Clinical Study Protocol

A randomized, open label, two-part, parallel-group, phase I study to evaluate the pharmacokinetics of Piperaquine oral dispersible Granules Formulation compared to Piperaquine hard Tablets administered as a single dose in fasting condition (Part 1) and of Piperaquine oral dispersible Granules Formulation administered as single dose in various fed states (Part 2) in healthy adult participants.

Study ID	MMV_SMC_22_01
Protocol Version; Date	Version 3.0; 8 November 2023
Study Registration	Intended registries: ClinicalTrials.gov, Tanzania Clinical Trial Register (TzCTR) - imis2.tmda.go.tz/
Sponsor	MMV Medicines for Malaria Venture ICC – Block G, 3rd floor 20 route de Pré-Bois P O Box 1826 1215 Geneva 15, Switzerland
Principal Investigator	Dr Florence Aphida Milando, MD, MPH Ifakara Health Institute (IHI) P.O. Box 74, Bagamoyo, Tanzania Email: fmilando@ihi.or.tz Tel: +255 712 935 292
Investigational Medicinal Product	Piperaquine (PQP)

1 GENERAL INFORMATION

1.1 List of Trial Personnel

Names	Institution	Position
Dr. Florence Aphida Milando,	IHI	Principal Investigator
Dr. Salim Abdulla	IHI	Project Director
Dr. Said Jongo	IHI	IHI Project Clinical Sciences and Medical Operations
Gloria Nyaulingo	IHI	Study Coordinator
Anneth-Mwasi Tumbo	IHI	Laboratory Scientist
Juliether Tiago	IHI	Lead Study Nurse
Beatus Simon Bongole	IHI	Pharmacist
Kamaka Kassimu	IHI	Senior Study Coordinator
Dr. Hussein Mbarak	IHI	Lead Clinician
Dr. Mohamed Ally Rashid	IHI	Study Clinician
Bakari Mwalimu	IHI	Study Clinician
Thabit Athuman	IHI	Site Clinical Data Manager
Ali Ali	IHI	Site Statistician

1.2 List of Facilities and Providers

Central/Local Safety Laboratory	**Laboratory of Ifakara Health Institute (IHI), Tanzania** Bagamoyo Research and Training Centre (BRTC) P.O. Box 74, Bagamoyo
Pharmacovigilance	Prime Vigilance The Surrey Research Park 1 Occam Court, Occam Road, Guilford, Surrey, GU2 7HJ, UK Tel: +44 (0) 1483 307 920 email: MMV@primevigilance.com
Bioanalytical Laboratory	**Swiss BioQuant AG** Kägenstrasse 18 4153 Reinach, Switzerland Tel: +41(0) 617 1698 12 : email: anita.kress@swissbioquant.com
ECG Analyses	**Banook** 84 Avenue du XXème Corps 5400 Nancy, France Tel : 33(0) 3 83 39 10 10 : email: noemie.maignan@banookgroup.com
Project Management, Clinical Monitoring, Data Management, Biostatistics, Medical Writing	**IQVIA** 3 Forbury Place, 23 Forbury Road Reading, RG1 3JH United Kingdom Tel: +447501 617 422 : email: liam.livingstone@iqvia.com
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1.3 Signatures (Sponsor and Investigator)

This clinical trial protocol has been reviewed and approved by the Sponsor.

Sponsor's Medical Director

Signature		
Name	Anne Claire Marrast, MD	Date of Signature (dd.mm.yyyy)
Title	Senior Medical Director	
Institution	Medicines for Malaria Venture ICC – Block G, 3rd floor 20 route de Pré-Bois P O Box 1826 1215 Geneva 15, Switzerland	

Sponsor's Director Clinical Sciences

Signature		
Name	Myriam el Gaaloul, PhD	Date of Signature (dd.mm.yyyy)
Title	Senior Clinical Scientist	
Institution	Medicines for Malaria Venture ICC – Block G, 3rd floor 20 route de Pré-Bois P O Box 1826 1215 Geneva 15, Switzerland	

Principal Investigator's Agreement:

- I have read this protocol MMV_SMC_22_01 "*A randomized, open label, two-part, parallel-group, phase I study to evaluate the pharmacokinetics of Piperaquine oral dispersible Granules Formulation compared to Piperaquine hard Tablets administered as a single dose in fasting condition (Part 1) and of Piperaquine oral dispersible Granules Formulation administered as single dose in various fed states (Part 2) in healthy adult participants.*" and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.
- I will ensure that all individuals and parties contributing to this study are qualified and I will implement procedures to ensure integrity of study tasks and data.
- I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.
- I will use only the informed consent forms approved by the Sponsor or its representative and will fulfil all responsibilities for submitting pertinent information to the Independent Ethics Committees responsible for this study.
- I agree that the Sponsor or its representatives shall have access to any source documents from which Case Report Form information may have been generated.
- I agree to conduct the study in compliance with the current version of the Declaration of Helsinki, ICH-GCP E6(R2) as well as all the national legal and regulatory requirements.

Principal Investigator

Signature		
Name	Dr. Florence Aphida Milando, MD, MPH	Date of Signature (dd/mm/yy)
Title	Principal Investigator	
Institution	Ifakara Health Institute	
Address	P.O. Box 74, Bagamoyo, Tanzania	
Phone	+255 712 935 292	

Site Project Clinical Sciences and Medical Operations

Signature		
Name	Said Abdallah Jongo, MD, MMed (Internal Medicine), PhD	Date of Signature (dd/mm/yy)
Title	IHI Project Clinical Sciences and Medical Operations	
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1.4 Table of contents

1.5 Abbreviations

$\%AUC_{extrap}$	Percentage of AUC that is due to extrapolation from tlast to infinity
ADR	Adverse drug reaction
AR	Adverse reaction
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
AUC_{0-24h}	Area under the plasma concentration curve from time zero to 24 hours
AUC_{0-168}	Area under the plasma concentration curve from time zero to 168 hours
AUC_{0-72}	Area under the plasma concentration curve from time zero to 72 hours
AUC0-∞	Area under the plasma concentration curve from time zero to infinity with extrapolation of the terminal phase
AUC0-t	Area under the plasma concentration curve from time zero to the last quantifiable concentration at time t
BA/FE	Bioavailability/food effect
BCTF	Bagamoyo Clinical Trial Facility
BCTU	Bagamoyo Clinical Trial Unit
BRTC	Bagamoyo Research and Training Center
CL/F	Apparent total plasma clearance
Cmax	Observed maximum plasma concentration
CRF	Case report form
DHA	Dihydroartemisinin
DOT	Directly Observed Treatment
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EMA	European Medicines Agency
FE	Food effect
Frel	Relative bioavailability
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IHI	Ifakara Health Institute
IHI-IRB	Ifakara Health Institute Institutional Review Board
IMP	Investigational medicinal product

IPTi	Intermittent preventative treatment in infants
iPTp	Intermittent preventative treatment in pregnancy
IRB	Institutional Review Board
LLN	Lower limit of normal
LLOQ	Lower Limit of Quantification
LOQ	Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMV	Medicines for Malaria Venture
NatHREC	National Health Research Ethics Sub-Committee
PI	Principal investigator
PIS	Participant Information Sheet
PK	Pharmacokinetics
PQP	Piperaquine phosphate
PT	Prothrombin time
SAE	Serious adverse event
SMC	Seasonal malaria chemoprevention
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
SP	Sulfadoxine-pyrimethamine
SPAQ	Sulfadoxine-pyrimethamine plus amodiaquine
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
T1/2	Elimination half-life
TdP	Torsade de pointes
Tmax	Time to reach Cmax
TMDA	Tanzania Medicines and Medical Devices Authority
TzCTR	Tanzania Clinical Trial Register
TZS	Tanzanian Shilling
ULN	Upper limit of normal
USD	United States Dollar
Vz/F	Apparent volume of distribution during the terminal phase
WBC	White blood cell count
WHO	World Health Organization
WOCBP	Women of child bearing potential
WONCBP	Women of non-child bearing potential
λz	Terminal elimination rate constant

1.6 Synopsis

Sponsor	Medicines for Malaria Venture, Geneva, Switzerland.
Study Title	A randomized, open label, two-part, parallel-group phase I study to evaluate the pharmacokinetics of Piperaquine oral dispersible Granules Formulation compared to Piperaquine hard Tablets administered as a single dose in fasting condition (Part 1) and of Piperaquine oral dispersible Granules Formulation administered as single dose in various fed states (Part 2) in healthy adult participants.
Study ID	MMV_SMC_22_01
Protocol Version; Date	Version 3.0; 8 November 2023
Intended Trial Registration	ClinicalTrials.gov Tanzania Clinical Trial Register (TzCTR) - imis2.tmda.go.tz/
Study Category with Rationale	Investigational Medicinal Product molecule is registered in Tanzania under the classification of Human Medicinal Product in combination with Dihydroartemisinin or Artemisinin in several brand names
Clinical Phase	Phase I
Background and Rationale	Malaria is still a major problem with an estimated 241 million cases of malaria that have occurred worldwide in 2020, with more than 90% occurring in the World Health Organization (WHO) African Region, leading to 627 000 deaths, of which 77% were in children under five years of age. In addition, 34 % (11.6 million) of pregnant women in the moderate to high transmission countries of the WHO African Region, were exposed to malaria infection (1). WHO strongly recommends with high-certainty evidence the following malaria chemo preventive therapies: seasonal malaria chemoprevention (SMC), intermittent preventive treatment in infants (IPTi), and intermittent preventive treatment of malaria in pregnancy (IPTp) (1). Despite the strong public health evidence of chemoprevention, only SP (sulfadoxine-pyrimethamine) and SPAQ (sulfadoxine-pyrimethamine plus amodiaquine) are currently recommended by WHO for chemoprevention, which use is currently threatened by increasing resistance to SP (1, 2). Medicines for Malaria Venture's (MMV) strategy is to re-combine existing and approved antimalarials used in combination with other antimalarials for the treatment of malaria, for the purpose of malaria chemoprevention. As part of this strategy, a review of the potential efficacy and duration of protection, the safety and tolerability, as well as the risk of emergence of resistance of currently approved compounds has been conducted, with a view to identify a new combination of two registered compounds that may be suitable for malaria chemoprevention. Piperaquine phosphate (PQP), as the partner drug for such a new combination, was considered to have potential for this purpose. PQP is currently marketed in a fixed dose combination with the short acting antimalarial dihydroartemisinin (DHA) as Eurartesim® in Europe (4) and as several brands in combination with DHA or

	artemisinin in Tanzania, for treatment of acute uncomplicated malaria. Based on efficacy data provided to support registration for malaria treatment, PQP is a long acting antimalarial, whose extended half-life (about 22 days) confers a protection for one month with the standard 3-day regimen with a protective effect of over 75% (3). It is therefore assumed that a monthly based treatment, for 3 to 4 consecutive months during the malaria season, shall achieve adequate efficacy. Malaria chemoprevention therapies must be highly safe and well tolerated, considering use in otherwise healthy, parasite-free or asymptomatic infants, children, and pregnant women. With no evidence of teratogenic liabilities, PQP is a potential safe option for malaria prevention in pregnant women and women of child-bearing potential (WOCBP) which is a key asset towards malaria eradication. Through their extensive use in many African and South-East Asian countries, the safety and tolerability of PQP for the treatment of uncomplicated malaria when combined to DHA, is well established. Safety data from a European registry have also been recently published for DHA-PQP (4). In healthy adult participants, PQP exposure from the currently approved hard tablet increased approximately 3-fold with high fat/high calorie meals (10). However, no significant impact on PQP exposure was observed with local low-fat meals in South-East Asia (5, 6, 7). For SMC (and other use cases), no food restrictions are ideal, as food intake of young children before and after drug administration varies and cannot be controlled. A new child-friendly, taste-masked dispersible granule formulation of PQP is being developed to increase bioavailability and minimize the food effect. The paediatric formulation for this study has been selected based on *in vitro* dissolution in biorelevant media. The aim of this pilot bioavailability/food effect (BA/FE) study is to evaluate in healthy adults, the PK profile of a PQP dispersible granules formulation when administered with different food restrictions.
Objective(s)	Primary objective: To determine the relative bioavailability of a single oral dose of PQP dispersible granule formulation (Test) as compared to PQP hard tablet formulation (Reference) in the fasted state. Secondary objectives: • To assess the effect of different types of meal composition on the PK of single doses of PQP dispersible granule formulation in healthy adult participants. • To further evaluate the PK of a single oral dose of PQP granule formulation in the fasted state and different fed states in healthy adult participants. • To further document safety/tolerability of PQP in healthy adult participants. Exploratory objectives: • To further document PQP metabolite profiling and PK depending on results of former study (optional objective) as well as the results of genetic testing of CYP450s polymorphism (optional). • To evaluate the palatability of the new PQP granule formulation in healthy adult participants.
Outcome (s)	Relative bioavailability: Using the ratio of the geometric means for the dispersible granules [test] over the hard tablet [reference] in fasted state for $AUC_{0\text{-}72h}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}168h}$, $AUC_{0\text{-}\infty}$, and C_{max}.

	Using the ratio of the geometric means for the dispersible granules between fed [high-fat meal, low-fat African meal, and milk] and fasted for AUC_{0-72h}, AUC_{0-t}, AUC_{0-168h}, $AUC_{0-\infty}$, and C_{max}. Safety: Occurrence of adverse events (AE) including serious adverse events (SAE) from the investigational medicinal product (IMP) administration throughout the entire study period (up to Day 30 after IMP administration).
Study Design	Single centre, randomized, open label, single dose, parallel-group design performed in two sequential parts. A total of sixty (60) healthy adult participants (male and female) will be enrolled in this study (24 subjects in Part 1 and 36 subjects in Part 2). Efforts will be made to ensure a reasonable gender balance.
Inclusion/ Exclusion Criteria	**Inclusion criteria** Participants must fulfil all of the following criteria to be eligible for enrolment in this trial: 1. Female or Male aged ≥18 years to ≤55 years at the date of signing informed consent. 2. Ability to provide written, personally signed, and dated informed consent to participate in the trial, in accordance with the ICH Good Clinical Practice (GCP) and applicable regulations, before any trial-related procedures. 3. An understanding, ability, and willingness to fully comply with trial procedures and restrictions. 4. Female participants must agree to follow contraceptive requirements as indicated in Section 13.2.2, from at least 30 days prior to first dosage to 16 weeks after last dosage. 5. Agrees not to donate sperm or ova from the time of the first administration of trial medication until twelve weeks after the end of the systemic exposure of the trial drug. 6. Participants must have a body weight of 50 kg or greater and a BMI between 18.0 kg/m² - 30.0 kg/m² (inclusive) at screening. 7. Satisfactory medical assessment with no clinically significant or relevant abnormalities as determined by; medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) and clinical laboratory evaluation that is reasonably likely to interfere with the participant's participation in or ability to complete the trial as assessed by the Investigator. **Exclusion criteria** Participants will be excluded from enrolment in this trial if they fulfil any of the criteria below: 1. Prior screen failure or randomisation in this trial. NOTE: Participants who initially failed due to temporary non-medically significant issues are eligible for re-screening once the cause has resolved. 2. Female participant who is pregnant (from history, examination or confirmed by a positive serum pregnancy test at screening and/or on Day -1) or breastfeeding. 3. Male participants with a female partner(s) who is (are) pregnant or lactating at screening and/or on Day -1 or is (are) expected to be during the trial period. 4. Has a mental incapacity or language barriers precluding adequate understanding, co-operation, or compliance with the trial requirements.

