cape Town, South Africa.

6.6 Pharmacogenetic Assessment

One 10 ml blood sample will be collected pre-dose on Day 0 in an EDTA tube from each patient who has consented, in writing, to participate in the pharmacogenetic assessments. If the Day 0 pre-dose blood draw is missed, the sample should be collected at the next time point at which a blood draw is scheduled. Only one blood sample should be collected from each consenting patient for pharmacogenetic purposes. These samples will be stored at the site at -20 °C pending shipment to a storage facility at ABF Pharmaceutical Services in Vienna, Europe. Later DNA extraction and analysis will be performed at a laboratory still to be defined. Any sample derived DNA that remains after analysis may be stored for up to 15 years to address scientific questions related to MMV390048.

7. SAFETY MONITORING

7.1 Responsibilities for Ensuring the Safety of Study Patients

The National Regulatory Authority, the study Sponsor (MMV) and all members of the Principal Investigator's clinical team share responsibility for ensuring that the patients participating in this study are exposed to the least possible risk that may result from participation in this study.

7.2 Principal Investigator

The Principal Investigator has a personal responsibility to closely monitor study patients and an inherent authority to take whatever measures are necessary to ensure their safety, including ensuring that procedures and expertise are available to cope with medical emergencies during the study. The Principal Investigator has the authority to terminate, suspend or require changes to a clinical study for safety concerns and may delay an individual's study drug administration or pause study drug administration in the whole trial if he/she has concerns that the study drug may place a patient at significant risk.

7.3 Study Sponsor

The Sponsor also has an institutional responsibility to ensure patient safety and undertakes to promptly notify the concerned Investigators, Ethics Committee and the Regulatory Authorities of findings that could adversely affect the safety of patients included in the study, impact the conduct of the study, or alter the Ethics Committee's approval/favourable opinion to continue the study. This includes the expedited reporting to these parties of all adverse drug reactions that are both serious and unexpected.

7.4 Medical Monitor

The Medical Monitor, will provide medical review during the execution of the study. This oversight will include the reviewing of safety information and the provision of applicable recommendations to both the Investigator and the Sponsor. This review is intended to facilitate the early detection of safety signals and to maximise the chances for the continued appropriateness of the study and the protection of the study patients.

The Medical Monitor will be responsible for the following safety monitoring:

- Reviewing the eligibility of potential patients in consultation with the Investigator as required
- Evaluation of study safety data on an ongoing basis, including the occurrence of treatment failure and clinically relevant findings
- Evaluation of adverse events, AESIs, SAEs and corresponding safety reports (including the assessment of severity, causality and expectedness of events).

Safety oversight is detailed in the Safety Monitoring Plan.

7.5 Safety Review Team (SRT)

The SRT will comprise at least the following people:

- the Principal Investigators
- the Medical Monitor
- at least one medically-qualified member of MMV
- the Project Director.

The members of the SRT are responsible for decisions related to the safety of patients and the continuation of the study. The SRT will assess preliminary safety, efficacy and pharmacokinetic data (if available) up to Day 14 of the first four *P. vivax* patients enrolled, and thereafter upon completion of Day 14 assessments of each cohort and whenever else indicated as a result of safety concerns. The SRT will decide on the appropriateness of subsequent doses to be administered and continuation of the study.

The SRT will be advised by the Data and Safety Monitoring Board (DSMB) and will attend the non-voting sessions of the DSMB Meetings.

7.6 Data and Safety Monitoring Board

During the study, an external and independent DSMB appointed by the Sponsor will meet to review study data. The board will consist of at least the following voting members:

- a Statistician
- two independent Medical Experts

The timing of the DSMB reviews and scope of the data review will be detailed in the DSMB Charter. The DSMB will be required to review the safety and efficacy data upon completion of Day 14 assessments of each cohort, and whenever else as indicated by safety concerns. The DSMB members will also be informed of and review all SAEs and AESIs as and when they are reported.

All procedures associated with DSMB reviews, including objectives, data handling and elements for review will be documented in the DSMB Charter. Meeting discussions and decisions will be documented in DSMB minutes. Voting sessions of the DSMB will be attended only by designated DSMB members.

Based on its review, the DSMB will make recommendations to the SRT regarding further conduct of the trial, and if considered necessary, may recommend pausing or stopping further administration of the investigational product. These recommendations will also be communicated to the Ethics Committee and Regulatory Authority as required.

7.7 Safety Surveillance During the Study

Patients will be monitored and safety data collected by way of clinical interviews, observations and examinations, through ECG reports and laboratory evaluations. Time points and the specific data collected for each of these evaluations are described in Section 5.

7.8 Adverse Events

The collection, evaluation and reporting of adverse events/reactions arising from this clinical study will be performed in accordance with:

- Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (2011/C 172/01);[41]
- International Council for Harmonization (ICH) guideline E2F: Note for guidance on development safety update reports (DSUR);[42]
- International Council for Harmonization (ICH) guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.[43]

The definitions of adverse events (AEs), adverse events of special interest (AESIs), adverse drug reactions (ADRs) including unexpected adverse drug reactions (UARs), serious adverse events (SAEs),

serious adverse reactions (SARs) and SUSARs (Suspected Unexpected Serious Adverse Reactions) are given below. It is of the utmost importance that all staff involved in the conduct of clinical research are familiar with the content of this section.

7.8.1 Adverse Event Definition

The following definitions will be employed for the reporting of Adverse Events:

Adverse Event

An adverse event is defined as any unfavourable and unintended sign, symptom, syndrome, or illness that develops or worsens during the period of observation in the clinical study. Clinically relevant abnormal results of diagnostic procedures including abnormal laboratory findings (e.g., requiring unscheduled diagnostic procedures or treatment measures, or resulting in withdrawal from the study) which are considered by the Investigator to be detrimental should be recorded as adverse events whether or not they have a causal relationship with the study drug. Where the laboratory result is a sign of another clinical condition, the clinical condition itself should be the reported adverse event. An event unequivocally caused by a significant deterioration of the underlying condition related to malaria is regarded as an adverse event.

Recrudescence or recurrence of *P. vivax* or *P. falciparum* infection during the course of the study will be captured on a specific form in the CRF. However, these events will not be reported as adverse events unless the resulting malaria is of an unexpected severity.

Worsening of the baseline conditions that are judged by the Investigator to be more significant than normal daily fluctuation of the disease symptoms should be regarded as adverse events.

Prior to enrolment, study site personnel will note the occurrence, nature and severity of each patient's medical condition(s). During the study, site personnel will note any change in the condition(s) and/or the occurrence and nature of any adverse events.

At each visit the patient will be asked about any change in his/her condition since the last evaluation.

Adverse Drug Reaction (ADR)

An ADR is an adverse event that is considered to be a response to a medicinal product which is noxious and unintended and which occurs at any dose. The term "response" means that a causal relationship between a medicinal product and the event is at least a reasonable possibility, and that there are facts (evidence) or arguments to support this.

Unexpected Adverse Reaction

An adverse reaction is regarded as an unexpected adverse reaction if its nature or severity is not consistent with the applicable reference safety information (Investigator's Brochure for drugs in clinical development or approved manufacturer's prescribing information for marketed drugs). Events that add significant information on the specificity, severity or frequency of previously described reactions, are also regarded as unexpected.

The expectedness of an adverse reaction is determined by the Sponsor in the reference safety information and will be evaluated in the context of previously observed events, rather than on the basis of what might be anticipated from the pharmacological properties of a medicinal product.

For this protocol, the reference document for the assessment of expectedness is the Investigator's Drug Brochure for MMV390048. Expected reactions to the antimalarial rescue treatment are described in the products' prescribing information.

Adverse Event of Special Interest (AESIs)

Any abnormalities listed below should be reported as AESIs:

- Events related to hematotoxicity:
  - A fall in hemoglobin of >2.0 g/dL, or greater than 25% from baseline,
  - A fall in absolute neutrophil to <1000/µl.
- Related to hepatotoxicity (refer to Appendix 6 for specific follow-up procedures):
  - ALT or AST >3 x ULN and TBL >2 x ULN (suspected Hy's Law if conjugated bilirubin >35%),
  - ALT or AST >3 x ULN with the appearance of worsening of fatigue, nausea, vomiting, fever, rash or eosinophilia,
  - ALT or AST rises rapidly to >5 x ULN in less than 4 weeks or persists for more than 2 weeks,
  - AST or ALT increase >8 x ULN.
- Related to cardiotoxicity:
  - QTcF prolongation from baseline of >60 ms,
  - QTcF at any time >450 ms,
  - T wave lability or T wave morphologic changes during follow-up,
  - Bundle branch block,
  - Any arrhythmia, except
    - sinus bradycardia that is
      - clinically asymptomatic, and
      - ≥40 bpm, and
      - not associated with any other relevant ECG abnormalities
    - sinus tachycardia that is
      - clinically asymptomatic, and
      - associated with a body temperature >38.0 °C, and
      - <110 bpm, and
      - not associated with any other relevant ECG abnormalities
    - respiratory sinus arrhythmia,
    - wandering atrial pacemaker,
    - 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.
- Related to dermatotoxicity:
  - Clinical signs of possible cutaneous adverse reactions such as:
    - dermatitis,
    - rash,
    - erythematous rash,
    - macular rash,
    - papular rash,
    - maculo-papular rash,
    - pruritic rash,
    - pustular rash,
    - vesicular rash.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

A SAE/SAR is any adverse event or reaction occurring at any dose that:

- Results in death

- Is life threatening, defined as an experience that places the patient, in the view of the Investigator, at immediate risk of death from the reaction as it occurred (note: this does not include a reaction that had it occurred in a more severe form, might have caused death)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation, unless this is for:
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the trial and has not worsened since the administration of the IMP
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
  - observation of a high risk patient to prevent a serious adverse event from occurring
  - social reasons or respite care in the absence of any deterioration in the patient's general condition
- Is a congenital anomaly or birth defect
- Results in a persistent or significant disability or incapacity (where this is defined as a substantial disruption of a person's ability to carry out normal life functions)
- Is considered an important medical event that may not result in death, be life-threatening or require hospitalisation, but may be considered as a serious adverse drug experience when, based upon appropriate medical judgement, it may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above (for example, an event may be defined as serious based on a deterioration in grade as per the severity grading table)
- Constitutes a possible Hy's law case (refer to Appendix 6 for specific follow-up procedures).