	5. Unable or unwilling to follow a standardised diet and meal schedule or unable to fast, as required during the trial. 6. Has milk intolerance. 7. Unable to swallow tablets. 8. Has veins on either arm that are unsuitable for intravenous puncture or cannulation (e.g., veins that are difficult to locate, or a tendency to rupture during puncture). 9. Known or suspected intolerance or hypersensitivity to the investigational products, any closely related compound, or any of the stated ingredients. 10. History of significant allergic reaction (e.g., anaphylaxis, angioedema) to any product (food, pharmaceutical, etc) but excluding untreated, asymptomatic, seasonal allergies. 11. Donated blood or blood products (excluding plasma) within 90 days prior to trial medication administration. 12. Has received or plans to receive a COVID-19 vaccination within two weeks before to one week after trial last visit. 13. Treated with medication containing PQP within 90 days or five half-lives preceding the dose of trial medication (whichever is the longer). 14. Ingested herbal remedies or dietary supplements containing St. John's Wort in the 30 days before the planned Day 1 of the dosing Part. 15. Taking medicinal products that are known to prolong the QTc interval (see http://www.crediblemeds.org/). An up-to-date list will be in the study specific manual. 16. Use of any medication that is either a moderate or strong inhibitor or inducer of CYP3A4 within 30 days or five half-lives (whichever is longer) prior to the planned day of dosing (see Drug Development and Drug Interactions, Table of Substrates, Inhibitors and Inducers, FDA). Anup to date list will be in the study specific manual. 17. Use of any other prescription medication (excluding hormonal contraception and hormone replacement therapy) within 14 days or ten half-lives (whichever is longer) prior to Day 1 of the dosing Part that the Investigator judges is likely to interfere with the trial or pose an additional risk in participating. 18. Use of any over-the-counter medication (including multivitamin, herbal, or homeopathic preparations; excluding paracetamol - up to 3 g of paracetamol per day permitted while participants are in-house, whereas while participants are outpatients a maximum of 1 g paracetamol per day will be allowed) during the seven days or ten half-lives of the drug (whichever is longer) prior to Day 1 of the dosing Part, that the Investigator judges is likely to interfere with the trial or pose an additional risk in participating. 19. Ingested any poppy seeds within the 24 hours prior to screening or admission. 20. Current use of tobacco in any form (e.g., smoking or chewing) or other nicotine-containing products in any form (e.g., gum, patch, electronic cigarettes). 21. History or clinical evidence of substance and/or alcohol abuse within the two years before screening. Alcohol abuse is defined as regular weekly intake of more than 14 units (for both males and females). 22. Participants must have not consumed other substances known to be potent inhibitors or inducers of CYP34A system such as grapefruit or cranberry juice-containing products in the 30 days before the planned IMP administration.

23. Any history of seizures, epilepsy, photosensitivity or documented retinopathy.
24. The history or presence of any of the following cardiac conditions known structural cardiac abnormalities; family history of long QT syndrome; cardiac syncope or recurrent, idiopathic syncope; exercise related clinically significant cardiac events.
25. Has vital signs consistently outside of the normal range at screening or Day-1.
26. Any clinically significant abnormalities in rhythm, conduction or morphology of resting ECG or clinically important abnormalities that may interfere with the interpretation of QTc interval changes. This includes participants with any of the following (at screening or Day -1):
    - sinus node dysfunction
    - clinically significant PR (PQ) interval prolongation (>220ms)
    - second- or third-degree atrioventricular (AV) block
    - sustained cardiac arrhythmia's including (but not limited to) atrial fibrillation or supraventricular tachycardia, or any symptomatic arrhythmia, with the exception of isolated extra-systoles.
    - abnormal T-wave morphology which may impact on the QT/QTc assessment.
    - QT interval corrected using the Fridericia's formula (QtcF) >450 ms
    - any other ECG abnormalities in the standard 12-lead ECG or an equivalent assessment which in the opinion of the Investigator will interfere with the ECG analysis
    - Participants with borderline abnormalities may be included if the deviations do not pose a safety risk, and if agreed between the appointed cardiologist and the PI.
27. Positive test results for alcohol or drugs of abuse at screening or Day -1.
28. Electrolyte imbalances, particularly results that are out of reference intervals for potassium, calcium or magnesium.
29. Has a positive test for Hepatitis B surface Antigen (HBsAg), Hepatitis C Antibody (HCV Ab), or Human Immunodeficiency Virus Antibody (HIV Ab) at screening.
30. Presence of malaria parasites by blood smear.
31. Has total bilirubin, ALT or AST consistently >upper limit of normal (ULN) at screening (up to two repeats may be taken during the screening period; participants may be included if two out of the three total results are ≤ULN) or has total bilirubin >ULN on Day -1 (mild variations from baseline may be allowed if considered not clinically significant by the Investigator).
32. Has a haemoglobin, platelet count, total white blood cell count, lymphocyte or monocyte count < lower limit of normal (LLN) (up to two repeats may be taken during the screening period and on Day -1 (participants may be included if two out of the three total results are greater or equal to LLN), at screening. Where there is a clear diurnal effect on the result participants may be included if variations are considered not clinically relevant by the Investigator.
33. Current or recurrent disease (e.g., cardiovascular, haematological, neurological, endocrine, immunological, renal, hepatic or gastrointestinal or other conditions, including cholecystectomy or gastrectomy) that could affect the action, absorption, distribution, metabolism or excretion of PQP or could affect clinical assessments or clinical laboratory evaluations.
34. Current or relevant history of physical or psychiatric illness that are not stable or may require a change in treatment, or use of prohibited therapies during the trial,

	that make the participant unlikely to fully comply with the requirements of the trial or to complete the trial, or any condition that presents undue risk from the investigational product or trial procedures. 35. Any other abnormal findings on vital signs, ECG, physical examination or laboratory assessments that the Investigator judges as likely to interfere with the trial or pose an additional risk in participating. 36. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participant at risk because of participation in the trial, or may influence the result of the trial or the participant's ability to participate in the trial. 37. Any conditions which in the opinion of the Investigator would make the participant unsuitable for enrolment or could interfere with the participation in or completion of the trial.
Measurements and Procedures	Participants will be screened within a window of ≤ 45 days prior to in-house admission on Day -1 where preliminary assessments will be performed and fasting initiated. Study drug administration will be performed on the following day (Day 1) under fasted (Part 1) or fed (Part 2) conditions. After 10 hours of fasting have elapsed: For administration under fasted conditions: PQP tablet / dispersible granules will be immediately administered to study participants orally. For administration under fed conditions: The study participant will start the randomly allocated meal 30 minutes before administration of the drug product and should consume the entire meal in 30 minutes or less. Thereafter, investigators will immediately administer PQP dispersible granules to study participants orally. Additional water will be permitted ad lib except for the period 1 hour before until 1 hour after administration of the drug product. Participants shall not consume any food for at least 4 hours after the dose. Thereafter, standardized meals scheduled at the same time reflecting breakfast, lunch or dinner will be provided throughout the in-house period. Scheduled safety assessments e.g., vital signs and ECGs, and PK sample collections will continue till discharge on Day 3 (a total 4 in-house days). Participants will attend the trial unit clinic for outpatient visits on Days 8, 15, 22 and 30.
Test Product	PQP dispersible granules 320 mg dose equivalent dispersed in 25 ml of water; single dose (320 mg) given orally.
Comparator	Reference therapy: PQP hard tablet 320 mg; single dose (320 mg) given orally with 240 ml of water.
Number of Participants	This is a pilot BA/FE study, and the sample-size is not based on formal statistical considerations. The number assigned to each treatment Group (n=12) is considered adequate to characterise the PK of the prototype formulation of PQP in various study conditions.
Study Duration	4 to 6 Months.
Study Schedule	First Participant In (JULY-2023); estimated Last- Participant Out (DECEMBER-2023)
Study Centre	Single-centre: Bagamoyo Clinical Trials Unit, IHI – BRTC.

Statistical Considerations	This pilot Phase 1 trial is not designed to test specific hypotheses. The trial is intended to determine the PK parameters of the prototype formulation dispersion granules of PQP in fasting state (Part 1) and to provide a preliminary assessment of the effect of various fed states (Part 2) on the systemic exposure of PQP. The Safety analysis set will consist of all randomised participants who received the study product. The PK analysis set will consist of those participants in the safety set who have sufficient blood samples taken for at least one of the PK variables to be calculated. The statistical methods and reporting will follow ICH E9 and international recommendations, including CONSORT. A statistical analysis plan (SAP) containing detailed statistical methodology will be written and signed off before the database hard lock. The plan may be updated to reflect adaptive features of the trial as appropriate.
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, ICH-GCP E6(R2) as well as all Tanzanian legal and regulatory requirements as stipulated by NaTHREC and TMDA.

2 BACKGROUND INFORMATION

In 2020, an estimated 241 million cases of malaria occurred worldwide, with more than 90% occurring in WHO African Region, leading to 627 000 deaths, of which 77% were in children under five years of age. In addition, there were an estimated 33.8 million pregnancies in the moderate to high transmission countries of the WHO African Region, of which 34 % (11.6 million) were exposed to malaria infection during pregnancy (8).

Despite the strong public health evidence of chemoprevention, only sulfadoxine-pyrimethamine (SP) and sulfadoxine-pyrimethamine plus amodiaquine (SPAQ) are currently recommended by WHO for chemoprevention, which use is currently threatened by increasing resistance to SP (2, 3). MMV's strategy is to re-combine existing and approved antimalarials used in combination with other antimalarials for the treatment of malaria, for the purpose of malaria chemoprevention. As part of this strategy, a review of the potential efficacy and duration of protection, the safety and tolerability, as well as the risk of emergence of resistance of currently approved compounds has been conducted, with a view to identify a new combination of two registered compounds that may be suitable for malaria chemoprevention.

Piperaquine (PQP), as the partner drug for such a new combination, was considered to have potential for this purpose. PQP is currently marketed in a fixed dose combination with the short acting antimalarial dihydroartemisinin (DHA) as Eurartesim® in Europe and is registered in Tanzania in several brand names as fixed dose combination with dihydroartemisinin (DHA) or Artemisinin, for treatment of acute uncomplicated malaria. The efficacy of PQP combined to the artemisinin derivatives has been demonstrated in the treatment of uncomplicated malaria in various clinical trials in different regions and has been in clinical use for at least 40 years and was approved by the European Medicine Agency in 2011.

PQP is a long acting antimalarial, whose extended half-life (about 22 days) confers a protection for one month with the standard 3-day regimen. Additionally, DHA-PQP was associated with a protective effect of over 75% (3). It is therefore assumed that a monthly based treatment with PQP (for 3 to 4 consecutive months during the malaria season) should achieve adequate chemoprevention efficacy.

In healthy adult participants, PQP exposure from the currently approved hard tablet increased approx. 3-fold with high fat/high calorie meal (European Medicine Agency). However, no significant impact on PQP exposure was observed with local low-fat meal in South-East Asia (6, 7, 8). For seasonal malaria chemoprevention (SMC) (and other use cases), no food restrictions are ideal, as food intake of young children before and after drug administration varies and cannot be controlled. A new child-friendly, taste-masked dispersible granule formulation of PQP is being developed to increase bioavailability and minimize the food effect. The paediatric formulation for this study has been selected based on *in vitro* dissolution in biorelevant media.

The aim of this pilot bioavailability/food effect (BA/FE) study will be to evaluate in healthy adults and after single dose, the pharmacokinetic (PK) profile of a PQP oral granules prototype as compared to the hard tablet formulation when administered in fasting conditions (Part 1) and then in Part 2 to evaluate the effect of different food conditions on the PK profile of PQP after administration of the PQP oral granules prototype formulation.

2.1 Introduction

Case management with highly effective antimalarial drugs has contributed to a decrease in malaria morbidity and mortality. However, preventive administration of antimalarial drugs is also recommended for use in selected high-risk populations, irrespective of malaria infection status, both to treat any unrecognized Plasmodium infections and to prevent new ones. These preventive treatments prevent

or cure undetected malarial illness with the goal to achieve therapeutic drug levels in the blood throughout the period of greatest risk (9). WHO strongly recommends with high-certainty evidence the following malaria chemo preventive therapies: SMC, intermittent preventive treatment in infants (IPTi), and intermittent preventive treatment in pregnancy (IPTp)(1).

Since malaria chemoprevention is administered to otherwise healthy infants, children, and pregnant women (who are either parasite-free or have circulating parasites but are asymptomatic), treatments must be highly safe and well tolerated. PQP has not shown any teratogenic liabilities and is therefore expected to be a potential safe option for malaria prevention in pregnant women and women of child-bearing potential (WOCBP) which is a key asset towards malaria eradication.

Sulfadoxine-pyrimethamine (SP) is recommended for IPTp along with the antenatal care visits starting from the second trimester of pregnancy and IPTi along with infant vaccination taking place usually at 10 weeks, 14 weeks and 9 months of age. Sulfadoxine-pyrimethamine plus amodiaquine (SPAQ) is recommended for SMC as a monthly administration during the malaria season for three to four consecutive months to children between three months and five years of age in areas of highly seasonal malaria transmission (1). In this context, SPAQ demonstrated a protective efficacy of >80 % in Burkina Faso (4).

2.1.1 General treatment / Administration

PQP exposure from the currently approved hard tablet in healthy adult participants, increased approximately 3-fold with high fat/high calorie meals (European Medicine Agency). However, no significant impact on PQP exposure was observed with local low-fat meals in South-East Asia (6, 7, 8). The present new child-friendly, taste-masked dispersible granule formulation of PQP is being developed to increase bioavailability and minimize the food effect. For SMC (and other use cases), no food restrictions are ideal, as food intake of young children before and after drug administration varies and cannot be controlled. In the present study, the PK profile of a PQP oral dispersible granules (the paediatric formulation prototype) will be evaluated relative to the PQP hard tablet formulation in fasting conditions (Part 1), and when administered with different food restrictions (Part 2) to assess BA/FE, in healthy adults.

2.1.2 Efficacy

Not applicable for the present BA/FE trial.

2.1.3 Mechanism of action, clearance and pharmacokinetics

PQP’s mechanism of action is unknown, but it likely mirrors that of chloroquine, a close structural analogue. Chloroquine binds to toxic haem (derived from the patient’s haemoglobin) within the malaria parasite, preventing its detoxification via a polymerisation step (10) PQP is a highly lipophilic compound, is highly bound to proteins (>99%) and tends to accumulate in red blood cells. In humans, PQP has a Tmax of approximately five hours after hard tablet administration. PQP is mainly metabolized by CYP3A4 and to a lesser extent by CYP2C9 and CYP2C19. PQP is also a CYP3A4 inhibitor, and a clinical study of Eurartesim® with midazolam showed a modest increase in the exposure of midazolam (<two-fold)(10). The terminal elimination half-life of PQP is around 22 days for adult patients.

2.1.4 Safety and tolerability

Through their extensive use in many African and South-East Asian countries, the safety and tolerability of PQP for the treatment of uncomplicated malaria when combined to DHA, is well established. Safety data from a European registry have also been recently published for DHA-PQP (5).

PQP as a combination antimalarial with DHA is well tolerated in both adults and children, with the main AEs reported being gastrointestinal disturbances such as nausea/vomiting, abdominal pain and diarrhoea (9, 10).

2.1.5 Safety profile and potential risks

Although transient asymptomatic alanine aminotransferase/aspartate aminotransferase (ALT/AST) elevations have been described, including in Phase 1 participants, these are generally mild in severity and considered as uncommon. PQP is known to induce QTc prolongation in human participants (11, 12). The following aspects of the PK and adverse event (AE) profiles of PQP, were considered in determining the Inclusion and Exclusion criteria and in designing the tolerability and safety monitoring of this study:

- PQP is known to cause a QTc interval prolongation, and this effect is concentration-related,
- PQP has a terminal elimination half-life of approximately 22 days, however, approximately 1% of the plasmatic Cmax is predicted at 672 hours (i.e. 28 days) after the administration of 1280 mg in healthy adults (13). Therefore, a follow-up of 30 days is considered acceptable to ensure that possible delayed effects on safety laboratory tests are appropriately documented.

As precautionary measures pertaining to QTc effects of PQP, the European Medicines Agency (EMA) has advised that:

- DHA-PQP (Eurartesim®), not be administered with a meal to avoid food-induced increase in PQP Cmax and consequently possible clinically relevant QTc prolongation,
- Baseline and post-dose electrocardiograms (ECGs) be obtained,
- Recent exposure to concomitant drugs known to induce QTc prolongation be avoided (10,14).

Therefore, during this study, healthy participants with risk factors for QTc prolongation will be excluded and enrolled participants will be monitored for QTc effects through ECG recording.

Clinical monitoring will include periodic biochemistry and haematology measurements as well as regular physical examination and AE recording.

Participants will remain in the Unit under medical supervision until 48 hours following the investigational medicinal product (IMP) administration and will be followed up to Day 30 (+/-1 day).

Despite significant human Ether-a-go-go Related Gene (hERG) blockade with PQP and a mean prolongation of 15-20 msec (fasting state) demonstrated in multiple Phase 1 studies, a meta-analysis has recently concluded that patients treated with the registered three-day regimen of DHA-PQP are not at higher risk of torsades de pointes (TdP), ventricular tachycardia or other arrhythmias when compared with the normal population (14). Based on these observations, although inducing a QTc prolongation that exceeds the ICH/FDA regulatory threshold of 10 msec, PQP is currently not considered as a torsadogenic drug provided it is taken in a fasted state and other clinical risk factors for QTc prolongation (including electrolyte imbalance and/or concomitant medications) are appropriately controlled (15). Healthy volunteers with long QTc are also excluded from clinical trials.

2.2 Justification for the dosage and dosage plan

This is a single-dose study and is considered sufficient to provide early assessment of the bioavailability of the PQP dispersible granules formulation (fasted) relative to the PQP hard tablet formulation (fasted) and understand the impact of food intake on the dispersible granules formulation. The rationale for the selected dose includes:

- As the new formulation is intended to have an increased bioavailability, a lower dose of 320 mg for the PQP dispersible granules formulation (test) has been selected. For comparison purpose, the

same dose level of 320 mg PQP has been selected for the hard tablet (reference); both administered in fasting conditions (Part 1). This compares to the approved daily dose of 960 mg PQP in tablet of Eurartesim® administered over 3 days in adult subjects dosed in fasting conditions.

- In the second study part, and based on the PK results of Part 1, it is intended to administer the same dose level of 320 mg PQP dispersible granules concomitant with different fed conditions. However, if from Part 1 of the study it is shown that PQP dispersible granules formulation provides a significant improvement in C_{max} values in the fasted state, this dose level may be adjusted for Part 2, in order to take into account a potential 3-fold increase in exposure which is the observed food effect when film-coated tablets (Eurartesim®) are administered with a high fat/high calorie meal. Such dose adjustment will be based on the safety and preliminary PK interim results of the granule formulation in the fasted state. The PQP dose selected in Part 2 (as dispersible granules formulation) will take into account a 3-fold factor increase in exposure when administered with food (see above) with such predicted exposure in the presence of food being not higher than after the administration of 960 mg PQP in tablet of Eurartesim® in adult subjects dosed in fasting conditions. Furthermore, sufficient data will be available to address key questions on both, safety and PK parameters to enable the review and recommendation by the SRC for the optimal dose of the granule formulation to be administered in Part 2.

3 OBJECTIVES AND PURPOSE

The present pilot BA/FE study aims to assess the relative bioavailability and food effect on the systemic exposure of a new child-friendly, taste-masked dispersible granule formulation of PQP among healthy adults. In addition, PK and safety profiles will be further evaluated and documented.

3.1 Study rationale and objectives

3.1.1 Study rationale

The present new child-friendly, taste-masked dispersible granule formulation of PQP is being developed to increase bioavailability and minimize the impact of food on PK exposure and consequently QTc effects. In healthy adult participants, the currently approved hard tablet had an approximately 3-fold increase in PQP exposure when administered with a high fat/high calorie meal (10). However, a local low-fat meal in South-East Asia had no significant impact on PQP exposure (6, 7, 8).

In the present study performed in healthy subjects, the PK profile of a PQP oral dispersible granules formulation (the paediatric formulation prototype) will be compared to the PQP hard tablet formulation in fasting conditions (Part 1), and when administered in different fed states (Part 2) to assess the BA/FE. This assessment is important since for SMC (and other use cases), food restrictions for treatment with oral PQP are not ideal, as food intake of young children before and after drug administration varies and cannot be controlled.

This study will establish whether the BA of the child-friendly dispersible granules formulation of PQP is improved in comparison to PQP hard tablet in fasting conditions and will inform dose selection of the granule formulation.

The study will also determine whether there is an effect of food on the exposure of PQP from the child-friendly dispersible granule formulation, and whether the magnitude of the food effect is similar, or decreased compared to the PQP hard tablet:

- Studies with a high fat meal are required by Regulators to determine the “worst case food effect”. In addition, as recognized by regulators (FDA): when drug administration with a high-fat meal causes unacceptable toxicity or a loss of drug efficacy, a low-fat meal can have less or no impact on systemic exposures, improve patient compliance, and alleviate localized gastric irritation. In these circumstances, and assuming that no clinically relevant safety impact is expected, administration of the drug with a low-fat meal may be more advantageous to patients.
- Given the low-fat content of standard meals within endemic regions, the food effect in African and Asian patients and in particular children in areas of SMC will likely be decreased.

3.1.2 Primary objective

- To determine the relative bioavailability of a single oral dose of PQP dispersible granule formulation (Test) as compared to PQP hard tablet formulation (Reference) in the fasted state.

3.1.3 Secondary objectives

- To assess the effect of different types of meal composition on the PK of single doses of PQP dispersible granule formulation in healthy adult participants.
- To further evaluate the PK of a single oral dose of PQP granule formulation in the fasted state and different fed states in healthy adult participants.

- To further document safety/tolerability of PQP in healthy adult participants.

3.1.4 Exploratory objectives

- To further document PQP metabolite profiling and PK depending on results of former study (optional objective) as well as the results of genetic testing of CYP450s polymorphism (optional).
- To evaluate the palatability of the new PQP granule formulation in healthy adult participants.

3.2 Scientific justification and rationale of study population

This study includes male and female participants aged 18 to 55 years at the date of signing informed consent who are residing within and surrounding areas of Bagamoyo town. Both genders will be enrolled to generate data on both sexes. Data from this trial will support development of a new piperaquine formulation with a reduced impact of food which will be more practical for paediatric population.

4 STUDY DESIGN

This is a randomized, open label, parallel-design study to evaluate the PK profile and relative bioavailability of single dose of a PQP oral granule formulation dispersed in water (test) as compared to the PQP hard tablet formulation (reference) in fasting conditions (Part 1) and to assess the BA/FE of the PQP dispersible granules formulation when administered with different food restrictions (Part 2) among African participants residing in Tanzania, in Bagamoyo Town and surrounding areas. A total of sixty (60) healthy adult participants (male and female) will be enrolled in Part 1 and Part 2.

- **Part 1**: PQP tablet / dispersible granule administered in **fasting condition** of at least 10 hours
    - Group 1: PQP hard tablet, 320 mg (N=12)
    - Group 2: PQP dispersible granule, 320 mg (N=12)
- **Transition to Part 2:**
    - To minimize the risk to healthy participants, a decision on transitioning from Part 1 to Part 2, will be taken by the Safety Review Committee (SRC) see Section 13.7, based on the safety and preliminary PK interim report of the granule formulation, compared to the PQP hard tablet, with safety data obtained up to Day 15 and PK data obtained up to Day 8. If necessary, doses may be readjusted for the Part 2 in order to assess the food effect. Description for the rationale and oversight related to the potential for dose adjustment is provided in Section 2.2.
- **Part 2**: PQP dispersible granule administered in **fed conditions (planned as 320 mg)**
    - Group 3: High-fat meal (N=12)
    - Group 4: Low-fat meal representative of African diet (N=12)
    - Group 5: Whole milk 250 ml (N=12)

In summary: Participants will be screened within a window of ≤ 45 days prior to in-house admission on Day -1. Each participant will be admitted to the trial unit on Day -1, and after a new eligibility check, will receive a single dose of PQP on Day 1 and will be discharged on Day 3 (a total 4 in-house days). Participants will attend the trial unit clinic for outpatient visits on Days 8, 15, 22 and 30. Details of procedures and parameters to be assessed at each study time points are outlined in Section 7 (Study Assessments and Visits) and summarized in Section 4.4 (Schedule of events).

4.1 Primary and secondary endpoint

4.1.1 Primary endpoint

- Relative bioavailability (Frel) using the ratio of the geometric means for the dispersible granule (test) over the hard tablet (reference) in fasted state for area under the plasma concentration-time curve from time zero to 72 hours (AUC0-72h), area under the plasma concentration-time curve from time zero to last detectable plasma concentration (AUC0-t), area under the plasma concentration-time curve from time zero to 168 hours (AUC0-168h), area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC0-∞, and Maximum plasma concentration (Cmax)(see Section 10 for further details).

4.1.2 Secondary endpoints

- PK parameters for the hard tablet (fasted) and the dispersible granule formulations (fasted and fed); Cmax, AUC0-24h, AUC0-72h, AUC0-t, AUC0-168h, AUC0-∞, time to maximum plasma concentration (Tmax), terminal elimination rate constant (λz), terminal elimination half-life (t1/2), apparent volume of distribution during the terminal phase (Vz/F), apparent total plasma clearance

(Cl/F), and percentage of AUC that is due to extrapolation from tlast to infinity (%AUCextrap) (see Section 10 for further details).

- Occurrence of AEs including serious adverse events (SAEs) from the IMP administration throughout the entire study period (up to Day 30).
- Findings at different time points from:
    - Physical examination, vital signs, clinical laboratory safety parameters, 12-lead ECG parameters. See Section 8 for specific parameters and time points.

4.2 Measures to minimize bias

4.2.1 Randomization

Healthy adult participants (male and female) will be randomly allocated to one of the 5 following treatment groups, dosing will be carried out in the fasted or fed state:

- During the study part 1, participants for fasted conditions will be randomly allocated to either group 1 (n=12) or group 2 (n=12), in order to assess the relative bioavailability of the dispersible granules formulation as compared to hard table formulation.
    - Randomization will occur in blocks of 2 (each block contains 1 assignment from each of the groups 1 and 2). Dosing under fasting conditions is detailed in Section 6.2.1.
- During the study part 2, participants for fed conditions will be randomly allocated to either group 3 (n=12), 4 (n=12) or 5 (n=12), in order to assess the food effect after dosing of PQP dispersible granules formulation.
    - Randomization will occur in blocks of 3 (each block contains 1 assignment from each of the groups 3, 4 and 5). Dosing under fed conditions is detailed in Section 6.2.2.

A computer-generated randomization schedule (produced by IQVIA) will be used and will be accessible only to the site delegated study staff who will prepare the treatment for each participant according to the randomization allocation. Specific instructions will be detailed in the relevant site manual.

4.2.2 Blinding

The trial will be open-label i.e., participant, investigator and sponsor will be unblinded to treatment and meal conditions assignation. Therefore, after treatment allocation by the site pharmacist according to the randomisation schedule, the study investigators will be provided with the explicit details related to the treatment (Part 1) or feeding conditions (Part 2).

4.3 Study duration and duration of participant's participation

Post administration duration of the study will be 30 days, plus the screening period of 7 to 45 days.

It is estimated that the clinical portion of the study will be completed in approximately 4-6 months.

4.4 Schedule of events

Procedures* and Assessments		SCREENING		IN-HOUSE (IP ADMINISTRATION & FOLLOWUP)															CLINIC FOLLOW-UP				
		A	B	D (-1) to D3															D5 to D30				
		D (-45 to -2)	D (-15 to -2)	Admission	Pre-Dose (h) Fasting 10 hrs 9.5	Pre-Dose (h) Fasting 10 hrs 0.5	IMP (-0.5)	Dose 0h	Post Dose; Hour (h) ± Minutes (m) ±7m* 1h	2h	3h	4h	5h	6h	7h	8h	12h	±10m* 24h	48h	Days(D) ± 1 Day D5	D8	D 15	D 22	D 30
Fasting Condition PART 1 (Groups 1 & 2)	Fasting (⇔)				⇔	⇔	NA	IMP	⇔	⇔	⇔	⇔												
Fed Conditions PART 2 (Groups 3, 4 & 5)	Fasting (⇔) & Fed				⇔	⇔	Fed	IMP	⇔	⇔	⇔	⇔												
INFORMED CONSENT		x^{o}																					
DEMOGRAPHIC		x																					
VITAL signs		x		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight & Height (x)/ Weight Only (w)		x		w																				
HISTORY: Medical, Prior medication, Drug & Alcohol abuse, Smoking		x																						
HISTORY: Updates check			X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PHYSICAL EXAMINATION	Full	x																						
	Symptom Directed		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Palatability Questionnaire								X^{c}																
12-Lead ECG Triplicate **(T)** or Single **(S)**			S	T		T				T		T	T	T		S	S	S	S	S	S	S	S	S
CONTRACEPTION		x**																						
ELIGIBILITY CHECK / REVIEW		X	X	X		X																		
RANDOMIZATION						X																		
AE /SAE Recording (Continuous)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments; [Numbers] = Blood volume (mL)																								
Biochemistry: **Panel 1** ALT, AST, T.bil, K^{+}, Ca^{2+}, Mg^{2+}, Na^{+}, Cl^{-}, $HCO3^{-}$, Creat, T.Pr, Alb			[2]																[2]			[2]		[2]
Biochemistry: **Panel 2** ALT, AST, T.bil, K^{+}, Ca^{2+}, Mg^{2+}				[2]															[2]					
Haematology (HB, PLT, WBC, Neu, Eos, Lym)			[1]																			[1]		[1]
Coagulation (PT, aPTT)			[3]																					
TBS for Malaria parasitology			[1]																					[1]
Serology (HIV 1 & 2, Hepatitis B & C)		[1]																						
Urinalysis			X	X																				
Urine for drugs of abuse			X	X																				
Breath test for Alcohol			X	X																				
Serum pregnancy test (WOCBP)		[1]		[1]																				[1]
FSH (post-menopausal females)		[1]																						
CYP genetic polymorphism sampling				[10]																				
PK sampling (PQP & Metabolite)						[2]			[2]	[2]	[2]	[2]	[2]	[2]	[2]	[2]	[2]	[2]	[2]	[2]	[2]	[2]	[2]	[2]
BLOOD VOLUME per Participant (ml)	PER VISIT	**3**	**7**	**13**		**2**			**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**4**	**2**	**2**	**5**	**2**	**7**
	Total for ALL scheduled study visits: **67**																							

Abbreviations:

D: Day (where Day 1 is the first day that IMPs are administered)
TBS: Thick Blood Smear
FSH: Follicular Stimulating Hormone

LABELS at Screening Period:

* Procedures must be completed within specified window (±), with ECG and vitals performed prior to blood sampling
** Contraception must be started for at least 30 days prior to dosing
x^{o} Written informed consent must be obtained prior to any study procedures.
x^{A} procedures must be repeated if performed >45 days prior to D1
x^{B} procedures must be repeated if performed >15 days prior to D1
X^{c} questionnaire to be completed within 10 minutes of IMP dosing
[#] Blood volume in mL

Note: COVID-19 tests will be carried out at regular intervals, prior to entry in the unit and throughout the residential period as per the latest COVID-19 Infection Control Guidelines and pre-entry algorithms

4.5 Safety hold and early termination of the study

If either of the following pausing criteria are met, trial activities will be put on temporary hold and the SRC chair will be consulted in order to perform thorough evaluation:

- Severe non-serious adverse reactions considered as, at least, possibly related to the IMP administration in two subjects in the same part, independent of within or not within the same system-organ-class.
- One participant experiences an SAE deemed related to study product administration.