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reactions (SUSAR) is any SAE where a causal relationship with the IMP is at least a reasonable possibility, but the event has not previously been listed in the Investigator Brochure and/or Summary of Product Characteristics.

7.8.2 Adverse Event Reporting

It is the Investigator's responsibility to document and report all adverse events occurring in the clinical trial whether spontaneously reported by the patient, observed by the Investigator (either directly or by laboratory or other assessments), or elicited by general questioning.

The period of observation for collection of adverse events extends from the time of dosing up to the end of the study (Day 35). Events reported prior to this will be recorded as medical history, unless the symptoms worsen during the post-dose period.

Serious adverse events will be reported from the time of screening until 30 days following the final study visit (if spontaneously reported by the patient). SAEs experienced after this 30-day period will only be reported if the Investigator is made aware of the event and suspects a causal relationship with the study drug.

The following information should be recorded for all adverse events:

- a description of the adverse event
- the dates of onset and resolution of the event
- the characteristics of the event (severity, seriousness)
- the action take in response to the event (including treatment required)
- the outcome of the event
- the relationship of the event to the IMP (causality assessment).

7.8.2.1 Severity

The Investigator will assess the severity/intensity of the adverse reactions and clinical laboratory changes using the CTCAE version 4.03, 2010 (Appendix 4).[40]

Clarification of the difference in meaning between "severe" and "serious":

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not to be confused with "serious", which is based on the outcome or criteria defined under the serious adverse event definition. An event can be considered serious without being severe if it conforms to the seriousness criteria, similarly severe events that do not conform to the criteria are not necessarily serious. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.8.2.2 Relationship to Investigational Medicinal Product

The Investigator must assess the relationship of each event to the IMP, and decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the IMP. If there is no valid reason for suggesting a relationship, then the adverse event should be classified as "not related". Alternatively, if there is any valid reason for suspecting a possible cause-and-effect relationship between the IMP and the occurrence of the adverse event (even if undetermined or untested), then the AE should be considered "related". This should be documented in the subject's source documentation and CRF.

The following may guide this assessment:

- Related / suspected – the temporal relationship between the event and the administration of the IMP (or protocol-mandated procedure) is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the patient's medical condition, other therapies, or accident
- Not related / not suspected – the event can be readily explained by other factors such as the patient's underlying medical condition, concomitant therapy, or accident, and no plausible temporal or biologic relationship exists between the IMP (or the protocol-mandated procedure) and the event.

7.8.2.3 Action Taken

All adverse events should be treated appropriately. The Investigator will decide upon the appropriate action to be taken in response to an adverse, which may include one or more of the following:

- No action taken (i.e. observation only)
- Patient withdrawn from study
- Administration of a concomitant medication
- Hospitalisation or prolongation of current hospitalisation (to be reported as an SAE)
- Administration of non-drug therapy
- Other

7.8.2.4 Outcome

Adverse event outcome will be classified as follows:

- Resolved: The adverse event has resolved and the patient returned to their condition prior to onset
- Resolved with sequelae: The adverse event resolved, but the patient has ongoing sequelae
- Resolving: The adverse event has almost resolved and the patient is returning to his/her condition prior to onset
- Ongoing: The adverse event has not resolved and the patient's condition remains unchanged at the last time of observation. In case of death from a different cause, events ongoing at the time of death will be classified as such.
- Death

7.8.3 Serious Adverse Event Reporting

SAEs must be recorded and reported whether or not the investigator considers the SAE to be related to the IMP.

Any SAE will be notified by the Principal Investigator to the pharmacovigilance vendor and to the MMV Medical Monitor or her back up within 1 business day of becoming aware of the event by telephone, email or fax.

Pharmacovigilance Vendor: PrimeVigilance
Email: MMV@primevigilance.com
Fax: +44 800 471 5694

MMV Medical Monitor: Dr Hilary Johnstone
Telephone: +27 83 704 4929 (all hours)
Email: hjohnstone@hjclinical.com
Fax: +27 86 617 5525

Medical Monitor back up: Dr Stephan Duparc
Telephone: +41 22 555 0351 (office) / +41 794 462 956 (mobile)
Email: duparcs@mmv.org
Fax: +41 22 555 0369

The initial report will be followed up by a full written report within 3 working days or 5 calendar days, whichever comes first, unless no further information is available. A follow-up report and any subsequent reports will be provided as soon as possible when new information becomes available.

The Investigator will be required to provide the following information:

- Patient's study number, date of birth and gender
- Description of the event
  - Date, time of onset
  - Clinical history
  - Associated signs and symptoms
  - Temporal association with the study drug
  - Medical management, including rationale
  - Pertinent laboratory tests
  - Severity (see CTCAE grading scale, Appendix 4)
  - Causal relationship to the study drug
- Other information
  - Relevant past medical history
  - Concomitant medications
  - Autopsy report or expectation of an autopsy in the case of death
- Outcome of the event

  - Date, time of resolution, if resolved
- Documentation of notification to the Ethics Committee (EC) by the Investigator

Photocopies of results, consultant report(s), a summary of the outcome of the reaction and the Investigator's opinion of IMP relationship to the SAE will accompany the SAE form if and when available.

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

A SUSAR that is fatal or life-threatening must be reported to the Regulatory Authority by MMV or delegate and to the relevant independent ethics committee (IEC) by the Principal Investigator or delegate within 7 days after MMV becomes aware of the event. If the initial report is incomplete, a complete report must be submitted within 8 days of sending the first report. If significant new information is received by MMV on a case already reported, this should be provided as a follow-up report within 15 days of receipt of the information.

A SUSAR that is not fatal nor life-threatening must be reported to the Regulatory Authority by MMV or delegate and to the IEC by the Principal Investigator or delegate within 15 days after MMV first becomes aware of the event.

Annual safety reporting to the Regulatory Authority and the IEC will be in agreement with the ICH guideline E2F "Note for guidance on development safety update reports (DSUR)".[42]

In addition, any other safety issue which may alter the current benefit–risk assessment of the IMP will be reported by the Sponsor (or delegate) on an expedited basis to the Investigator, Regulatory Authority and IEC.

MMV will ensure that all SAE data are stored in the safety database maintained by the appointed pharmacovigilance vendor, PrimeVigilance.

7.8.4 AESI Reporting

All AESIs must be recorded and reported whether or not the investigator considers them to be related to the IMP.

Any AESI will be notified by the Principal Investigator to PrimeVigilance and to the MMV Medical Monitor or her back up within 3 business days of becoming aware of the event by telephone, email or fax. Telephonic reports must be followed up in writing within 1 business day.

AESIs which are also classified as SAEs, will be reported using SAE forms only and within the timelines specified for SAE reporting.

MMV will ensure that all AESI data are stored in the safety database maintained by the appointed pharmacovigilance vendor, PrimeVigilance.

7.8.5 Adverse Event Follow-up

All adverse events must be followed up by the Investigator until:

- the event is resolved, or
- no further medically relevant information in relation to the event can be expected, and
- the Investigator considers it justifiable to terminate the follow-up.

Events that are ongoing at the time of the patient's last follow-up visit (Day 35) should continue to be followed up by the Investigator until resolution or 30 days after the last study visit, whichever is sooner, except for SAEs which should be followed until one of the above-mentioned criteria is applicable. MMV retains the right to request additional information for any patient with ongoing adverse events or SAEs at the end of the study, if considered necessary.

7.9 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Occurrence of malaria is an efficacy endpoint for this study and forms part of the efficacy evaluation of the study. If the presence of *P. falciparum* malaria is confirmed by positive PCR at the time of the onset of these signs/symptoms and if, in the Investigator's opinion, the signs and symptoms are of the expected intensity, frequency, and duration for the individual patient in the context of this study, then the events will be classified as Disease-Related Events (DREs), will be recorded as such in the CRF and reported appropriately in the final clinical study report. These events will not be subject to the standard process for expedited reporting even although they may meet the standard criteria for seriousness.

The following malaria signs/symptoms will not be classified as DREs:

- If microscopy is negative for parasitemia at the time of the onset of the event, usual AE/SAE reporting procedures and criteria will apply, and the event will not be classified as a DRE.
- Observed malaria symptoms or signs that are of greater intensity, frequency, or duration than would be expected in the context of this study, will be regarded as medically important events and must be reported promptly (i.e. in an expedited manner) to the Sponsor using an SAE report form, and will not be classified as DREs.