If either of these two criteria is met by participants who received either of the study PQP products, the principal investigator (PI) will inform the sponsor for initiation of a temporary hold. After confirmation of the temporary hold, the Sponsor will request an ad hoc meeting of the SRC to review the event(s) and any associated safety data. Following the SRC review and recommendation, a decision will be made by the PI and the Sponsor to either trigger a longer-term safety hold, terminate the study, or resume administration of investigational product. The Institutional Review Boards (IRBs), ethical committee and regulatory authority will be promptly informed of this event, recommendations and decisions.

Irrespective of the temporary hold criteria, the Sponsor, PI or applicable ethical committees or regulatory agencies may decide to put the study on hold based on any other constellation of AEs, or based on any other legitimate reason, such as:

- Ethical concerns
- Safety issues with the study drug
- When the safety of the participants is doubtful or at risk
- Inaccurate or incomplete data
- Administrative decision
- Unforeseen events such as endemic/pandemic

If a safety-hold or study termination is deemed necessary, the applicable ethical committees and regulatory agencies will be notified. For a safety hold to be lifted, there must be a written concurrence by the entity or entities that initiated the hold that the study can resume.

5 SELECTION OF THE STUDY PARTICIPANTS

5.1 Study setting

The study will be conducted at the Bagamoyo Clinical Trial Facility (BCTF) in Bagamoyo, Tanzania where screening, enrolment and follow up of healthy participants will be done. BCTF is part of the Bagamoyo Research and Training Center (BRTC) located on the outskirts of Bagamoyo and therefore has access to the institutional research clinical laboratory with adequate facilities for the conduct of safety and several other assessments. Furthermore, during the study, the site will be equipped with an adequate number of 12-lead ECG machines to record digitalized cardiac parameters, which will be performed and reviewed in real-time by the delegated, experienced study clinician and subsequently transmitted for further assessment centrally by an ECG vendor. The team has several years of experience in the conduct of clinical trials from phase I to IV. The Investigators team have been trained on Protecting Human Research Participants. In addition, the site team has been trained on the principles of ICH-GCP. Regular advanced life support trainings (including certificates) are conducted on site by the emergency unit from Muhimbili National Hospital. The site has a well-equipped emergency care unit for handling medical emergencies and stabilization of participants with the on-call emergency response clinical team whenever there are participants in the facility. The team is trained and certified by the emergency department experts from the Muhimbili National Hospital. There is a standby ambulance for transporting participants, once stabilized, for further intensive care and management under the escort of the emergency response team on-call. The nearest emergency support service department is available within 5 minutes, with intensive care service department available within 30 minutes. The site is supported by the institutional quality assurance team. In addition, the Ifakara Health Institute (IHI) has put a COVID-19 response plan in place containing corresponding precaution measurements that are also implemented at the site.

5.2 Recruitment

This study is planned to be conducted in healthy adult participants (male and female, including WOCBP). The expected population is to be enrolled from the study centre catchment area among the residents of Bagamoyo town and surrounding areas of Bagamoyo district. Initial work in the community will only commence after all approvals have been received from the relevant ethics committees and regulatory authority. Local authorities will be informed about the study in order to approach the community. Locally applicable methods of advertisement will be used to disseminate the study advertisement, including flyers and announcements via speakers. Targeted and potential community members will be invited to attend community sensitization meetings which will be conducted at designated community areas and may also involve ward leaders, community health workers as well as key opinion leaders in the community. To ensure adequate delivery of the information, meetings will primarily be conducted in Swahili.

At the community sensitization meetings, Investigators will explain the current burden of malaria in particular among infants and children living in malaria endemic areas. The need for age-relevant formulation for malaria treatment and possible prophylaxis will be discussed in a culturally appropriate manner. Investigators will also explain the concept of the clinical trial and the community members will be made aware of the potential risks and unproven benefits of the investigational product to be used in this trial. The outline of the proposed trial including the rationale, aims and study procedures such as consenting, screening, the need for the use of contraception, randomization, inhouse observation and follow-up process will be shared. It will also be made clear that the study will require screening for malaria and other chronic conditions such as HIV and hepatitis. It will be made clear that screening processes will include a range of criteria to be checked covering clinical status as well as ability to comply with protocol, ethical and regulatory requirements. Moreover, it will be explained that exclusion

from participating in the trial does not mean the potential participant is unhealthy and that, the confidentiality of all this information will be protected. Opportunity will be provided for the community members to ask questions and get responses from the Investigators. Potentially interested participants will be asked to provide details that will enable the study team to generate list of potential participants who will be invited to the clinic-based sensitization meeting at BCTF. During the clinic sensitization meetings, Investigators will provide further details in the participant information sheet on the mechanism of the study product, risks, benefits and procedures such as blood sampling, in-patient stay, follow up visits and the need of efficient contraception. Study team members will discuss the existing understanding of the participants with regards to the study and will share more detailed information and clarify any questions in Swahili. At the same occasion they will confirm that the participants are able to read and write (to ensure adequate informed consent for participants). Those interested and considered as potential participants for screening will be provided with the participant information sheet to read at home and for opportunity to discuss with their family members. Potential candidates will be contacted and invited to a screening visit at the BCTF where they will undergo the individual informed consent process prior to any study screening procedures.

To ensure that enrolment goals are met, this recruitment plan allows for longitudinal screening of participants. In addition, longitudinal compliance with study visits and procedures will be encouraged through the provision of a study calendar to participants, using multiple contact methods (phone calls, home visits by community mobilizers, having names and phone numbers of close contacts), transportation to the BCTF if needed.

Adults will be recruited using a rolling recruitment, screening and enrolment process. This process will continue until all 60 study participants have been enrolled and dosed. The recruitment strategies are based on the experience from previous trials conducted by the clinical team in BCTF aiming to achieve adequate participant enrolment to reach target sample size.

The planned total number of participants for this trial will be 60. This is a pilot BA/FE study and is not formally powered, however 12 healthy adult participants are considered sufficient to characterise the PK of the child-friendly taste-masked granule formulation of PQP.

5.2.1 Inclusion criteria

Participants must fulfil all of the following criteria to be eligible for enrolment in this trial:

1. Female or Male aged ≥18 years to ≤55 years at the date of signing informed consent.
2. Ability to provide written, personally signed, and dated informed consent to participate in the trial, in accordance with the ICH Good Clinical Practice (GCP) and applicable regulations, before any trial-related procedures.
3. An understanding, ability, and willingness to fully comply with trial procedures and restrictions.
4. Female participants must agree to follow contraceptive requirements as indicated in Section 13.2.2, from at least 30 days prior to first dosage to 16 weeks after last dosage.
5. Agrees not to donate sperm or ova from the time of the first administration of trial medication until twelve weeks after the end of the systemic exposure of the trial drug.
6. Participants must have a body weight of 50 kg or greater and a BMI between 18.0 kg/m² - 30.0 kg/m² (inclusive) at screening.
7. Satisfactory medical assessment with no clinically significant or relevant abnormalities as determined by; medical history, physical examination, vital signs, 12-lead ECG and clinical laboratory evaluation that is reasonably likely to interfere with the participant's participation in or ability to complete the trial as assessed by the Investigator.

5.2.2 Exclusion criteria

Participants will be excluded from enrolment in this trial if they fulfil any of the criteria below:

1. Prior screen failure or randomisation in this trial. NOTE: Participants who initially failed due to temporary non-medically significant issues are eligible for re-screening once the cause has resolved.
2. Female participant who is pregnant (from history, examination or confirmed by a positive serum pregnancy test at screening and/or on Day -1) or breastfeeding.
3. Male participants with a female partner(s) who is (are) pregnant or lactating at screening and/or on Day -1, or is (are) expected to be during the trial period.
4. Has a mental incapacity or language barriers precluding adequate understanding, co-operation, or compliance with the trial requirements.
5. Unable or unwilling to follow a standardised diet and meal schedule or unable to fast, as required during the trial.
6. Has milk intolerance.
7. Unable to swallow tablets.
8. Has veins on either arm that are unsuitable for intravenous puncture or cannulation (e.g., veins that are difficult to locate, or a tendency to rupture during puncture).
9. Known or suspected intolerance or hypersensitivity to the investigational products, any closely related compound, or any of the stated ingredients.
10. History of significant allergic reaction (e.g., anaphylaxis, angioedema), to any product (food, pharmaceutical, etc) but excluding untreated, asymptomatic, seasonal allergies.
11. Donated blood or blood products (excluding plasma) within 90 days prior to trial medication administration.
12. Has received or plans to receive a COVID-19 vaccination within two weeks before to one week after trial last visit.
13. Treated with medication containing PQP within 90 days or five half-lives preceding the dose of trial medication (whichever is the longer).
14. Ingested herbal remedies or dietary supplements containing St. John's Wort in the 30 days before the planned Day 1 of the dosing Part.
15. Taking medicinal products that are known to prolong the QTc interval (see http://www.crediblemeds.org/). An up to date list will be in the study specific manual.
16. Use of any medication that is either a moderate or strong inhibitor or inducer of CYP3A4 within 30 days or five half-lives (whichever is longer) prior to the planned day of dosing (see Drug Development and Drug Interactions, Table of Substrates, Inhibitors and Inducers, FDA). An up to date list will be in the study specific manual.
17. Use of any other prescription medication (excluding hormonal contraception and hormone replacement therapy) within 14 days or ten half-lives (whichever is longer) prior to Day 1 of the dosing Part that the Investigator judges is likely to interfere with the trial or pose an additional risk in participating.
18. Use of any over-the-counter medication (including multivitamin, herbal, or homeopathic preparations; excluding paracetamol - up to 3 g of paracetamol per day permitted while participants are in-house, whereas while participants are outpatients a maximum of 1 g paracetamol per day will be allowed) during the seven days or ten half-lives of the drug (whichever is longer) prior to Day 1 of the dosing Part, that the Investigator judges is likely to interfere with the trial or pose an additional risk in participating.
19. Ingested any poppy seeds within the 24 hours prior to screening or admission.
20. Current use of tobacco in any form (e.g., smoking or chewing) or other nicotine-containing products in any form (e.g., gum, patch, electronic cigarettes).
21. History or clinical evidence of substance and/or alcohol abuse within the two years before screening. Alcohol abuse is defined as regular weekly intake of more than 14 units (for both males and females).

22. Participants must have not consumed other substances known to be potent inhibitors or inducers of CYP34A system such as grapefruit or cranberry juice-containing products in the 30 days before the planned IMP administration.
23. Any history of seizures, epilepsy, photosensitivity or documented retinopathy.
24. The history or presence of any of the following cardiac conditions: known structural cardiac abnormalities; family history of long QT syndrome; cardiac syncope or recurrent, idiopathic syncope; exercise related clinically significant cardiac events.
25. Has vital signs consistently outside of the normal range at screening or Day-1.
26. Any clinically significant abnormalities in rhythm, conduction or morphology of resting ECG or clinically important abnormalities that may interfere with the interpretation of QTc interval changes. This includes participants with any of the following (at screening or Day -1):
    - sinus node dysfunction
    - clinically significant PR (PQ) interval prolongation (>220ms)
    - second- or third-degree atrioventricular (AV) block
    - sustained cardiac arrhythmia's including (but not limited to) atrial fibrillation or supraventricular tachycardia, or any symptomatic arrhythmia, with the exception of isolated extra-systoles
    - abnormal T-wave morphology which may impact on the QT/QTc assessment
    - QT interval corrected using the Fridericia's formula (QTcF) >450 ms
    - any other ECG abnormalities in the standard 12-lead ECG or an equivalent assessment which in the opinion of the Investigator will interfere with the ECG analysis
    - Participants with borderline abnormalities may be included if the deviations do not pose a safety risk, and if agreed between the appointed cardiologist and the PI.
27. Positive test results for alcohol or drugs of abuse at screening or Day -1.
28. Electrolyte imbalances, particularly results that are out of reference intervals for potassium, calcium or magnesium.
29. Has a positive test for Hepatitis B surface Antigen (HBsAg), Hepatitis C Antibody (HCV Ab), or Human Immunodeficiency Virus Antibody (HIV Ab) at screening.
30. Presence of malaria parasites by blood smear.
31. Has total bilirubin, ALT or AST consistently >upper limit of normal (ULN) at screening (up to two repeats may be taken during the screening period; participants may be included if two out of the three total results are ≤ULN), or has total bilirubin >ULN on Day -1 (mild variations from baseline may be allowed if considered not clinically significant by the Investigator).
32. Has a haemoglobin, platelet count, total white blood cell count, lymphocyte or monocyte count < lower limit of normal (LLN) (up to two repeats may be taken during the screening period and on Day -1 (participants may be included if two out of the three total results are greater or equal to LLN), at screening. Where there is a clear diurnal effect on the result participants may be included if variations are considered not clinically relevant by the Investigator.
33. Current or recurrent disease (e.g., cardiovascular, haematological, neurological, endocrine, immunological, renal, hepatic or gastrointestinal or other conditions, including cholecystectomy or gastrectomy) that could affect the action, absorption, distribution, metabolism or excretion of PQP or could affect clinical assessments or clinical laboratory evaluations.
34. Current or relevant history of physical or psychiatric illness that are not stable or may require a change in treatment, or use of prohibited therapies during the trial, that make the participant unlikely to fully comply with the requirements of the trial or to complete the trial, or any condition that presents undue risk from the investigational product or trial procedures.
35. Any other abnormal findings on vital signs, ECG, physical examination or laboratory assessments that the Investigator judges as likely to interfere with the trial or pose an additional risk in participating.

36. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participant at risk because of participation in the trial, or may influence the result of the trial or the participant's ability to participate in the trial.
37. Any conditions which in the opinion of the Investigator would make the participant unsuitable for enrolment or could interfere with the participation in or completion of the trial.

5.3 Discontinuation of individual participants

A participant has the right to withdraw from the study at any time and for any reason and is not obliged to give his or her reasons for doing so. Following the withdrawal of consent, with the exception of safety data, which should be collected if possible and in accordance with the participant's agreement, no further evaluations should be performed and no attempts should be made to collect additional data. Data collected before withdrawal of consent may be retained and used, except when the participant explicitly asks the Investigator to destroy all identifiable samples taken from the participant and does not allow to analyse his/her data. Participant withdrawal and any agreements made with the participant will be documented in the participant's charts and the investigator will ensure to implement all necessary steps.

A participant can be discontinued from the study by the Investigator at any time in the interests of the participant's health and well-being or for any of the following reasons:

1. Administrative decision by the Investigator
2. Participant non-compliance with study requirements
3. Any event which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures
4. Recommendation by the SRC

If, for any reason, a participant is discontinued from the study before the end of treatment evaluations, the Investigator is required, as feasible, to perform the safety procedures planned for the end of treatment. e.g., if a participant develops an AE of Grade 2 or higher, he/she will continue with close-up until the AE is resolved, stabilized, or is otherwise explained. The reason(s) for discontinuation will be recorded in the electronic case report form (eCRF) and source documents.

5.4 Replacement of individual participants

On the day prior to study product dosing (Day-1), at least one additional participant will be invited as a backup for any other participant withdrawn prior to initiation of fasting. Replacement participants may be enrolled to ensure that a sufficient number of participants complete the trial unless AE rules preclude. Replacement participants must be agreed upon by the Investigator and the Sponsor.

6 TREATMENT OF PARTICIPANTS

6.1 Identity of investigational products (treatment / medical device)

6.1.1 Experimental intervention (Piperaquine tetraphosphate dispersible granules)

- Piperaquine tetraphosphate dispersible granules are white to off-white granules that contain 26.67% w/w of piperaquine tetraphosphate. The granules have been developed and manufactured by Piramal Pharma Ltd. In Ahmedabad, India. For a 320 mg dose, 1.2 g of granules should be weighed and dispersed in 25 ml of water for oral administration.
- Dispersible granule formulation will be used in Part 1 for group 2 and in Part 2 for groups 3, 4 and 5 (Section 4).
- The procedure for final preparation, dosing / weighting of the dispersible granules and dispensing condition in respect to stability data will be provided in details in the pharmacy manual

6.1.2 Comparator (Piperaquine tetraphosphate tablets)

- Piperaquine tetraphosphate tablets, 320 mg, are white to off-white, round, bi-convex, uncoated tablets, plain on both sides. The tablets for oral administration have been manufactured by Piramal Pharma Ltd. In Ahmedabad, India.
- Tablet formulation will be used as comparator during Part 1, for group 1 (Section 4)
- Tablet formulation will be administered orally under DOT (directly observed treatment) with 240 mL of water.

6.2 Administration of experimental and control interventions

Dosing will be carried out in the fasted or fed conditions in Part 1 and 2 respectively.

6.2.1 Administration under fasted conditions: Part 1 (Groups 1 and 2)

- All participants will fast of all food and drink except water (minimum of 10 hours). During this period, water will be permitted ad lib except for the period 1 hour before until 1 hour after administration of the drug product. At the end of fasting period, participants will receive PQP tablets or dispersible granules depending on the randomization (Section 4.2.1). Participants will also not consume any food for at least 4 hours after the dose.
- Participants should receive standardized meals scheduled at the same time throughout the in-house stay.

6.2.2 Administration under fed conditions: Part 2 (Groups 3, 4 and 5)

- All participants will fast of all food and drink except water (minimum of 10 hours). During this time, water will be allowed ad lib except for the period 1 hour before until 1 hour after drug administration.
- At the end of fasting period, depending on randomization (Section 4.2.1), assigned food (high-fat meal, low-fat meal representative of African diet or 250 ml of whole milk) will be consumed entirely within a period of less than 30 minutes.
- At 30 minutes after the start of breakfast / assigned food and beverage (see above), the PQP dispersible granules will be administered. No food will be allowed for at least 4 hours after the dose.
- Subjects should receive standardized meals scheduled at the same time throughout the in-house stay.

6.3 General approach for preparing meals for administration under fed conditions

A respective manual / SOP will be used with the help of dietitian and delegated kitchen staff to standardized regular meals based on the following basic guidance.

- for the present FE study, both high-fat and low-fat meals will be assessed. The requirement to derive exposure measures and PK parameters in fed conditions can be achieved by establishing the caloric and content breakdown (carbohydrates, proteins, and fat (>50% for high-fat meal vs 25% for low-fat meal) for the test meals (16).
- Efforts will be made to standardise the content, volume, and viscosity in standardizing the meal composition reflecting local African diet especially for the low-fat meals. The guidance below provides a description for the reference approach to estimate composition of the ingredients for standardization of the recipe used locally. Specific ingredients and amount for the recipe will be described in the respective study manual, including a list of the locally used ingredients adjusted to meet composition requirements.

Table 1: FDA Guide for composition of fat in high-fat and low-fat meals

Meal Type	Total Kcal	Fat			Protein	Carbohydrate
		Kcal	Grams	Percent	Kcal	Kcal
High-Fat	800-1000	500-600	55-65	≥50	150	250
Low-Fat	400-500	100-125	11-14	25	-	-

6.3.1 Standard meals at regular intervals throughout the in-house stay.

- During screening, participants will be informed about the sense and purpose of the dietary requirements and the percentage composition of the meals.
- Any food allergy will lead to exclusion from the study.
- During in-house stay, all participants of a trial will receive standard meals for breakfast, lunch, or dinner independent of any individual preferences. This will be initiated at the time of entering the clinical trial facility (pre-fast dinner) and resume at breakfast 4 hours post IMP.

6.4 Packaging, labelling and storage conditions

PQP hard tablets and dispersible granules will be supplied to the clinical trial centre. The study IMP will be packed in HDPE bottles and dispatched with labels listing the batch numbers. The study drugs should be stored at less than 30 °C.

6.5 Dose modifications

As described in Section 4, based on the safety and preliminary PK interim report of the granule formulation on Day 15, if necessary, doses may be readjusted for the Part 2 in order to assess the food effect for the optimal dose.

6.6 Compliance with study intervention

The pharmacist will prepare the dose for each participant and label it with the participant ID. Additional details regarding the labelling, dispensing and inventory will be provided in the respective pharmacy manual. Study treatment will be administered under the direct supervision of investigator site personnel, who will monitor the participants to ensure treatment compliance.

If vomiting occurs at any time following ingestion of the study product, no re-dosing will be provided and the participant will continue to be followed for safety and PK analyses. The onset time and frequency of vomiting will be documented in the source documents as an AE. Participants who have vomited after administration of the dose may be replaced at the discretion of the Investigator and the Sponsor.

6.7 Concomitant interventions (treatments)

Prior therapy as indicated in the exclusion criteria Section (Section 5.4) will not be permitted.

No medications will be allowed while the participant is in the study except the use of contraceptives as described in Section 13.2.2 or when considered medically indicated by the investigator for the treatment of AEs/SAEs. In case of occasional headache and other pain, paracetamol (not exceeding 3g/day) may be administered at the discretion of the Investigator. If any medication or intervention listed in participant restrictions described in Sections 13.2.2 and 13.2.3 is required, the participant may be withdrawn from the study at the discretion of the Investigator and the Sponsor.

Medications taken within specified periods before the first dose of study medication will be documented as a prior medication and may be exclusionary in reference to the exclusion criteria and / or participant restrictions described in Section 13.2.3. Medications taken after the first dose of study medication (e.g., to treat any AEs) will be documented as concomitant medications.

6.8 Study drug accountability

The clinical site will be provided with PQP tablets and granules by the Sponsor (MMV) prior to the initiation of the study when the approval has been obtained from the relevant ethics committee and import licence from the regulatory authorities. The site pharmacist will be accountable for IMP and other medications by ensuring that they are all inventoried and stored as indicated in the Pharmacy Manual Additional details on the requirements and documentation for accountability will be described in the general study site internal quality assurance (QA) and Pharmacy Manuals. Accurate and adequate records maintenance from shipment to the sites until return or disposal including the physical location, dates (receipt, expiry, use, return), lot/batch number and quantities (received, used, destroyed) will be maintained.

Study products and study accountability logs will be available to the sponsor or sponsor’s representative as part of the study monitoring procedures.

6.9 Return or destruction of study drug / medical device

Unused IMP will either be destroyed in accordance with the site’s pharmacy manual and national law or returned to the Sponsor.

7 STUDY ASSESSMENTS AND VISITS

For the study timepoints described below, when multiple procedures are scheduled at the same time point(s), the chronology of events will be specified in the relevant study specific manual and should be adhered to, where possible.

7.1 Clinical assessment parameters

7.1.1 Vital signs

The following vital sign parameters will be collected (blood pressure, heart rate, axillary temperature and respiratory rate) will be collected in supine position at indicated specified time points (Section 4.4 Schedule of events):

- axillary body temperature
- after at least five minutes of supine / semi supine rest
    - Respiratory rate
    - Heart rate
    - Blood pressure (Systolic and Diastolic)

If the result of the measurement is out of range, the Investigator will make an assessment of clinical significance and appropriate course of action will be taken as follows:

- If out of range at screening, vital signs may be repeated as clinically indicated, if the abnormality is assessed as clinically significant, participant will be counselled and excluded.
- If out of range after IMP administration, appropriate course of action will be followed as described in Section 8.2.3.

7.1.2 Medical history and review of systems

General questioning about the relevant past and present medical history, prior and concomitant treatment history, family and social history and review of systems. This information will primarily focus on the medical conditions relevant for enrolment criteria.

7.1.3 Physical Examination

A complete physical examination will assess general appearance including height and weight (at screening) and weight repeated (at Day-1) and the following body system: skin, lymph nodes, head, eyes, ears, nose, throat, respiratory, cardiovascular, abdomen, extremities, musculoskeletal, and neurological.

A targeted symptom directed physical examination will be assessed at any study visits as deemed necessary by the Investigator based on history of presenting complaint or clinical observations.

7.1.4 12-lead ECG safety recording

Instructions for recording, handling, review, repeat and electronic transmission of the ECGs will be included in a separate ECG Manual. The following general guidance will apply;

- To be performed after at least ten minutes of supine / semi supine rest
- **Triplicate ECG** (three repeat ECGs, at least 1 minute apart) and **Single ECG** recorded in supine position;
    - will be performed for time-points indicated in Section 4.4 Schedule of events
- **Abnormal ECGs;** may be confirmed by repeat and will be assessed for clinical significance by the investigator.

- All recorded ECGs will be reviewed by the investigator or delegate and the review will be documented in the CRF (for normality and clinical significance). If a participant shows an abnormal ECG, additional safety recordings may be performed, and the abnormality be followed to resolution if required.
- If needed a cardiologist will be consulted for participant review and ECG assessment, particularly for abnormal assessments recorded post investigational product (IP).
- All digitalized ECGs recorded at baseline (pre-dose on Day-1 and Day1) and post IMP administration will be transmitted electronically for central ECG assessment by the ECG vendor and the reports will be analysed and summarized cumulatively in reference to the clinical participant data at the final safety report.

7.2 Laboratory assessment parameters

The following parameters for each laboratory test will be measured at indicated specified time points (Section 4.4 Schedule of events) using procedures outlined in the respective site laboratory manual. See Section 8 (Assessment of safety) for further details related to grading, assessment, reporting and follow-up of abnormal laboratory values.

- **Biochemistry:** Defined in two Biochemistry Panels
    - **Biochemistry Panel 1:** Alanine Transaminase (ALT), Aspartate Transaminase (AST), Total bilirubin (T.bil), Potassium (K^+), Calcium (Ca^{2+}), Magnesium (Mg^{2+}), Sodium (Na^+), Chloride (Cl^-), Bicarbonates ($HCO3^-$), Creatinine (Creat), Total serum Proteins (T.Pr), Albumin (Alb)
    - **Biochemistry Panel 2:** ALT, AST, T.bil, K^+, Ca^{2+}, Mg^{2+}
- **Hematology and coagulation:** Hemoglobin (HB), platelets (PLT), white blood cells (WBC) and WBC differentials (Neutrophils, Eosinophils, Lymphocytes), prothrombin time (PT) and activated partial thromboplastin time Coagulation (aPTT)
- **Malaria parasitology:** Thick Blood Smear
- **Urinalysis performed by dipstick:** Protein and blood (Note: Urinalysis should be deferred if a participant is menstruating, but should be performed as soon as possible). If deemed necessary, based on a clinically significant positive test, microscopic examination of urine and quantification of analytes (as appropriate) will be performed.
- **Serology:** (HIV 1 & 2, Hepatitis B & C)
- **Drugs of abuse:** Urine and Alcohol breath test: Benzodiazepines, Opiates, Amphetamines, Methamphetamines, Methadone, Cocaine, Cannabinoids, Barbiturates, Phencyclidine, Tricyclic antidepressants
- **Contraception requirements:**
    - Serum pregnancy test for WOCBP
    - Follicular stimulating hormone (FSH) for post-menopausal female

7.2.1 PK assessment

Blood samples for PK assessment will be taken from either arm following procedures stipulated in the respective site sample collection manual. The exact date and time of PK blood sampling will be recorded in the source documents. Procedures for processing, storage and transfer plasma samples including the required controlled temperature environment will be detailed in the relevant PK manual provided by the Good Laboratory Practice (GLP) certified Bioanalytical Laboratory vendor. Blood volumes and time points for PK sampling are indicated in Section 4.4 (Schedule of events).

7.2.2 Exploratory assay

Blood samples for CYP polymorphism will be collected as indicated in Section 4.4 (Schedule of events). This exploratory sample is optional and will only be indicated for those participants who will indicate their willingness to this optional sample in the tick-box provided in the respective consent form.

7.2.3 Total blood volume

The blood volumes planned to be collected from each participant during the course of this study are detailed in Section 4.4 (Schedule of events). The total blood volume collected during the scheduled study visits (of approximately 75 days) for any given participant will be approximately 70 mL. Additional samples may be required in the event of AEs/SAEs, laboratory safety tests or in case a laboratory test needs to be repeated as judged by the Investigator.

7.2.4 Exploratory questionnaire: Palatability

A palatability / tasting questionnaire will be presented to each participant immediately after dosing and asked to be completed within 10 minutes of dosing with IMP.

7.3 STUDY VISITS

7.3.1 Screening period (Day-45 to Day-2)

Written informed consent will be obtained prior to any study procedures including a consent for collection of pharmacogenetic assessment.

- All participants will be screened and assessed for eligibility prior to administration of the study medication. For convenience and synchronization, to accomplish this, procedures at screening are allocated under columns ([A]) or, ([B]) as defined in Section 4.4 (Schedule of events).
    - ICF (informed consent form) must be signed prior to any other procedures and will be valid if performed less than or equal to 45 days prior to Day1.
    - With the exception of contraception for WOCBP which must be performed >=30 days prior to D1, all other events shown under screening column ([A]) must be performed within the valid ICF window and not later than Day-2.
    - Events indicated under screening column ([B]) must be performed within the valid ICF window and between Day-15 and Day-2.
- This alignment of procedures, will provide the healthy participants with sufficient reflection time and ensure that investigators perform required procedures following protocol and clinically acceptable time windows prior to IMP administration (e.g., contraception for WOCBP >=30 days prior to study treatment) while maintaining compliance to GCP and protocol requirements (e.g., only after ICF is signed).
- The selection criteria for the study may be reviewed upon completion of each set of screening assessments. Participants who fail at earlier procedures, e.g., screening column ([A]), may not necessarily continue with the subsequent screening procedures unless otherwise indicated or deemed necessary to do so.
- As long as the chronological order of procedures and time windows to IMP administration are maintained, events under screening columns ([A]) and ([B]) may be completed in the same visit day, except contraception for WOCBP which must be performed >=30 days prior to study treatment.
- Note: Depending on the latest COVID-19 Infection Control Guidelines; COVID-19 tests will be carried out at regular intervals, prior to entry in the unit and throughout the residential period as per and pre-entry algorithms.

In cases that re-screening is justified, certain procedures such as contraception and HIV testing may not be clinically justified within the timeframe of re-screening. The investigator's medical justification for not repeating such procedures must be documented and proceed with justified assessments. On repeating screening, a new screening number will be assigned only if ICF window has expired, in which case, the previous screening number must not be re-used for the same or different study participant.

7.3.2 In-house visit procedures

Overall, in-house visits will cover the following main procedures / activities:

- Admission of eligible participants to the trial facility one day prior to study treatment (Day-1)
    - Number and schedule of participants to be dosed in a single day will depend on a combination of factors targeted to optimize implementation of study assessments without risking the safety of participants or losing quality. The overall tentative study schedule will be used as a reference for future scheduling.
    - Replacement of participants during the in-house visits is described in Section 5.4.
- Random treatment allocation and administration of study IMP on the following day (Day1)
- Post IMP continuous assessments and safety monitoring (Day1, Day2)
- Completion of in-house assessments and discharge from the trial facility (Day3).

7.3.2.1 Day -1

At the time of admission:

- Eligibility review and confirmation of willingness to continue with study participation
- Admission to in-house trial unit
- In-house baseline assessments indicated for Day-1
    - Review medical history (including medications) for any updates since last seen by the study clinician
    - Body Weight
    - ECG (see Section 4.4)
    - Vital signs collection (see Section 7.1.1)
    - Symptom directed physical exam
    - Collection of relevant laboratory parameters including serum pregnancy test (WOCBP) (see Section 4.4)
- Review of baseline assessment results indicated for Day-1
- Fasting initiation and monitoring during the 10 hours of pre-IP fasting period (Section 6.2).

7.3.2.2 Day 1

- The following pre-IP baseline assessments and procedures will be initiated about 60 minutes before the end of 10 hours fasting duration (i.e., after 9 hours of fasting have elapsed):
    - Restricted water intake for the period 1 hour before until 1 hour after administration of the study IMP

  Completion of Pre-IP baseline assessment within 30 minutes prior to the end of 10 hours fasting duration, preferably in the following order:
    - Review of medical history for any updates
    - ECG (see Section 4.4)
    - Vital signs
    - PK Samples collection
    - Randomization (see Section 4.2.1)

- After 10 hours of fasting have elapsed, administration procedures for the study drug will vary between part 1 and part 2 depending on the dosing conditions as follows:

  Part 1: Administration under fasted conditions
  - At 10 hours of fasting; Investigators should immediately administer the drug product to study subjects (see Section 6.2.1).

  Part 2: Administration under fed conditions
  - At 10 hours of fasting; The study participant will start the randomly allocated meal 30 minutes before administration of the drug product, and should consume the meal in 30 minutes or less
  - Investigators should immediately administer the drug product to study subjects (see Section 6.2.2).

- Post IMP procedures and restrictions on Day1
  - Participants will be asked to complete the palatability questionnaire (within 10 minutes of dosing).
  - Participants will be requested to remain in a semi-supine position for the first four hours after dosing, except to use the bathroom. Participants may then be ambulatory but should not engage in strenuous activities.
  - Additional water is allowed ad lib except for the period 1 hour before until 1 hour after drug administration.
  - No food is allowed for at least 4 hours after the dose.
  - Standard meals will be provided at the standard schedule each day over the duration of in-house stay.

  Vital signs, ECGs and PK samples collection:
  - Will be performed on a strict schedule (see Section 4.4 Schedule of events) beginning from 1 hour to 12 hours post IMP on Day1.

7.3.2.3 Days 2 and 3

- Standard meals will be provided at the standard schedule each day over the duration of in-house stay.

Vital signs, ECGs and PK samples collection and AE review:
- Procedures will be performed on a strict schedule at approximately 24 hours and 48 hours post IMP on Day2 and Day3 (see Section 4.4 Schedule of events)
- On Day3 safety laboratory samples will also be collected

Discharge on Day3
- Participants will be discharged after the completion of procedures on Day3
- At discharge, they will be reminded to contact the study team in case of any questions or concerns and will be reminded on the next visit day. Discharge procedures will be detailed in the relevant study manual.

7.3.3 Clinic follow-up visits

7.3.3.1 Days 5, 8, 15, 22 and 30

Vital signs, ECGs and laboratory (safety and PK Samples) and AE review:
- Procedures will be performed on a strict schedule (see Section 4.4 Schedule of events)
- End of study (i.e. Day 30).

7.3.4 Unscheduled visits

Unscheduled visits may occur at any time during the study. They may occur after Day 30 to follow any AE/SAE occurring during the study period to resolution or stability. Clinical assessments will be performed at the discretion of the investigator as medically indicated.

8 ASSESSMENT OF SAFETY

8.1 Safety parameters

Specify the study procedures and visits including permitted time windows that will be used for a concrete assessment of the safety, at which point and how the parameters be measured (methodology).

8.1.1 Collection and reporting of 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)".
- International Conference on Harmonization (ICH) guideline E2F "Note for guidance on development safety update reports (DSUR)".
- International Conference on Harmonization (ICH) guideline E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting".

It is the Investigator's responsibility to document and report all AEs occurring in the clinical trial. The period of observation for collection of AEs extends from the time of signing consent to the final visit.

All AEs must be recorded until the end of the study. All SAEs which come to the attention of the Investigator within 30 days from the end of the study treatment must also be recorded.

The definitions of AEs, adverse drug reactions (ADRs), serious adverse events (SAEs) 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.

8.1.2 Definition of adverse events

According to ICH Topic E6, an adverse event (AE) is any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to it.

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended and which occurs at any dose (in pre-approval clinical experience) or at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function (in post-approval clinical experience). The term "response" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. This means that there are facts (evidence) or arguments to suggest a causal relationship.

According to ICH Topic E9, a treatment emergent adverse event/adverse reaction is an event that emerges during treatment, having been absent pre-treatment, or worsens relative to the pre-treatment state.

In a clinical trial, in addition to the above mentioned "treatment-emergent" AEs/ADRs, any unfavourable and unintended sign, symptom or disease occurring in the study during any wash-out periods must also be recorded as an AE/ADR.

8.1.3 Types and recording of adverse events

An AE/ADR may be:

- a new symptom or medical condition;
- a new diagnosis;
- an intercurrent illness or an accident;
- a worsening of a medical condition/diseases existing before the start of the clinical trial;
- the recurrence of a disease;
- an increase in frequency or intensity of episodic diseases;
- a change in a laboratory parameter.

The criteria for determining whether an abnormal test result should be reported as an AE/ADR are as follows:

- the test result is associated with accompanying symptoms, and/or
- it requires additional diagnostic testing or medical/surgical intervention, and/or
- it leads to a change in trial dosing outside of protocol-stipulated dose adjustments, or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/or
- it is considered to be an adverse event by the Investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE/ADR. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE/ADR. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present before inclusion in the trial. In the latter case the condition should be reported as medical history.

These data will be recorded in the CRFs, regardless of whether they are thought to be associated with the study or the drug under investigation.

8.2 Grading of adverse events

8.2.1 Standard Toxicity Grading

For each AE, the Investigator will assess the maximum severity. In general, All AEs/SAEs (except laboratory abnormalities) will be graded by the Investigator using the AE severity grading according to the WHO system:

WHO intensity grades are defined as follows:	
1	Mild – No interference with routine activity.
2	Moderate – Interferes with performance of some activities of daily living, but responds to symptomatic therapy or rest.
3	Severe – Significantly limits ability to perform activities of daily living despite symptomatic therapy.
4	Very severe – Incapacitates patient despite symptomatic therapy; requires hospitalization

WHO Handbook for Reporting Results of Cancer Treatment. WHO Offset Publication No. 48. World Health Organization; Geneva, Switzerland. 1979:16–21.

8.2.2 Grading of abnormal values for safety laboratory assessments

The site manual for the reference intervals and grading for selected abnormal values, utilizes the population references for specified laboratory parameters to grade abnormal laboratory values using adopted schemes of reference for toxicity grading (17, 18, 19).

8.2.3 Abnormal assessments to be considered as adverse events

Each abnormal value will additionally be classified as clinically significant or not clinically significant according to the clinician's medical judgment. In general, abnormalities that require intervention will be classified as clinically significant. Borderline abnormal laboratory findings and other objective measurements should NOT be routinely captured and reported as AEs, as they will be collected and analysed separately. However, abnormal laboratory findings or other objective measurements that meet the criteria for an SAE, result in discontinuation of the IMP, require medical intervention or are judged by the Investigator to be clinically significant changes from baseline values should be captured and reported on the AE pages of the eCRF.

When recording an abnormal laboratory finding on the AE pages of the eCRF, a clinical diagnosis should be provided rather than the abnormal value itself, if this is available (for example, "anaemia" rather than "decreased red blood cell count" or "haemoglobin = 10.5 g/dL").

8.3 Association of adverse events – relatedness to the medicinal (investigational) product

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related/suspected	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not related/ not suspected	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

The Investigator should also comment on the AE page of the eCRF whether an AE is not related to the study treatment, but it is related to the study participation of the subject (study procedures, wash-out periods etc.).

8.4 Serious adverse events

An AE/AR is defined as serious if:

- it results in death;
- it is life-threatening (the term "life-threatening" in the definition of "serious" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe);
- it requires a hospitalisation or prolongs existing hospitalisation;
- it results in persistent or significant disability/incapacity;
- it is a congenital abnormality/birth defect;
- it is considered medically important (medical and scientific judgement should be exercised in deciding whether other AE/ADRs are to be considered serious, such as important medical events that may not be immediately life-threatening but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; convulsions that do not result in hospitalisation; development of drug dependency or drug abuse).
- For the purpose of this protocol an AE will be considered as serious should the AE constitute a possible Hy's Law case (defined as a subject with any value of ALT or AST greater than or equal to 3x ULN together with an increase in bilirubin to a value greater than 2xULN (>35% direct) and NOT associated to an ALP value greater than 2xULN.

A non-serious AE/ADR is any symptom or sign which does not fulfil any of the above-mentioned seriousness criteria.

The causality of SAEs (i.e. their relationship to study treatment) will be assessed in the same way as for non-serious AEs.

Note that SAEs that could be associated with any study procedure should also be reported.

A SUSAR is any SAE where a causal relationship with the IMP is at least a reasonable possibility, but is not listed in the Investigator Brochure and/or Summary of Product Characteristics (SmPC).

8.5 Expectedness of adverse reactions

An adverse reaction, the nature or severity of which is not consistent with the applicable reference safety information (Investigator's brochure [IB] for drugs in clinical development or SmPC for marketed drugs) is unexpected. Reports which add significant information on the specificity, increase in the occurrence or severity of a known and already documented serious adverse reaction are unexpected events. The expectedness of an adverse reaction is determined by the Sponsor in the reference safety information. This should be done from the perspective of events previously observed, not 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 PQP. AEs that are not related to the IMP do not need an expectedness assessment against the reference safety information. From a regulatory perspective, expectedness of a serious adverse reaction determines whether it does or does not need reporting in an expedited fashion.

8.6 Adverse events reporting obligations

The window for reporting of AEs/SAEs starts with the signature of the informed consent and ends with the participant's last visit or the last planned data collection. Inability to fulfil pre-IP fasting requirement will be considered as screening failure.

8.7 Recording of adverse events

All (serious and non-serious) AEs detected by the Investigator or delegates, or spontaneously notified by the subject at each visit/examination must be reported in the respective section of the CRF.

The following information should be reported for each AE, whether or not it can be attributed to the trial drug:

- description of AE
- date of onset/date of resolution
- characteristics of the event (seriousness, intensity)
- actions taken (treatment required must be reported in the eCRF)
- outcome
- relationship with trial drug (causality assessment) and/or study participation

Findings and values related to physical examinations and measurements of ECG, vital signs, (axillary temperature, blood pressure, and heart rate) and laboratory parameters will be defined as AEs if they are considered clinically relevant deteriorations compared with baseline and pre-dose values, as judged by the Investigator.

8.7.1 Adverse Event Reporting in eCRF

Complete and accurate data on all AEs experienced for the duration of the reporting period, will be reported on an ongoing basis in the AE pages of the eCRF.

It is important that each AE report include a description of the event, whether it is considered serious, its duration (onset and resolution dates), its severity, its relationship to the IMP, any other potential causality factors, any treatment given or other action taken (including dose modification or discontinuation of the IMP) and its outcome.

Additional guidance can be found in the eCRF Completion Guidelines provided by the Contract Research Organization (CRO).

8.7.2 Reporting mechanism to sponsor, Ethics Committees and Regulatory Authorities

If any SAE/SUSAR occurs, the investigators will take appropriate action immediately and will strive to identify the causes of the events. Any SAE/SUSAR will be notified by the PI to the MMV Medical Director or delegate, see Figure 1.

Any SAE/SUSAR will be notified by the Investigator to the MMV Medical Director, and to the pharmacovigilance provider (Prime Vigilance) within 24 hours by email or fax.

- MMV Senior Medical Director: Dr Anne Claire Marrast, MD
    - Email: marrasta@mmv.org
    - Tel: + 41 79 323 70 65
- Prime Vigilance Contact :
    - e-mail: MMV@primevigilance.com
    - Back up fax: +44 800 471 5694

The initial report will be followed up by a full written report within three working days or five calendar days, whichever comes first, unless no further information is available. When new information becomes available a follow-up report will be provided as soon as possible. Further follow-up reports will be provided as and when new information becomes available. 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/SUSAR will accompany the SAE form if and when available.