Common signs and symptoms associated with malaria are detailed in Appendix 3 and may be recorded as DREs as described above.

7.10 Pregnancy

Patients will be informed that following multiple high doses to rats, but not dogs, MMV390048 was associated with testicular toxicity of a nature expected to be fully reversible on cessation of dosing. Studies of embryo-fetal development showed effects at doses also associated with maternal toxicity. The relevance of these effects to humans is unknown.

Pregnancy in a female patient is not expected since women of childbearing potential are excluded from participation in the study. Male patients will be instructed to notify the investigator of any pregnancy in their partner(s) during the study. This must be reported in an expedited manner and followed up as described beneath. Pregnancy does not constitute an adverse event as such and the pregnancy outcome will not be recorded in the CRF unless it is considered to be an adverse event.

The Investigator must notify PrimeVigilance and the MMV Medical Monitor or her back-up in an expedited manner (within 3 business days) of any pregnancy in a partner of which he/she becomes aware and which occurs from the date of informed consent until 120 days after the administration of MMV390048. Part I of the Pregnancy Report Form should be used for this notification. In all cases, the pregnancy must be followed until birth of the child, and the newborn followed up for 6 months thereafter. The outcome of the pregnancy and birth must be reported as above by completing Part II of the Pregnancy Report Form used for the initial notification. The timelines of the outcome reporting vary as follows:

- Normal outcomes must be reported within 45 days of birth/delivery
- Abnormal outcomes must be reported in an expedited manner as described in Section 7.7.3. An additional SAE Report form must be completed if the patient's partner sustains a serious event,

while a Parent-Child/Fetus Report (PCFR) must be completed should the child/fetus sustain an event.

MMV will ensure that all pregnancy-related safety data are stored in the safety database maintained by the appointed pharmacovigilance vendor, PrimeVigilance.

7.11 Procedures in Case of Medical Emergency

The Principal Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study.

Emergency equipment and drugs will be available within the clinical unit and their use in the context of the study will be documented on the CRF.

7.12 Procedures in Case of Overdose

The treatment of AEs associated with overdose should be supportive and for the underlying adverse symptoms. To date, no patient has experienced an overdose with MMV390048. A maximum tolerated dose has not yet been established, but single dose treatments up to and including 120 mg have been well tolerated. At present, there are no recommendations for treatment of overdose, other than withholding further treatment and treating the patient symptomatically. Overdose is unlikely in this study, where only a single dose will be administered at the clinical centre under the supervision of the Investigator. The Medical Monitor should be informed immediately, however, if this occurs.

8. DATA HANDLING

8.1 Data Collection

The Investigator must maintain adequate and accurate records documenting the study conduct and all patient-related data for subsequent verification. These documents are categorised as follows:

- The Investigator's study file
- The patients' clinical source documents

The Investigator's study file will contain the protocol, any amendments, the case report form, IEC and regulatory approvals together with the relevant correspondence, an example of the patient informed consent form and patient information sheet, IMP records, staff curricula vitae and authorisation forms as well as other appropriate documents or correspondence.

Patient clinical source documents may include signed informed consent forms, patient hospital or clinic records, physician's and nurse's notes, records of study-specific assessments (e.g. vital signs, temperature measurements, original laboratory reports and ECG recordings), and patient screening and enrolment logs.

All study-related documents must be kept on file by the Investigator until at least 15 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 15 years have elapsed since the formal discontinuation of clinical development of the IMP. However, these documents should be maintained for a longer period if required by local applicable regulatory requirements. No documents should be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the documents to another party or move them to another location, the Sponsor must be notified in writing before the documents are reassigned or moved.

If the Investigator cannot guarantee the archiving requirement at the investigational centre for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in a sealed container(s) away from the centre so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the patients, appropriate copies should be made prior to storing away from the centre.

8.2 Data Management

Data management, including the development and management of a secure database, will be performed in accordance with regulatory requirements.

The Investigator will indicate that he/she has a thorough review of the data in the CRF and will certify the content (including laboratory result data) by signing off the data (either electronically or with wet ink as applicable).

The designated data management vendor will review the data entered into the CRFs by investigational staff for completeness and accuracy. A formal querying process will be followed whereby the data management team will request the site personnel to clarify any apparent erroneous entries or inconsistencies and will request additional information from the site as required.

Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology. Concomitant medications will be coded using the WHO Drug Dictionary (WHO-DD).

After all data have been captured and reviewed, all queries have been resolved with the site and any protocol non-compliances that were identified during the data management processes have been confirmed by the site, the database will be declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time may only be made by the data manager, in consultation with the Sponsor and in accordance with documented database unlock and relock procedures.

8.3 Monitoring

An assigned study monitor(s) will contact and visit the Investigator regularly and will be allowed to inspect the various records of the study provided that patient confidentiality is maintained in accordance with local requirements.

It is the monitor's responsibility to inspect the CRFs at regular intervals throughout the study to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to regulatory requirements and ICH GCP guidelines.

The Investigator will ensure that relevant study documents and pertinent hospital or clinic records are readily available for inspection by the study monitor for verification of the study data. The Investigator agrees to co-operate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

8.4 Quality Control

Quality Control will be performed according to the contracted CRO's internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor.

9. STATISTICAL METHODS

9.1 Statistical Analysis Plan

A detailed statistical analysis plan (SAP), describing the purpose, timing, presentation of results and access to results will be finalised and approved before the first patient is enrolled.

If a change in the planned analysis is considered necessary after finalization of the SAP (except if the protocol requires modifications), such changes will be described and justified in the clinical study report.

This exploratory study is not powered to compare dose cohorts.

9.2 Analysis populations

Populations for analysis will be determined after database lock using the criteria defined in the SAP.

Safety Analysis Set (Safety)

The safety analysis set will consist of all enrolled patients who received any amount of study medication.

Microbiological Intent-To-Treat Analysis Set (mITT)

The microbiological intent-to-treat (mITT) analysis set will consist of all patients included in the safety analysis set with parasitologically confirmed malaria at baseline and at least one post-baseline efficacy assessment (clinical and parasitological data), and for whom no major protocol deviations are reported with the potential to affect the evaluation of efficacy. The list of protocol deviations will be reviewed and approved prior to database lock.

Per-Protocol Analysis Set (PP)

The per-protocol (PP) analysis set will consist of all patients from the mITT who complete the study with no major protocol deviation.

Pharmacokinetic (PK) Population

The PK population will include all patients in the safety population who have at least one quantifiable post-dose plasma concentration.

9.3 Determination of Sample Size

Each of the three cohorts in each of the *P. vivax* and *P. falciparum* malaria arms will be assessed separately for futility, unless data for a particular cohort(s) are regarded as inconclusive and the dose is repeated in a subsequent cohort(s). In this case, data from all cohorts in a particular arm receiving the same dose will be combined for the purpose of assessment of futility. A maximum of 102 subjects (excluding replacements) will be enrolled in the study.

Up to 3 cohorts of 17 patients each will be enrolled sequentially per malaria arm (*P. vivax* and *P. falciparum*) according to the following procedure:

After Cohort 1:

- After the first cohort, the arm will be terminated for futility if less than 60% of patients are ACPR responsive on Day 14.
- If the arm is not terminated for futility after Cohort 1, Cohort 2 may be enrolled to investigate:
  - a lower dose if the Cohort 1 response rate was greater than 80% (i.e. success criteria were met), or

  - a repeat dose if the Cohort 1 response rate was greater than 60% but less than 80% (i.e. the data was regarded as inconclusive).

After Cohort 2:

- If Cohort 2 investigated a lower dose than Cohort 1:
  - the same progression criteria described for Cohort 1 will be applied to Cohort 2 to determine whether a further dose de-escalation or dose repeat is permitted.
  - the SRT may elect to re-escalate to an intermediate dose depending on the success criteria at the doses from Cohorts 1 and 2.
- If Cohort 2 investigated the same dose as Cohort 1:
  - the arm will be terminated for futility if 72% or less of the cumulative patients from both cohorts are ACPR responsive on Day 14.
  - if the arm is not terminated for futility after Cohorts 1 and 2, Cohort 3 may be enrolled to investigate:
    - a lower dose if the combined Cohort 1 and 2 response rate was greater than 80% (i.e. success criteria were met), or
    - a repeat dose if the combined Cohort 1 and 2 response rate was greater than 72% but less than 80% (i.e. the data was regarded as inconclusive).

Throughout:

- At any stage, the SRT may elect to repeat a dose rather than de-escalate even though success criteria may have been met.

The minimum Day 14 ACPR responder count to meet the cohort success criteria will be 14 out of 17 patients. Assuming a binomial distribution, the point estimate of the response rate with 14 out of 17 responders will be 82.4% with the lower margin of the 90% confidence interval (Clopper-Pearson method) greater than 60% (60.4% to 95.0%). A responder count of 11 to 13 out of 17 patients will be regarded as inconclusive and the dose may be repeated in a subsequent cohort. The maximum Day 14 ACPR responder count to declare futility of a dose level after one cohort will be 10 out of 17 patients (response rate of 58.8% or less) and will be associated with a risk of false conclusion of futility of less than 0.1% (alpha <0.001) assuming that the true population response is at least 90%.