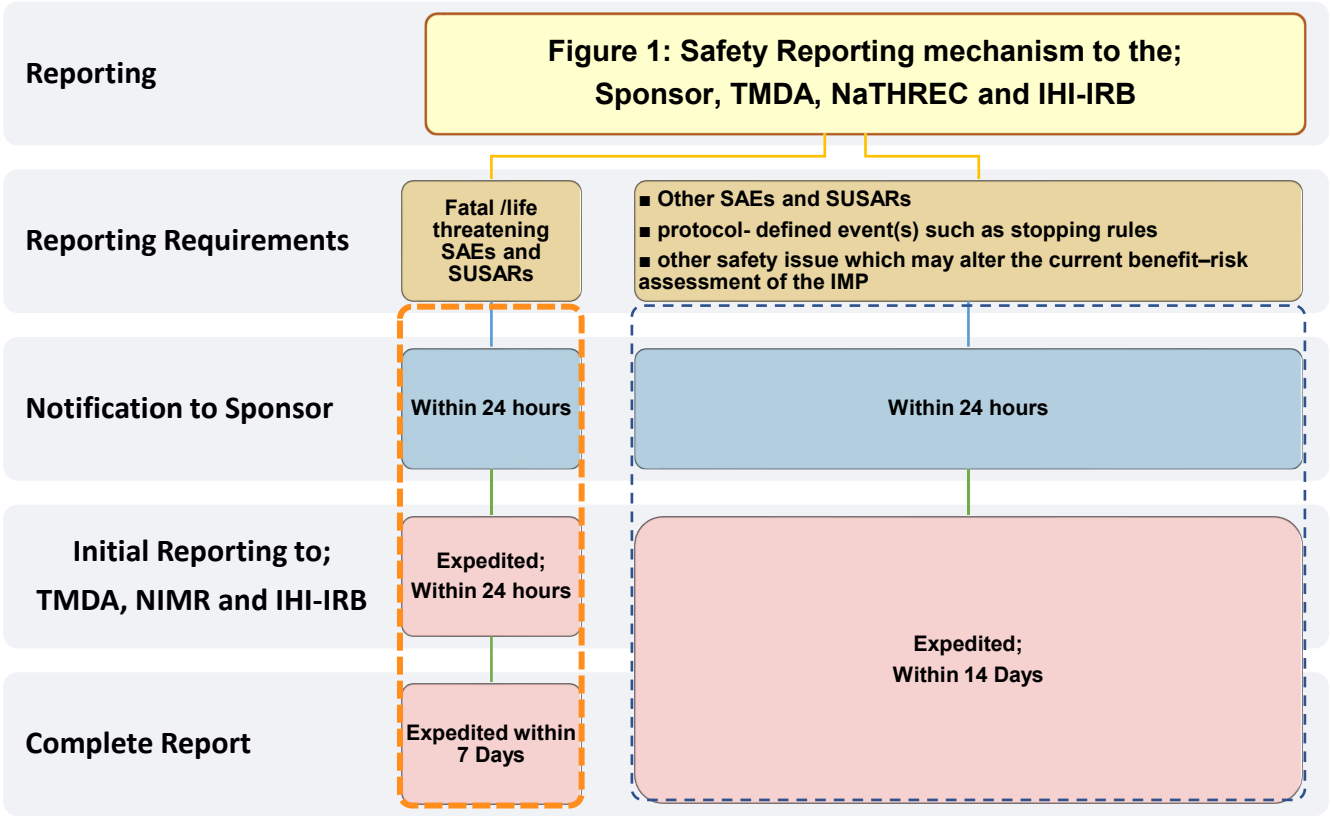
The Sponsor will also perform an evaluation of the seriousness, causality and expectedness of all SAEs. All SAEs judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship to an IMP (i.e. definitively, probably or possibly related) will qualify as serious adverse reactions. If the Sponsor disagrees with the Investigator's causality assessment, both the opinion of the Investigator and the Sponsor are provided with the report.

All SAEs will be included in the safety/pharmacovigilance database.

All SAEs including SUSARs that are fatal or life-threatening should be reported to a Competent Authority and Ethics Committees within 24 hours followed by a complete report within 7 additional calendar days of their occurrence. All other SAEs and SUSARs that are not fatal or life-threatening must be filed as soon as possible but no later than 14 calendar days after first knowledge by the Sponsor.

Annual safety reporting to the national Competent Authority and the Ethics Committee will be in agreement with ICH guideline E2F "Note for guidance on development safety update reports (DSUR)".

Figure 1. Safety reporting mechanism to the sponsor, TMDA, NaTHREC and IHI-IRB.



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 Health Authorities, Ethics Committees and the Investigator.

8.8 Follow-up observation for study participants with adverse reactions

All AEs must be documented and followed up until the event is either resolved or a satisfactory explanation is found, or the investigator considers it medically justifiable to terminate the follow-up.

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

If a study participant experiences a clinically significant finding or a worsening of an ongoing medical condition after signing the Informed Consent, the event will be recorded as an adverse event.

Any AEs that are unresolved at the participant's last AE assessment in the study (i.e. at the follow up visit) are to be followed up by the Investigator for as long as medically indicated. MMV retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The Investigator will decide on

- Study drug discontinued
- Healthy participant withdrawn from study
- Concomitant Medication required
- Hospitalization required or prolonged (this should also be reported as an SAE
- Other

The PI or delegate will follow up all AEs wherever possible until the symptom has resolved or stabilised. The date of confirming outcome will be recorded. The course of AEs will be assessed by reference to the following as a guide.

- Recovered: The AE has resolved and the participant returned to his condition prior to onset.
- Recovered with sequelae: The AE resolved, but the participant has sequelae.
- Recovering: The AE has almost resolved and the participant is returning to his condition prior to onset.
- Death: The study participant died. Causal relationship is no object.
- Ongoing: Even on the final day of observation the AE had not resolved and the participant's condition remained unchanged. In case of death, the participant died of other causes not related to the AE from which there was no recovery.

8.8.1 Pregnancy follow-up

Through the Informed Consent Process all female participants will be instructed to immediately inform the Investigator if they become pregnant during the study or within the following 3 months after the last dosing and that, pregnancy should be followed through delivery or termination of the pregnancy.

A Pregnancy Form will be completed by the Investigator and submitted to the MMV Study Medical Director and Prime Vigilance preferably within 24 hours after the Investigator becomes aware of the pregnancy. The event of pregnancy itself should not be recorded on the Adverse Event Section of the eCRF. The Investigator will provide counselling to the pregnant participant about the risks of the pregnancy and the possible effects on the fetus and thereafter, she will be asked to give written consent to allow for follow up and further collection of data on her pregnancy and the outcome of the child.

Monitoring of the participant should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child, spontaneous abortion) will be reported on the Adverse Event Section of the eCRF if the database has not been locked at that time point. In addition, the updated Pregnancy Form will be regularly submitted with latest information on the course and outcome of the pregnancy as becomes available. The investigator should ensure that the new-born undergoes a thorough clinical investigation within the first 4 weeks after birth and that this assessment is thoroughly documented and submitted on a Pregnancy Form to the Sponsor.

Male participants may continue in the trial if pregnancy of their female partner occurs. A Pregnancy Form will be completed and submitted to the MMV Study Medical Director and Prime Vigilance preferably within 24 hours after the Investigator becomes aware of the pregnancy.

9 DESCRIPTION OF DATA MANAGEMENT

9.1 Specification of source documents

CRFs will be designed in collaboration between the site, sponsor and the contracted data management vendor (IQVIA), and will be used to record details of the trial and will serve as source documents for sponsor required data. The procedures for collecting the data are outlined in the respective data management manual / SOPs. Data in the individual participant files will include clinical information, blood sampling data for the specimens acquired to perform the different tests listed, and administrative information such as contact information. The forms will also include descriptions of AEs/ARs resulting in medical consultation or hospitalization. These forms, together with the investigator's notes, are considered to be source data. Additional hospital notes including laboratory reports and clinical notes in the event of emergency or hospitalization will also be collected and included as source notes.

9.2 Data management system

Data will be recorded using paper CRFs. The information will then be transcribed into the eCRFs within the electronic data capture system (eDC) by delegated data entry personnel. Data will be independently counter checked by study monitor(s) who will review the accuracy of data entry and transfer based on the study monitoring plan. The electronic system to be used will include only validated systems that are clinical trial compliant with audit trail capabilities.

9.3 Data security, access, archiving and back up

All source documents will be kept in each participant's folder. As required by the Tanzanian regulatory authority (TMDA), all records, documents and information related to this trial will be kept in safe custody at the clinical trial site for a period of not less than twenty years after study termination or premature termination of the clinical study.

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10 STATISTICS

10.1 Hypothesis

This pilot BA/FE phase 1 trial is not designed to test specific hypotheses.

10.2 Determination of sample size

This is an exploratory trial to evaluate PK and safety of each treatment group and the sample-size is not based on formal statistical power. The number assigned to each treatment arm (n=12) is considered adequate to assess the trial objectives.

10.3 Description of statistical methods

The statistical methods and reporting will follow ICH E9 and international recommendations, including CONSORT.

10.4 Statistical Analysis Plan

A statistical analysis plan (SAP) containing detailed statistical methodology will be written and signed off before the database hard lock. The plan may be updated to reflect adaptive features of the trial as appropriate.

10.5 Analysis sets

The analysis of data will be based on different analysis sets according to the purpose of analyses. Participant eligibility for each analysis set will be finalised before the database hard lock.

The Safety analysis set will consist of all randomized participants who received at least one dose of the IMP.

The PK analysis set will consist of those participants in the safety set who have sufficient blood samples taken for at least one of the PK variables to be calculated.

In all populations, analyses will be based on the treatment received, regardless of the randomization (any such deviations will be reported). A participant who withdraws prior to the last planned observation in a trial period will be included in the analyses up to the time of discontinuation.

10.6 Safety analyses

Participant disposition will be summarised using descriptive statistics.

Individual participant demographics (age, gender and race) and body measurement data (height, weight and BMI) will be listed and summarised descriptively by treatment group and overall. Other baseline characteristics (e.g., medical history, previous medication) will be listed only.

All adverse event data will be listed and summarised by treatment group, by system organ class (SOC) and preferred term (as per Medical Dictionary for Regulatory Activities [MedDRA] coding), severity and relationship. Any SAEs and/ or AEs that led to withdrawal will be summarised and listed.

Vital signs data (see Section 7.1.1) will be listed and summarized, along with changes from baseline, using descriptive statistics (mean, median, standard deviation, minimum, maximum). Out-of-reference-range values will be flagged as high (H) or low (L) and as being clinically relevant or not: the number of participants presenting out-of-range and clinically relevant values will be summarized.

All safety clinical laboratory data will be listed. Laboratory test results will also be compared to laboratory reference ranges and those values outside of the applicable range will be flagged as high (H) or low (L) and as being clinically relevant or not: the number of participants presenting out-of-range and clinically relevant values will be summarized. The quantitative laboratory data, along with changes from baseline

will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum). Change from baseline values at each assessment will be calculated as the assessment value minus the baseline value. The qualitative urinalysis data will be listed only.

All ECG data (PR, QRS, QT, QTcB, QTcF and HR) and overall ECG evaluation will be listed. ECG data, along with changes from baseline will be summarized using descriptive statistics (mean, median, standard deviation, minimum, maximum). Furthermore, categorical analysis of QTcF data will be presented as follows:

- Absolute QTcF interval prolongation
    - QTcF interval > 450 ms
    - QTcF interval > 480 ms
    - QTcF interval > 500 ms
- Change from baseline in QTcF interval
    - QTcF interval increases from baseline > 30 ms
    - QTcF interval increases from baseline > 60 ms

Mean value of change from baseline QTcF parameters will be plotted by group and time point. Out-of-reference-range values will be flagged as being clinically relevant or not: the number of participants presenting out-of-range and clinically relevant values will be summarised.

10.7 PK Analyses

The PK analyses will be performed by a PK analysis vendor (bioanalytical laboratory). PK parameters and concentrations data will be summarized using descriptive statistics by treatment, using tabular and graphical displays.

Non-compartmental analysis will be used for estimation of pharmacokinetic parameters. The following pharmacokinetic parameters will be calculated for piperaquine:

- C_{max} Maximal plasma concentration
- t_{max} Time at which the maximum plasma concentration occurs
- $t_{1/2}$ Terminal elimination half-life
- $AUC_{0-\infty}$ Area under the plasma concentration-time curve from time 0 extrapolated to infinite time
- AUC_{0-t} Area under the plasma concentration curve from time zero up to the last quantifiable concentration
- $AUC0_{0-24h}$ Area under the plasma concentration curve from time zero to 24 hours
- AUC_{0-72h} Area under the plasma concentration curve from time zero to 72 hours
- AUC_{0-168h} Area under the plasma concentration curve from time zero to 168 hours
- $\%AUC_{extrap}$ Percentage of AUC that is due to extrapolation from tlast to infinity
- CL/F Apparent total plasma clearance
- Vz/F Apparent volume of distribution during the terminal phase
- λz Terminal rate constant
- F_{rel} Relative Bioavailability (Note: If the dose is adjusted in Part 2 of the study the F_{rel} calculations will be dose adjusted).

The individual plasma concentration data, and the actual time for piperaquine administration and blood sampling will be used in the derivation of the PK parameters. If there is any doubt in the actual time a sample was taken, then the scheduled time will be used. AUC values will be calculated using the linear/log trapezoidal method, applying the linear trapezoidal rule up to C_{max} and the log trapezoidal rule for the remainder of the curve. Samples below the lower limit of quantification (LLOQ) prior to the first

quantifiable concentration will be set to zero. Samples with concentrations below limit of quantification (LOQ) after the first quantifiable concentration will be set to 'missing' and omitted from the analysis. Other PK parameters will be calculated according to standard equations. Details of the PK analysis, including the primary and secondary analysis, will be documented in the PK analysis plan.

10.8 Primary Analysis

The relative bioavailability will be assessed using the ratio of the geometric means for the granule dispersible [test] over the hard tablet [reference] in fasted state for $AUC_{0\text{-}72h}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}168h}$, $AUC_{0\text{-}\infty}$, and C_{max}.

10.9 Secondary Analyses

- The relative bioavailability will be assessed using the ratio of the geometric means for the dispersible granules formulation between fed [high-fat meal, low-fat African meal, and milk] over the dispersible granule formulation fasted [reference] for $AUC_{0\text{-}72h}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}168h}$, $AUC_{0\text{-}\infty}$, and C_{max}.
- PK parameters for the hard tablet (fasted) and the dispersible granule formulations (fasted and fed); C_{max}, $AUC_{0\text{-}24h,}$ $AUC_{0\text{-}72h}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}168h}$, $AUC_{0\text{-}\infty}$, time to maximum plasma concentration (t_{max}), terminal elimination rate constant (λz), terminal elimination half-life ($t_{1/2}$), apparent volume of distribution during the terminal phase (Vz/F), apparent total plasma clearance (Cl/F), and percentage of AUC that is due to extrapolation from t_{last} to infinity ($\%AUC_{extrap}$).
- AE counts and numbers of subjects with AEs will be summarized for each arm by MedDRA system organ class and preferred term. Concomitant medications, subject withdrawal, vital signs, laboratory tests, and ECG parameters will be summarized.