If a particular dose is repeated, the minimum combined Day 14 ACPR responder count across the two cohorts to meet the success criteria will be 28 out of 34 patients (82.4% response rate; 90% confidence interval of 68.1% to 92.0%). A responder count of 25 to 27 out of 34 patients will be regarded as inconclusive and the dose may be repeated in a third cohort. The maximum combined Day 14 ACPR responder count to declare futility of a dose level after two cohorts will be 24 out of 34 (response rate of 70.6% or less) and will be associated with a risk of false conclusion of futility of less than 0.2% (alpha <0.002) assuming that the true population response is at least 90%.

If a particular dose is repeated across three cohorts, a combined Day 14 ACPR responder count across the three cohorts of at least 41 out of 51 patients (80.4% response rate; 90% confidence interval of 69.0% to 89.0%) will be required to meet the dose success criteria. An observed response rate across the three cohorts of 78.4% or less (at most 40 out of 51 patients) will be associated with a risk of false conclusion of futility of less than 2% (alpha <0.011) assuming that the true population response is at least 90%.

If patients drop out for reasons not related to safety and/or efficacy concerns, attempts will be made to replace them to ensure that data from 17 evaluable patients are available for each cohort.

The sample size is considered adequate to gain preliminary efficacy and safety data in the target population.

9.4 Data Analysis

All relevant data obtained in this study and documented in the CRF will be listed individually and tabulated. All statistical analyses will be performed using SAS® (version 9.3 or higher).

Data from the *P. vivax* and *P. falciparum* malaria arms will be analysed and reported separately. Summary statistics will be produced by cohort and overall.

Data will be summarised as follows: Continuous variables by descriptive statistics (number of patients [n], mean, standard deviation [SD], minimum, median and maximum, and categorical variables by absolute and relative frequencies (n and %) or contingency tables.

Unless indicated otherwise, summary statistics will be reported by cohort for observed data only and missing data will not be imputed. If a baseline value is missing, no change from baseline will be calculated.

Data listings will include scheduled, unscheduled, retest and early withdrawal data.

9.5 Baseline Data and Patient Disposition

The number of patients recruited and receiving study drug will be presented by cohort, arm and overall, as will be number of patients included in the various analysis sets.

Demographic and baseline characteristics will be presented by dose cohort and for the safety and mITT sets respectively.

Study completions and withdrawals will be summarised, including the reasons for any withdrawals in the safety set. Protocol violations will be listed per patient. A description of the nature of the violation will be included, as well as a final classification of the violation as major or a minor in terms of its effect on the safety and efficacy endpoints of the study.

9.6 Efficacy Analyses

9.6.1 Primary efficacy

The primary endpoint to determine the efficacy of MMV390048 will be :

- the crude adequate clinical and parasitological response (ACPR) at Day 14 for *P. vivax* patients, and
- the PCR-adjusted adequate clinical and parasitological response (ACPR) at Day 14 for *P. falciparum* patients.

Crude ACPR does not distinguish between re-infection (by a new clone of parasite) and recrudescence (recurrence of the original clone of parasite that is present at baseline). On a specified day, the crude ACPR is the proportion of patients that have no evidence of asexual parasitemia as detected microscopically (i.e. have neither recrudescence nor new infection).

PCR-adjusted ACPR is an assessment of response that differentiates between recrudescence (recurrence of the original clone of parasite that is present at baseline) and new infection. Recrudescence is distinguished from new-infection by genotyping the parasite clone. On a specified day, the PCR-adjusted ACPR is the proportion of patients that have no evidence of recrudescence as determined microscopically and genotypically as an absence of the same asexual parasitemia (clone) as the original infection.

The proportion of patients with ACPR at Day 14 will be summarised in the mITT set by cohort, arm and overall. Standard descriptive statistics as well as 90% confidence intervals using the Clopper-Pearson method will be provided.

If the data and number of doses tested allows this analysis, a dose-response analysis of the crude and PRC-corrected ACPR rates will be performed at Days 14 and 28. Model predictions will be reported with 90% confidence bands. The dose required to produce a 95% response rate will be reported with its 90% confidence interval using the inverse prediction method.

9.6.1.1 Sensitivity analysis

For each cohort separately, the primary analysis will be repeated on the PP set if it differs from the mITT set by more than 20%. The crude and PCR-adjusted ACPR responder rates at Day 28 will also be summarized.

9.6.2 Secondary efficacy criteria

Secondary efficacy variables will be summarised descriptively with incidence rates or standard descriptive methods, including 90% confidence intervals, as appropriate. Time to event variables will be summarised with Kaplan-Meier estimates of the survival function.

9.6.2.1 Recurrence, recrudescence and new-infection at Day 14

The proportion of patients with recurrence (*P. vivax* and *P. falciparum*), recrudescence (*P. falciparum* only) and re-infection (*P. falciparum* only) over 28 days will be summarized in the mITT set. Time to recurrence, recrudescence and new-infection will be estimated by the Kaplan-Meier method, and censored at the time of the last recorded visit, if recurrence has not been observed by that time.

9.6.2.2 Parasite clearance time (PCT)

PCT is defined as the time from dosing to the first negative (no parasites) blood film. This negative film must be confirmed by a second negative film, taken within 6 to 12 hours of the first. Parasite clearance will be concluded following confirmation of the second negative film. Kaplan-Meier estimates will be used to evaluate parasite clearance time of baseline parasitemia.

The time to a microscopically determined 50%, 90% and 99% reduction of asexual parasites will be determined. For patient data that supports extrapolation, the parasitemia will be estimated by log-linear extrapolation of the parasitemia curve.

The proportion of aparasitemic patients at 24, 48 and 72 hours after administration of study drug will also be determined.

9.6.2.3 Fever clearance time (FCT)

Kaplan-Meier estimates will be used to evaluate fever clearance time.

Patients entered in the study on the basis of history of fever and who do not subsequently have an increased body temperature measurement indicating presence of fever pre-dose, will not be included in the analysis of fever clearance time.

9.6.2.4 Parasite Reduction Rate (PRR)

The parasite reduction rate is calculated as the slope of the linear portion of the regression fit of natural log parasitemia (per mL) versus time (in hours).

The calculations and modeling for the PRR will be further discussed in the SAP. This will be calculated using microscopically determined parasitemia.

The percent reduction in asexual parasites from baseline (microscopically measured) at 24, 48 and 72 hours after administration of study drug will be determined.

9.7 Pharmacokinetics Analyses

The following PK parameters will be estimated from patients' individual plasma concentrations of MMV390048 by applying a non-compartmental approach using WinNonlin Professional. Concentration values reported as below the limit of quantification will be set to zero where appropriate.

- C_{max}: The maximum concentration observed in the concentration time course following administration of the drug.
- t_{max}: The time at which the C_{max} is observed.
- AUC_{0-t}, AUC_{0-inf}: The area under the concentration time curve from time = 0 hours until a defined endpoint. The AUC will be calculated using linear interpolation up to C_{max} followed with log-linear interpolation until the last time point. Last denotes the last measured time point. Infinity denotes extrapolation of the AUC to infinity. Unit = hr·ng/mL.
- Elimination half-life ($t_{½}$): The transformed log linear elimination phase gradient.

Descriptive statistics including mean, standard deviation, coefficient of variation, median, minimum and maximum, geometric mean and geometric mean CV% will be calculated for each PK parameter by cohort. Mean and median concentration-versus-time graphs will be presented.

9.8 PK/PD Analyses

The relationship between MMV390048 PK and the antimalarial PD responses will be characterized. The time to increase of qPCR detected parasite levels after an initial microscopic clearance, and time to the nadir in the qPCR parasite load, will be summarised descriptively by dose cohort. Standard descriptive statistics as well as 95% confidence intervals for the median will be provided.

9.9 Exploratory Analyses

Details of the relevant statistical methods to be employed in exploratory analyses will be described in a separate analysis plan.

For patients with gametocytes at baseline the time to gametocyte clearance will be estimated using the Kaplan-Meier method.

For patients without gametocytes at baseline, the time to gametocyte appearance will be estimated using the Kaplan-Meier method.

Integrated number of gametocytes (AUC) at Days 14 and 28 will be calculated separately for patients with gametocytes at baseline and for those without gametocytes at baseline that develop gametocytes during the study.

The log parasite counts over time will be summarized descriptively by treatment arm and visit.

Exploratory model-based analyses will be performed as data allow to investigate the relationship between:

- microscopic and qPCR quantitative parasite assessment
- parasite genotypes of interest and parasite clearance kinetics/efficacy

For those patients who consent separately, pharmacogenetic samples will be obtained and stored for future analysis to look at genetic polymorphism (e.g. CYP_{2C8}, CYP_{2C19}).

The exploratory analyses may not be reported as part of the CSR.

9.10 Safety Analyses

All safety analyses will be based on the safety analysis set.

9.10.1 Adverse Events

All adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by Preferred Term within each MedDRA System Organ Class (SOC).

Adverse drug reactions (ADRs) are adverse events regarded by the Investigator as related to the IMP (Sections 7.7.1 and 7.7.2.2). If the relationship of the event to the IMP is unknown or missing, the worst case scenario will be assumed and the AE will be considered to be treatment-related.

All AEs will be listed. The verbatim term, the preferred term, start and end date of the event, onset day and time relevant to dosing, duration (days), severity, drug relationship, action taken and outcome will be detailed.

An overview of the following adverse events will be presented:

- All adverse events
- SAEs
- AESIs
- AEs resulting in death
- AEs resulting in study discontinuation
- ADRs
- Drug induced liver toxicity (Hy's law).

Summaries will consist of the number of patients with at least one event in each category (patients with multiple events in each category are counted only once in each category) as well as the number of events (mentions), and will be presented by dose group and overall for the Safety analysis set. The percentage of patients with at least one event in each category will be calculated relative to the total number of patients in the Safety analysis set.

Additionally, summaries of AEs and ADRs by severity will be performed using the most severe grade.

9.10.2 Laboratory Data

Laboratory values that fall outside a clinically accepted reference range will be evaluated and commented on by the Investigator, and graded according to the CTCAE version 4.03, 2010 (Appendix 4).[40]

All clinically significant abnormal laboratory results will be listed.

The proportion of patients with clinically significant abnormal values as reported by the Investigator will be provided by lab parameter, dose cohort and scheduled visit. For each laboratory parameter, shift tables of baseline categories based on normal ranges (below, within, above) versus categories at each post baseline scheduled visit will be provided. Summary statistics of values and changes from baseline over time will be computed for all safety laboratory parameters.

9.10.3 Vital Signs

Supine blood pressure and heart rate (absolute values and change from baseline) will be summarised by dose cohort and scheduled visit.

9.10.4 ECG

The proportion of patients with a clinically significant abnormal ECG result (heart rate, RR interval, PR interval, QRS interval, QT interval and QTc interval) will be provided. A summary of changes in 12-lead ECG parameters from baseline will be provided per cohort and time point.

Mean changes in ECG parameters from baseline to 1, 2, 4, 6, 8, 24 and 72 hours post-dose will be summarized by dose level and by cohort. Shifts of corrected QT (QTc) values (based on Guidance for Industry, ICH guidelines, October 2005)[44] from the baseline values will be tabulated. QTc values will be calculated according to Fridericia's formulae. Individual changes from baseline will be classified into the following categories:

- <30 ms increase from baseline,
- ≥30 ms and <60 ms increase from baseline, and
- ≥60 ms increase from baseline.

Possibly clinically significant QTc values according to ICH guidelines, October 2005 will be tabulated into the following categories:

- QT/QTc < 450 ms
- 450 ms ≤ QT/QTc < 480 ms
- 480 ms ≤ QT/QTc < 500 ms
- QT/QTc ≥ 500 ms

9.11 Interim Analyses

Up to two interim analyses are planned for each of the *P. vivax* and *P. falciparum* malaria arms separately, after each cohort completes its Day 14 assessment.

The purposes of the first interim analyses after Cohorts 1A and 1B respectively, are to determine if the respective malaria arm must be stopped for futility or if enrolment of a second cohort is indicated. The arm will be stopped for futility if no more than 10 out of 17 patients are responders for the primary ACPR endpoint. If there are 11 to 17 responders out of 17 patients, a second cohort of 17 patients may be enrolled. The dose for Cohort 2 will be determined based on the responder rate in Cohort 1 (refer to Section 9.3) and corresponding safety and PK data.

Second interim analyses will occur after each of Cohorts 2A and 2B. The purpose of these analyses is to determine:

- if a dose should be stopped for futility (refer to Section 9.3)
- whether or not enrolment of a third cohort is required and to select the appropriate dose for that cohort (refer to Section 9.3). If two distinct dose levels have been tested in Cohorts 1 and 2, a dose-response logistic regression model may be fitted to support the termination and dose selection decisions.

The interim analyses will be conducted on data to at least Day 14 of each cohort. If PCR correction data are not available at the time of the interim analyses, decisions regarding dose and cohort progression may be based on the crude ACPR for both *P. vivax* and *P. falciparum*.

Details of the interim analyses will be described in the SAP.

10. ETHICAL AND REGULATORY OBLIGATIONS

10.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki.[45]

10.2 Good Clinical Practice

The study will be conducted according to the protocol and to Standard Operating Procedures (SOPs) that meet the current regulatory requirements and guidelines laid down by the International Council on Harmonisation of Good Clinical Practice (ICH GCP) in clinical studies.[46]

10.3 Independent Ethics Committee/Institutional Review Board Approval

10.3.1 Initial Approval

Prior to the shipment of IMP and the enrolment of patients, the IEC/IRB must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Patient Information Sheet and Consent Form, any other written information that will be provided to the patients, any advertisements that will be used in patient recruitment and any patient compensation.

10.3.2 Approval of amendments

Any required amendments to the protocol will be compiled by the Sponsor in consultation with the Principal Investigator, and submitted to the IEC/IRB for approval. Amendments requiring IEC/IRB approval may be implemented only after a copy of the IEC/IRB's approval letter has been transmitted to the Sponsor.

Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented prior to receiving Sponsor or IEC/IRB approval. However, in this case, approval must be obtained as soon as possible after implementation.

10.3.3 Reporting of SAEs (including SUSARs)

All SAEs (including SUSARs) occurring during the study at any investigational site will also be reported to the IEC/IRB in accordance with their reporting requirements and within the required timelines. The actual reporting of the events will be performed as instructed by the Sponsor.

10.3.4 Periodic Safety Reports and End of Study Notification

Each IEC/IRB will be sent periodic/annual safety updates in order to facilitate their continuing review of the study (ICH GCP Section 3.1.4) in accordance with their requirements, and will also be informed about the end of the study within the required timelines.

10.4 Regulatory Authority Approval

The study will be performed in compliance with Ethiopia's regulatory requirements. As with the IEC/IRB, clinical study authorisation from the Regulatory Authority must be obtained prior to the start of the study. In addition, the Regulatory Authority must approve amendments (as instructed by the Sponsor), receive SUSAR reports, and be notified of the end of the study.

10.5 Other Required Approvals

In addition to IEC/IRB and regulatory authority approval, any other locally required approvals will be obtained prior to recruitment of patients into the study and shipment of the IMP.

10.6 Insurance

The Sponsor has civil liability insurance, which covers this study.

10.7 Informed Consent

The informed consent document will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient can be entered into the study. The informed consent document contains a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time.

The Investigator is responsible for ensuring that informed consent is obtained from each patient in writing in accordance with local practice prior to the performance of any protocol procedures and prior to the administration of study medication. If the patient is unable to write, witnessed consent is permitted according to local ethical considerations. A copy of the signed and dated informed consent form will be given to the patient. The signed and dated original consent form will be retained with the study records. If modifications are made according to local requirements, any new version has to be approved by the Sponsor.

If new safety information results in significant changes in the risk/benefit assessment, the consent form and patient information sheet should be reviewed and updated if necessary. The patient should be informed of the new information, given a copy of the revised consent form and give their consent to continue the study.

10.8 Patient Confidentiality

The Investigator must ensure that the patient's privacy is maintained. On the CRF or other documents submitted to the Sponsors, patients will be identified by a patient ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the Investigator.

The Investigator shall permit direct access to patients' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, Regulatory Authorities and IECs/IRBs.

10.9 Data Protection

The Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with GCP. Patients in this database will be identified by patient number only. The Informed Consent Form will also explain that for data verification purposes, authorised representatives of the Sponsor, a regulatory authority, or an IEC may require direct access to parts of the hospital or practice records relevant to the study, including patient medical history.

11. ADMINISTRATIVE ISSUES

11.1 Pre-study Documentation Requirements

The documents required before the IMP can be shipped to the investigational site will be collected in accordance with the SOPs of the contracted CRO and the requirements of each country.

11.2 End of Study

The end of the study shall be defined as the Last Patient Last Visit.

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, both the Sponsor and the Investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the patient's interests.

11.3 Study Documentation and Data Storage

The Investigator must retain a comprehensive and centralised filing system of all study-related documentation that is suitable for inspection by the Sponsor and representatives of Regulatory Authorities.

The Investigator must retain essential documents until notified by the Sponsor, and at least for five years after study completion, as per Directive 2005/28/EC Article 17. Patient files and other source data (including copies of protocols, CRFs, original reports of test results, IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be kept for the maximum period of time permitted by the institution. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

11.4 Audits and Inspections

Authorised representatives of Sponsor, a regulatory authority, or an IEC may visit the centre to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and whether data were recorded, analysed and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Council for Harmonisation (ICH), and any applicable local regulatory requirements. All necessary data and documents will be made available by the Investigator for inspection.

The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection at their centre.

11.5 Disclosure of Information

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The Investigator may use this information for the purposes of the study only.

It is understood by the Investigator that the Sponsor will use information developed in this clinical study in connection with the development of the IMP and, therefore, may disclose it as required to other clinical Investigators and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

11.6 Publication

All information concerning MMV390048 and the Sponsor's operations, such as the Sponsor patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by the Sponsor and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by the Sponsor in connection with the development of MMV390048. This information may be disclosed as deemed necessary by the Sponsor. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide the Sponsor with complete test results and all data developed in this study.

This confidential information shall remain the sole property of the Sponsor, shall not be disclosed to others without the written consent of the Sponsor, and shall not be used except in the performance of this study.

The Sponsor encourages publication of study results. However no study data shall be disclosed prior to the final analysis of the data and only on express permission of the Sponsor. Should an Investigator wish to publish results from this study, a copy of the manuscript must be provided to the Sponsor for approval, at least 30 days before the intended date of submission to the intended publisher.

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APPENDIX 1: DEFINITION OF SEVERE MALARIA

World Health Organisation Criteria 2012[3]

Clinical features of severe malaria in adults:

- impaired consciousness (including unrousable coma);
- prostration, i.e. generalized weakness so that the patient is unable to sit, stand or walk without assistance;
- multiple convulsions: more than two episodes within 24h;
- deep breathing and respiratory distress (acidotic breathing);
- acute pulmonary edema and acute respiratory distress syndrome;
- circulatory collapse or shock, systolic blood pressure <80mm Hg in adults and <50mm Hg in children;
- acute kidney injury;
- clinical jaundice plus evidence of other vital organ dysfunction; and
- abnormal bleeding.

Laboratory and other findings:

- hypoglycemia (<2.2mmol/l or <40mg/dl);
- metabolic acidosis (plasma bicarbonate <15mmol/l);
- severe normocytic anemia (hemoglobin <5g/dl, packed cell volume <15% in children; hemoglobin <7g/dl, packed cell volume <20% in adults)
- hemoglobinuria;
- hyperlactatemia (lactate >5mmol/l);
- renal impairment (serum creatinine >265µmol/l equivalent to 3 mg/dL); and
- pulmonary edema (radiological).

APPENDIX 2: PROHIBITED ANTIMALARIAL DRUGS

The following medication (with antimalarial activity) should not be used within the specified time period prior to enrolment or during the entire study period (except when used as definitive antimalarial treatment at point of standard of care:

- Ever:
  - MMV390048

- Within 6 weeks prior to screening:
  - Piperaquine
  - Mefloquine
  - Naphthoquine
  - Sulphadoxine-pyrimethamine

- Within 4 weeks prior to screening:
  - Amodiaquine
  - Chloroquine
  - Hydroxychloroquine and all other 4-aminoquinolines
  - Pyronaridine
  - Tafenoquine

- Within 14 days prior to screening:
  - All Artemisinin derivatives including artemether, arteether, artesunate and dihydroartemisinin
  - Quinine
  - Halofantrine
  - Lumefantrine
  - Quinidine
  - Arterolane
  - Proguanil
  - Chlorproguanil
  - Primaquine
  - Atovaquone
  - Pentamidine
  - Clindamycin
  - Rifampin
  - Dapsone and all sulphones
  - All sulfonamides (sulphonamides) or sulfonamide containing preparations including co-trimoxazole (trimethoprim-sulfamethoxazole)
  - All tetracycline class antibiotics including minocycline and doxycycline
  - Quinolone antibiotics including fluoroquinolones
  - Azithromycin and all other macrolides
  - Erythromycin and all other macrolides

- Within 7 days prior to screening:
  - Any herbal products or traditional medicines

APPENDIX 3: COMMON SIGNS AND SYMPTOMS OF MALARIA

The following are common signs and symptoms of malaria:

Signs of Malaria:

- Fever (axillary temperature of ≥37.5°C)
- Chills/Shivering/Rigors
- Tachycardia
- Hypotension

Symptoms of Malaria:

- Headache
- Myalgia (muscle ache)
- Arthralgia (joint ache)
- Fatigue/lethargy
- Malaise (general discomfort/uneasiness)
- Sweating/hot spells
- Anorexia
- Nausea
- Vomiting
- Abdominal discomfort

APPENDIX 4: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

A full CTCAE manual including quick reference documents, can be found online at http://evs.nci.nih.gov/ftp1/CTCAE/About.html and should be reference for the grading of all adverse events and laboratory abnormalities. Version 4.03 dated June 2010 will be referenced.

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1:
  - mild, or
  - symptomatic or mild symptoms, or
  - clinical or diagnostic observations only, or
  - intervention not indicated
- Grade 2:
  - moderate, or
  - minimal, local or non-invasive intervention indicated, or
  - limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries, using the telephone, managing money, etc.)
- Grade 3:
  - severe or medically significant but not immediately life-threatening, or
  - hospitalisation or prolongation of hospitalisation indicated, or
  - disabling, or
  - limiting self care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
- Grade 4:
  - life-threatening consequences, or
  - urgent intervention indicated
- Grade 5:
  - death related to adverse event.

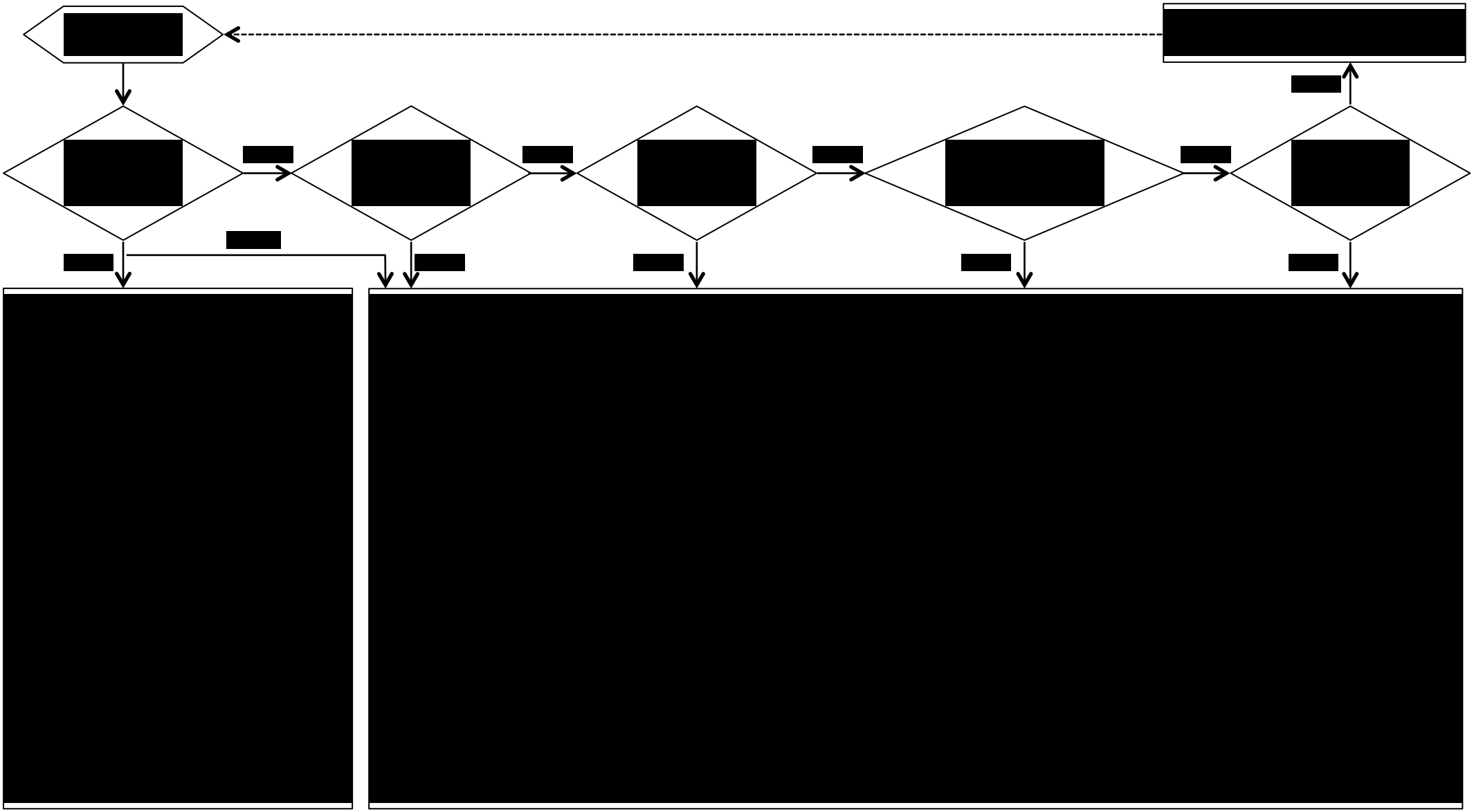
If an adverse event is not listed in the CTCAE table, the Investigator will assess the severity using the above-mentioned guideline.

APPENDIX 5: ESTIMATED VOLUME OF BLOOD DRAWS

Maximum Estimated Volume of Blood Draws from Each Patient:

Assessment		Sample volume (ml)	Max no. of samples	Total volume (ml)
Pharmacokinetic Drug levels		2	18	36
Microscopy and qPCR for parasitemia		0.5	29	14.5
Parasite genotyping for PCR correction		0.3	3	0.9
Parasite genotyping for resistance markers		0.2	2	0.4
Safety	Clinical chemistry (incl. haptoglobin if required)	5	9	45
	Hematology	2	10	20
	G6PD enzyme	2	1	2
Genotyping	Human (optional)	10	1	10
Total			**Over 35 days**	**128.8 mL**

APPENDIX 6: FOLLOW-UP OF ANY AESI RELATED TO HEPATOTOXICITY



Adverse events of special interest (AESIs) related to hepatotoxicity are defined as follows for this study:

1. ALT or AST >3 x ULN and TBL >2 x ULN (suspected Hy's Law if conjugated bilirubin >35%),
2. ALT or AST >3 x ULN with the appearance of worsening of fatigue, nausea, vomiting, fever, rash or eosinophilia,
3. ALT or AST rises rapidly to >5 x ULN in less than 4 weeks or persists for more than 2 weeks,
4. AST or ALT increase >8 x ULN.

<u>The following actions should be taken for any patient experiencing one of these events:</u>

- Stop herbal remedies and concomitant medications that are not medically necessary as applicable.
- Notification of appropriate personnel of the AESI
  - MMV Medical Monitor or her back-up
  - Pharmacovigilance vendor
  - SRT through MMV Medical Monitor
- Obtain detailed additional medical history and review of medical records
- Admit patient and carry out the following liver event special investigations within 24 hours:
  - Viral hepatitis serology including:
    - Hepatitis A IgM antibody
    - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)
    - Hepatitis C RNA
    - Hepatitis E IgM antibody
    - Cytomegalovirus (CMV) polymerase chain reaction (PCR), pp65 antigen, or IgM antibody
    - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing)
  - Blood sample for PK analysis, obtained as soon as possible. Record the date/time of the PK blood sample draw on the CRF.
  - Minimum safety laboratory assessments:
    - Creatinine
    - Alkaline phosphatase (ALP)
    - Gamma-glutamyl transferase (GGT)
    - Serum creatine phosphokinase (CPK)
    - Lactate dehydrogenase (LDH)
    - Fractionate bilirubin, if total bilirubin >2 x ULN
    - Full blood count with differential to assess eosinophilia
    - Prothrombin time
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AESI report form.
- Record use of concomitant medications (including paracetamol), herbal remedies and other over-the-counter medications or putative hepatotoxins on the concomitant medications report form.
- A statement concerning whether the patient has consumed alcohol since the time of enrolment, with a description of frequency and intensity, if relevant. A blood alcohol level should be obtained if the patient's history and/or clinical presentation suggest proximal use or intoxication with alcohol.
- Discuss case details with MMV Medical Monitor, in particular any concomitant medications, over the counter medications, herbal remedies, prior exposure, previous episodes etc.

- Ensure appropriate medical attention, including admission to the Intensive Care Unit and referral to a more specialised hospital as required.
- Contact external experts for opinion and advice if possible.
- Consider whether it is necessary to perform any of the additional tests specified for a suspected Hy's law case beneath
- At least twice weekly monitoring of liver function tests (and other safety laboratory tests as indicated) until liver function tests have resolved, stabilised or returned to baseline values.

In addition to the follow-up described above, for patients with ALT or AST >3 x ULN and TBL >2 x ULN and fraction of conjugated bilirubin >35% (suspected Hy's law case), the event will be regarded as an SAE and the following should be performed at minimum:

- Notification of appropriate groups
  - Ethics committees and Regulatory Authority as required
  - Other investigators
  - Global Safety Board through Sponsor
- Request liver imaging (ultrasound, computerised tomography or magnetic resonance imaging) to evaluate liver disease
- Laboratory assays:
  - Serum acetaminophen adduct HPLC assay,
  - Antinuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies and quantitative IgG or gamma-globulins
- Mandatory specialist consultation and follow-up of liver function tests, prothrombin time and other safety laboratory tests as indicated at least twice weekly until values have resolved, stabilised or returned to baseline values.

For all AESIs related to hepatotoxicity, the following should be reported to MMV using the AESI report form (or SAE report form for a suspected Hy's Law case) and recorded in the patient's source data and CRF where applicable:

- The date (and visit number) on which the blood sample was obtained with results which met one of the hepatotoxicity AESI criteria
- The enrolment date, malaria arm and dose of MMV390048 administered to the patient, and the date and time of dosing
- The specific abnormal laboratory values, as well as those of each of the other LFTs noted above (regardless of value) and, when relevant, results of isoenzyme or fractionation analyses. The investigator should also document the corresponding laboratory values at screening/baseline.
- Other notable abnormalities in laboratory values (e.g. complete blood count, eosinophilia, or electrolyte abnormalities, if present)
- Results of any other relevant investigations (e.g. ECGs, pathology reports, radiology reports)
- The dates and nature of any relevant adverse events (e.g. jaundice) reported since enrolment, with particular attention to hypotension, fever, rash, hepatitis symptoms (e.g. appearance or worsening of fatigue, nausea, anorexia, nausea, emesis, abdominal pain), or other adverse events that might have occurred in close proximity to the elevation in the laboratory value(s) of interest
- Any associated physical examination findings (including vital signs and abdominal examination findings)
- The use of concomitant medications (e.g. acetaminophen, traditional and herbal remedies, other over the counter medications, or putative hepatotoxins) since enrolment, as well as the dates of exposure to the concomitant medication(s). Nutritional supplements, vitamins and/or herbal preparations that the patient might have taken during this time frame should be included.

- Reported alcohol consumption since enrolment, with a description of frequency and intensity as relevant. Blood alcohol level should be reported if the patient's history and/or clinical presentation suggested use of, or intoxication with, alcohol.
- The dates and actual results of any previous and historical elevations of relevant laboratory parameters
- Past or recent history of exposure to known factors that can cause, or are associated with, elevations in liver function tests. Examples of these factors include alcohol abuse and/or dependence, hepatitis (infectious or chemical), infectious mononucleosis, gallbladder disease, liver disease of any kind, jaundice, myocardial infarction, heart failure and/or episodes of hypotension.
- Any family history of hepatitis (from any cause) or hepatotoxicity from medications

General considerations:

- The investigator should contact the MMV Medical Monitor with any questions regarding the most appropriate course of action, and/or specialist referral for further evaluation.
- The investigator must follow any patient with clinically significant elevations of one or more liver function tests until there is clear evidence that the value(s) have stabilised and/or normalised.
- A detailed explanation should be provided regarding the circumstances surrounding any patients that are lost to follow up.
- The Medicines for Malaria's Global Safety Board will review aggregate data from available sources for underlying trends.

APPENDIX 7: CLINICAL ASSESSMENT SCHEDULE SCREENING TO DAY 35 (WHEN qPCR RESULTS ARE AVAILABLE WITHIN 24 HOURS OF SAMPLING)

Description	Screen	Pre-dose	Treatment and follow-up											EOS
Day	**0**	**0**	**0**	**1**	**2**	**3**	**7**	**10/11**	**14**	**17/18**	**21**	**24/25**	**28[a]**	**35**
Informed Consent	X													
Demographics	X													
Medical history	X	X												
Social history	X													
Eligibility criteria	X	X												
Minimum admission period	X----------					X[b]								
IMP administration[c]			0 hours											
Height	X													
Body weight	X												X	X
Malaria signs & symptoms[d]	X	X	2, 4, 8, 12, 16, 20 hpd	24, 30, 36, 42 hpd	48, 54, 60, 66 hpd	72 hpd	X	X	X	X	X	X	X	X
Physical examination[e]	X	X	2, 4, 8, 12, 16, 20 hpd	24, 30, 36, 42 hpd	48, 54, 60, 66 hpd	72 hpd	X	X	X	X	X	X	X	X
BP, pulse and body temp[f]	X	X	2, 4, 8, 12, 16, 20 hpd	24, 30, 36, 42 hpd	48, 54, 60, 66 hpd	72 hpd	X	X	X	X	X	X	X	X
12 lead ECG[g]	X	X	1, 2, 4, 6, 8 hpd	24 hpd		72 hpd							X	X
Hematology & chemistry	X			24 hpd	48 hpd		X	X	X		X		X	X
Platelet count			12 hpd (Pf only)											
Pregnancy test[h]	X													X
Blood film microscopy[i]	X	X	4, 8, 12, 16, 20 hpd	24, 30, 36, 42 hpd	48, 54, 60, 66 hpd	72 hpd	X	X	X	X	X	X	X	
qPCR for parasitemia[j]	X	X	4, 8, 12, 16, 20 hpd	24, 30, 36, 42 hpd	48, 54, 60, 66 hpd	72 hpd	X	X	X	X	X	X	X	
Parasite genotyping[k]		X		24 hpd				X----------					X	
PK blood sample[l]		X	0.5, 1, 2, 4, 6, 8, 12, 16 hpd	24 hpd	48 hpd	72 hpd	X	X	X		X		X	X
Pharmacogenetic sample[m]		X												
Stopping criteria review			X----------										X	
G6PD enzyme test[n]			<----------										X	
Definitive antimalarial Rx[o]			<----------										X	
Concomitant meds	X----------													X
Adverse event			X----------											X
SAE reporting	X----------													X[p]

hpd = hours post-dose; Rx = treatment	
a	Day 28 or day of withdrawal (NB: all evaluations to be done prior to administration of definitive antimalarial therapy).
b	Patients will remain in the CRU until complete microscopic clearance of parasitemia (two consecutive negative samples) but for a minimum of 72 hours post-dose.
c	Patients to remain fasting (except for water permitted *ad libitum*) from 3 hours prior to dosing until 1.5 hours post-dose.
d	During the admission period, malaria signs and symptoms will be assessed at 2, 4, 8, 12, 16, 20 and 24 hours post-dose and every 6 hours thereafter until microscopy is negative for parasitemia on two consecutive occasions or until 72 hours post-dose [whichever is first], and twice daily thereafter until discharge from the CRU.
e	Full physical examination to be performed at screening, Day 28 and Day 35. Brief symptom-directed physical examinations to be performed at all other time points. During the admission period, these will be performed at 2, 4, 8, 12, 16, 20 and 24 hours post-dose and every 6 hours thereafter until microscopy is negative for parasitemia on two consecutive occasions or until 72 hours post-dose [whichever is first], and twice daily thereafter until discharge from the CRU.
f	Vitals signs (BP, pulse and axillary body temperature) will be measured after 5 minutes in the supine position at all time points indicated. During the admission period, assessments will be performed at 2, 4, 8, 12, 16, 20 and 24 hours post-dose and every 6 hours thereafter until microscopy is negative for parasitemia on two consecutive occasions or until 72 hours post-dose [whichever is first], and twice daily thereafter until discharge from the CRU.
g	12-lead ECGs will be performed as scheduled and as clinically indicated. Recordings will be performed after patients have been in the supine position for at least 10 minutes. All recordings will be performed as single recordings, except for the pre-dose recording which will be performed in triplicate. Patients requiring definitive antimalarial therapy prior to Day 28 will have a single ECG recording performed prior to administration of the treatment.
h	For females only, point-of-care pregnancy tests to be performed at screening (whole blood/serum) and Day 35 (urine).
i	Thick and thin blood films will be obtained at screening to confirm eligibility and within 30 minutes prior to dosing for baseline values. After dosing, blood films will be prepared and examined at 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, 66 and 72 hours post-dose, and 6-hourly thereafter if parasitemia is still present until microscopy is negative for parasitemia on two consecutive occasions. Thereafter, thick and thin blood films will then be examined at each visit as indicated in the schedule. Sets of four blood films (2 thick, 1 thin and 1 combined) will be prepared at each time point.
j	EDTA blood samples for qPCR will be taken at screening, pre-dose and 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, 66 and 72 hours post-dose, and 6-hourly thereafter if parasitemia is still present until microscopy is negative for parasitemia on two consecutive occasions. Thereafter, qPCR samples will be taken at each visit as indicated in the schedule.
k	Dry blood spot cards for parasite genotyping will be collected pre-dose, 24 hours post-dose and at the time of **first re-appearance of parasites** in the event of recurrence of parasitemia, but only in patients for whom this occurs after Day 7. Separate DBS cards will be collected for genotyping for PCR correction (2 cards containing at least 3 spots each to be collected pre-dose, 24 hours post-dose and upon recurrence) and for genotyping for resistance markers (1 card with at least 3 spots to be collected pre-dose and upon recurrence only).
l	Blood samples (2 mL) for PK analyses will be collected as detailed in the schedule, as well as at 4 hours (±1 hour) post-definitive antimalarial therapy, at the time of failure (if applicable) or in the case of any drug-related SAE.
m	Pharmacogenetic sample to be taken only from patients who consented separately to this.
n	G6PD enzyme test to be performed for *P. vivax* patients only on Day 28, or earlier if patient meets individual stopping criteria.
o	Definitive antimalarial treatment in accordance with local standard of care, to be administered on Day 28, or earlier as required as per individual stopping criteria.
p	Spontaneously-reported SAEs to be collected until 30 days post EOS follow-up visit.

APPENDIX 8: CLINICAL ASSESSMENT SCHEDULE SCREENING TO DAY 35 (WHEN qPCR RESULTS ARE NOT AVAILABLE WITHIN 24 HOURS OF SAMPLING)

Description	Screen	Pre-dose	Treatment and follow-up																EOS
Day	**0**	**0**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28[a]**	**35**
Informed Consent	X																			
Demographics	X																			
Medical history	X	X																		
Social history	X																			
Eligibility criteria	X	X																		
Minimum admission period	X----------					----------X[b]														
IMP administration[c]			0 h																	
Height	X																			
Body weight	X																		X	X
Malaria signs & symptoms[d]	X	X	2, 4, 8, 12, 16, 20 hpd	24, 30, 36, 42 hpd	48, 54, 60, 66 hpd	72 hpd	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[e]	X	X	2, 4, 8, 12, 16, 20 hpd	24, 30, 36, 42 hpd	48, 54, 60, 66 hpd	72 hpd	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BP, pulse and body temp[f]	X	X	2, 4, 8, 12, 16, 20 hpd	24, 30, 36, 42 hpd	48, 54, 60, 66 hpd	72 hpd	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12 lead ECG[g]	X	X	1, 2, 4, 6, 8 hpd	24 hpd		72 hpd													X	X
Hematology & chemistry	X			24 hpd	48 hpd			X		X		X			X				X	X
Platelet count			12 hpd (Pf only)																	
Pregnancy test[h]	X																			X
Blood film microscopy[i]	X	X	4, 8, 12, 16, 20 hpd	24, 30, 36, 42 hpd	48, 54, 60, 66 hpd	72 hpd	X	X	X	X	X	X	X	X	X	X	X	X	X	
qPCR for parasitemia[j]	X	X	4, 8, 12, 16, 20 hpd	24, 30, 36, 42 hpd	48, 54, 60, 66 hpd	72 hpd	X	X	X	X	X	X	X	X	X	X	X	X	X	
Parasite genotyping[k]		X		24 hpd					X----------										----------X	
PK blood sample[l]		X	0.5, 1, 2, 4, 6, 8, 12, 16 hpd	24 hpd	48 hpd	72 hpd		X		X		X			X				X	X
Pharmacogenetic sample[m]		X																		
Stopping criteria review			X----------																----------X	
G6PD enzyme test[n]			<----------																----------X	
Definitive antimalarial Rx[o]			<----------																----------X	
Concomitant meds	X----------																			----------X
Adverse event			X----------																	----------X
SAE reporting	X----------																			----------X[p]

hpd = hours post-dose; Rx = treatment	
a	Day 28 or day of withdrawal (NB: all evaluations to be done prior to administration of definitive antimalarial therapy).
b	Patients will remain in the CRU until complete microscopic clearance of parasitemia (two consecutive negative samples) but for a minimum of 72 hours post-dose.
c	Patients to remain fasting (except for water permitted *ad libitum*) from 3 hours prior to dosing until 1.5 hours post-dose.
d	During the admission period, malaria signs and symptoms will be assessed at 2, 4, 8, 12, 16, 20 and 24 hours post-dose and every 6 hours thereafter until microscopy is negative for parasitemia on two consecutive occasions or until 72 hours post-dose [whichever is first], and twice daily thereafter until discharge from the CRU.
e	Full physical examination to be performed at screening, Day 28 and Day 35. Brief symptom-directed physical examinations to be performed at all other time points. During the admission period, these will be performed at 2, 4, 8, 12, 16, 20 and 24 hours post-dose and every 6 hours thereafter until microscopy is negative for parasitemia on two consecutive occasions or until 72 hours post-dose [whichever is first], and twice daily thereafter until discharge from the CRU.
f	Vitals signs (BP, pulse and axillary body temperature) will be measured after 5 minutes in the supine position at all time points indicated. During the admission period, assessments will be performed at 2, 4, 8, 12, 16, 20 and 24 hours post-dose and every 6 hours thereafter until microscopy is negative for parasitemia on two consecutive occasions or until 72 hours post-dose [whichever is first], and twice daily thereafter until discharge from the CRU.
g	12-lead ECGs will be performed as scheduled and as clinically indicated. Recordings will be performed after patients have been in the supine position for at least 10 minutes. All recordings will be performed as single recordings, except for the pre-dose recording which will be performed in triplicate. Patients requiring definitive antimalarial therapy prior to Day 28 will have a single ECG recording performed prior to administration of the treatment.
h	For females only, point-of-care pregnancy tests to be performed at screening (whole blood/serum) and Day 35 (urine).
i	Thick and thin blood films will be obtained at screening to confirm eligibility and within 30 minutes prior to dosing for baseline values. After dosing, blood films will be prepared and examined at 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, 66 and 72 hours post-dose, and 6-hourly thereafter if parasitemia is still present until microscopy is negative for parasitemia on two consecutive occasions. Thereafter, thick and thin blood films will then be examined at each visit as indicated in the schedule. Sets of four blood films (2 thick, 1 thin and 1 combined) will be prepared at each time point.
j	EDTA blood samples for qPCR will be taken at screening, pre-dose and 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 54, 60, 66 and 72 hours post-dose, and 6-hourly thereafter if parasitemia is still present until microscopy is negative for parasitemia on two consecutive occasions. Thereafter, qPCR samples will be taken at each visit as indicated in the schedule.
k	Dry blood spot cards for parasite genotyping will be collected pre-dose, 24 hours post-dose and at the time of **first re-appearance of parasites** in the event of recurrence of parasitemia, but only in patients for whom this occurs after Day 7. Separate DBS cards will be collected for genotyping for PCR correction (2 cards containing at least 3 spots each to be collected pre-dose, 24 hours post-dose and upon recurrence) and for genotyping for resistance markers (1 card with at least 3 spots to be collected pre-dose and upon recurrence only).
l	Blood samples (2 mL) for PK analyses will be collected as detailed in the schedule, as well as at 4 hours (±1 hour) post-definitive antimalarial therapy, at the time of failure (if applicable) or in the case of any drug-related SAE.
m	Pharmacogenetic sample to be taken only from patients who consented separately to this.
n	G6PD enzyme test to be performed for *P. vivax* patients only on Day 28, or earlier if patient meets individual stopping criteria.
o	Definitive antimalarial treatment in accordance with local standard of care, to be administered on Day 28, or earlier as required as per individual stopping criteria.
p	Spontaneously-reported SAEs to be collected until 30 days post EOS follow-up visit.

APPENDIX 9: STUDY CONTACT DETAILS

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