10.10 Interim analyses

No formal interim analysis is planned for this study, other than the safety/PK report that will be performed for the SRC review at the transition from Part 1 to Part 2.

10.11 Deviation(s) from the original statistical plan

As outlined above, the statistical analysis plan will be written and signed off before the database hard lock. Deviations from the original statistical analysis plans will be avoided, and in the unlikely event that they occur, will be reported and justification will be provided in the final report.

10.12 Handling of data

All data will be inspected for potential errors and a summary of missing data will be generated including the percentages of those with non-missing data, drop outs and replacement of participants. Unrecorded values will be treated as missing. The appropriateness of the method(s) for handling missing data may be reassessed at the data review prior to database lock. Further details on the data handling will be included in the site and/or study data management manual.

11 DUTIES OF THE INVESTIGATOR

11.1 Investigator's confirmation

This study will be conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice E6 (R2) (ICH-GCP), the EU Clinical Trials Directive (2001/20/ECC), IHI-IRB, NatHREC and TMDA.

11.2 Safety reporting

11.2.1 Serious adverse event reporting

All SAEs are to be reported immediately (within 24 hours of awareness of the SAE by the Investigator) to the Sponsor in writing. All written reports should be transmitted to the Sponsor by e-mail using the SAE report form. This includes a description of the event, onset date and type, duration, severity, relationship to the IMP, outcome, measures taken and all other relevant clinical and laboratory data. In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone, followed by a completed SAE report form. The initial report is to be followed by submission of additional information (follow-up SAE form) as it becomes available. Additional information related to safety assessment is provided in Section 8.

Expedited reporting to local Regulatory Authorities (TMDA), Independent Ethics Committee (NatHREC) and Institutional Review Board (IHI-IRB) will be done by the Investigator on behalf of the Sponsor in following their reporting requirements. Reporting mechanism for expedited reporting is demonstrated in Figure 1.

11.2.2 Project facilities and subcontracts

- Screening and safety assessments will be done at Bagamoyo Research and Training Centre (BRTC) Laboratory of Ifakara Health Institute in Tanzania. This will be backed up by:
    - Lancet Laboratories Tanzania Conservation House, Second Floor, Ali Hassan Mwinyi Road
    - Muhimbili National Hospital, P.O Box 65000 in Dar-es-Salaam, Tanzania
- See Section 1.2 for the list of providers involved in this clinical trial.

12 ETHICAL CONSIDERATIONS

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the local law and regulatory authority's requirements. In agreement with local requirements, the Independent Ethics Committee (IEC) and regulatory authorities will receive regular safety reports and will be informed about study stop/end.

12.1 Independent Ethics Committee (IEC)

Prior to enrolment of any participant into this trial, the study protocol and the informed consent form will be reviewed and approved by the National Health Research Ethics Committee (NaTHREC) in Tanzania.

Premature study end or interruption of the study will be reported within 14 days by the Sponsor or by the PI to the IRB and IECs. The regular end of the study and the final clinical study report will be submitted in accordance with the applicable timelines after the end of the study.

12.2 Evaluation of the risk-benefit ratio

Potential risks with PQP are mentioned in Section 20.5 . The participants will not profit from any direct benefit of the study drug, but they may profit from a comprehensive health check. If a chronic or underlying disease is identified, participants will be referred accordingly within the national health system.

In addition, there is the potential that the gained knowledge about new drug formulation could help in malaria control efforts. This could lead to societal benefits if a new PQP formulation improves bioavailability and is less sensitive (PK) to the impact of food.

12.3 Participant information and consent

Written informed consent of a participant, using the NaTHREC approved consent form, must be obtained before any study procedure is performed. Upon showing interest, NaTHREC -approved language and an appropriate and study-specific Participant Information Sheet(s) (PIS) will be made available to the potential participant and the opportunity to discuss the study will be given.

The participants will be fully informed orally by the delegated study staff about all aspects of the trial, the potential risks and their obligations. The following general principles will be emphasized:

- The participation in the study is entirely voluntary
- The refusal to participate involves no penalty or loss of medical benefits
- The participant may withdraw from the study at any time
- The participant is free to ask questions at any time to allow him or her to understand the purpose of the study and the procedures involved
- The study involves research of an investigational drug
- There is no direct benefit from participating
- The participant's general practitioner may be contacted to corroborate their medical history or seek additional information
- The participant's blood samples taken as part of the study will be stored at the site and samples may be sent outside Tanzania to collaborating laboratories. These samples will be identified only by code numbers.
- The aims of the study and tests to be carried out will be explained
- Reimbursement will be provided for participation as described in the protocol.
- All relevant clinical and laboratory results (serology, lab tests and interpretations of physical exams) will be shared directly with the concerned participants

- Relevant aspects regarding data protection and confidentiality

The participant will be given enough time to make an informed decision about his/her participation in the study. The participant will be asked to read, and consider the statement before signing and dating the Informed Consent Form. The consent form must be signed and dated by the delegated study staff at the same time as the participant signs. A copy of the fully signed form and PIS will be given to the participant and the original will be retained as part of the study records.

12.4 Registration of clinical trial

The study will be registered at:

- ClinicalTrials.gov
- Tanzania Clinical Trial Register (TzCTR) - imis2.tmda.go.tz/.

12.5 Participant confidentiality

The Investigator must assure that participants' confidentiality will be maintained and that their identities are protected from unauthorized parties. Participant's identity will not be disclosed to the Sponsor. The Investigator will maintain a Participant Identification List so that the participants can be identified.

Individual participant medical information obtained as a result of this study is considered confidential and non-anonymized disclosure to third parties is prohibited. Participant confidentiality will be further ensured by utilizing participant identification codes to correspond to treatment data in the computer files. No patient identifiable data will be collected in the eEDC tool except for date of birth, as this information is critical for the inclusion of participants and for the statistical analysis of the data. However, data minimization is applied and only month and year of birth are collected for participants.

As part of the informed consent process, the participants will be informed in writing that representatives of the Sponsor (like monitors, auditors, etc.), a Regulatory Authority or Ethics Committee may require direct access to parts of their medical records relevant to the study, including participants' medical history, and that all personal data will be handled strictly confidentially and in accordance with local data protection laws.

Blood samples collected for PK analysis, which cannot be done in Tanzania will be coded and shipped to Switzerland.

If the results of the study are published, it will be done without providing identifying information on the participants.

12.6 Participants requiring particular protection

Only healthy and literate participants will be asked to participate in this phase I clinical trial. Female participants must understand and be able to follow the contraception requirements detailed in the ICF.

12.7 Insurance

A clinical trial insurance will be provided by the Sponsor. A copy of the certificate will be filed in the investigator site file and the trial master file.

The Sponsor is insured to indemnify the Investigator against any claim for damages brought by a participant who suffers from a research related injury during the performance of the trial according to the protocol, except for claims that arise from malpractice and/or negligence. This is covered by the clinical trial's host institute (IHI).

In accordance with local regulations, the Sponsor will contract insurance for all study participants.

The Bagamoyo Clinical Trial Unit (BCTU) will be primarily responsible for providing participant's medical care whether it is related or not related to the study for the duration of the trial. If specialist, emergency care or hospitalization is needed, this will be provided at no cost to the participant at the Bagamoyo District Hospital or referral centers in Dar-es-Salaam, Tanzania.

For all unrelated conditions to the study procedures, the participant will be responsible for seeking and funding this care through the normal channels provided by the Ministry of Health and Social Welfare of Tanzania. The obligation to provide medical care for conditions arising during the trial that are not related to study product or study procedure will end with the last study visit of the participant.

12.8 Participant reimbursement

Participants will not be paid for their participation, but all expenses related to trial participation will be covered by the study. This will include meals during their in-patient stay and reimbursement for the transport fare (incurred when coming to BCTU for scheduled or unscheduled visits). In addition, they will be given 25,000 TZS (~USD 11) as compensation for their time at each scheduled visit and meals or snacks during the study related visits at the site.

12.9 Protocol amendments

All protocol modifications must be documented in writing. A protocol amendment can be initiated by either the Sponsor or any Investigator. The Investigator will provide the reasons for the proposed amendment in writing and will discuss with the Sponsor and the PI. Any protocol amendment must be approved and signed by the Sponsor and the PI and must be submitted to the appropriate IEC for information and approval, in accordance with local requirements, and to Regulatory Authorities if required. Approval by IEC (and Regulatory Authority, if applicable) must be received before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study participants, or when the change involves only logistical or administrative aspects of the study, e.g. change of telephone number(s).

13 QUALITY CONTROL AND QUALITY ASSURANCE: DESCRIPTION OF MEASURES

The PI will ensure that all study personnel are appropriately qualified and trained on all important study related aspects, including a protocol-specific training, GCP training, training on data entry and handling, study interventions and assessments and applicable documentation is maintained on site.

13.1 Risk management

The risk management log will be set up by the Sponsor. Potential risks to the study, their assessment and management will be documented by the Sponsor in a Risk Management Log. The log will be updated continuously throughout the study duration.

Special attention will be paid to risks associated with participant safety, critical study procedures and critical data.

13.2 Risk identification, assessment and mitigation

13.2.1 Study-specific preventive measures

Participants will require adherence to the preventive measure as described or indicated in Sections 13.2.2 and 13.2.3 below.

13.2.2 Birth control and pregnancy testing

Target group for birth control	Contraception required
Female participants of non-childbearing potential (WONCBP): Defined as either postmenopausal (evidence of menopause based on a combination of amenorrhea for at least one year and increased serum follicle-stimulating hormone (FSH) level (>30 IU/L), or surgical sterilisation (evidence of hysterectomy and/or bilateral oophorectomy)	None
Female participants of childbearing potential (WOCBP)	Reliable contraception in accordance with the Tanzania Clinical Trial Guidelines (https://www.tmda.go.tz/), must start one complete menstrual cycle prior to the first day of dosing and continue until 16 weeks after the IMP administration (to cover a full menstrual cycle of 30 days starting after 5 half-lives of last dose of IMP). Note: Highly effective birth control methods include: combined (estrogen and progestogen containing) oral/intravaginal/transdermal hormonal contraception associated with inhibition of ovulation, progestogen-only oral/injectable/implantable hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner or sexual abstinence.

13.2.3 Participant restrictions

Items participants must not consume or do	When participants must stop	When participants can re-start
Tobacco in any form (e.g., smoking or chewing) or other nicotine-containing products in any form (e.g., gum, patch, electronic cigarettes)	Any time at the facility during trial participation	When not in the facility
Meals/snacks/water	See Section 6	See Section 6
Not consume any other substances known to be potent inhibitors or inducers of the CYP3A4 system. This includes food or drink products containing cranberry, pomegranate, star fruit, grapefruit, pomelos, exotic citrus fruits or Seville oranges (including marmalade and juices made from these fruits)	Within 30 days or five half-lives (whichever is longer) before the planned first trial drug administration.	After trial completion/last visit.
Caffeine-containing or Xanthine-containing products	48 hours before the planned first trial drug administration and each out-patient/ follow-up visit.	After trial completion/last visit.
Energy drinks or drinks containing taurine, glucuronolactone (e.g. Red Bull)	48 hours before the planned first trial drug administration and each out-patient/ follow-up visit.	After trial completion/last visit.
Alcohol	48 hours before the planned first trial drug administration and each out-patient/ follow-up visit. On other days: less than 14 units a week and less than three units in one day is permitted.	After trial completion/last visit.
Strenuous physical activity	48 hours before screening, admission and out-patient/follow-up visit.	After trial completion/last visit.
Activity	Participants will be requested to remain in a semi-supine position for the first four hours after dosing each day, except to use the bathroom.	

Items participants must not consume or do	When participants must stop	When participants can re-start
	Participants may then be ambulatory but should not engage in strenuous activities and should rest semi-supine for at least five minutes prior to any vital signs or at least ten minutes prior to ECG measurement.	
Any prescription medication	14 days or five half-lives (whichever is longer) before the planned first trial drug administration.	After trial completion/last visit. If participants have a medical need to take any medication or have any medications prescribed to them by a doctor, they should follow the medical advice but inform the Investigator as soon as possible afterwards. Participants should be informed not to stop taking any medication that has been prescribed by their general practitioner or other doctor.
Any over-the-counter medication	Seven days or five half-lives (whichever is longer) before the planned first trial drug administration.	
Any herbal remedy or dietary supplement containing St John's Wort	30 days before the planned first trial drug administration.	After trial completion/last visit.
Blood and plasma donation	90 days before the planned first trial drug administration.	Three months after trial completion/last visit.
Contraception: Participants must comply with the appropriate contraceptive requirements	As indicated in Section 13.2.2	As indicated in Section 13.2.2
COVID-19 vaccination	Four weeks before the planned first trial drug administration	Seven days after trial completion/last visit.

13.3 Monitoring

To ensure compliance with the protocol, monitoring visits by a professional representative of the sponsor will be scheduled to take place regularly, and at appropriate intervals according to the monitoring plan.

Monitoring will be conducted according to ICH-GCP. The individuals responsible for monitoring the study will have access to all records necessary to ensure the integrity/validity of the recorded data and will periodically review the progress of the study. The monitor must contact the site prior to the start of the study to discuss the protocol and data collection procedures with the site personnel.

The investigator must agree to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

Additional site visits may be made during the course of the trial and at the end of the surveillance period as delineated in a monitoring plan approved by IHI and the Sponsor.

The monitoring plan will include the percentage of participant charts to be reviewed, which and what proportion of data fields will be monitored, as well as who will be responsible for conducting the monitoring visits and who will be responsible for ensuring that monitoring findings are addressed. Additionally, the sponsor will perform a Site Qualification visit to assess the suitability of the site for conducting the trial. The trial will only begin following a written approval from the sponsor.

13.4 Audits and inspections

For the purpose of compliance with ICH-GCP and regulatory guidelines, it may be possible that the sponsor/designee or a national ethics or regulatory authority may conduct a site audit/inspection. This may occur at any time from start to conclusion of the study.

The QA designated site staff will conduct internal audits to check that the trial is being conducted, data recorded, analyzed and accurately reported according to the protocol, sponsor's SOPs and in compliance with ICH GCP. The audits will also include laboratory activities according to an agreed audit schedule.

The investigator agrees to allow the auditor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor to discuss findings and any relevant issues.

If a regulatory authority requests an inspection, the investigator must inform the sponsor or its designee immediately about this request. The investigator(s) and the study coordinator(s) must make the relevant records available for inspection and must be available to respond to reasonable requests and audit queries made by authorized representatives of regulatory agencies. The sponsor will provide any needed assistance in responding to regulatory audits or correspondence.

13.5 Confidentiality, data protection

The study will be monitored by the CRO subcontracted by the sponsor. CRO representatives and representatives of the local Regulatory Authorities and Ethics Committees will be allowed access to all information resulting from this study including the access to study-related documentation. The subjects' confidentiality will be respected as required by local law.

All parties agree to adhere to the principles of medical confidentiality in relation to Clinical Study Subjects involved in the Clinical Study. Neither party shall disclose the identity of Clinical Study Subjects to third parties without prior written consent of the Clinical Study Subject.

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant study ID on all trial documents, study participant card, and any electronic database. All documents will be stored securely and only accessible by trial staff and authorized personnel only.

The trial will comply with the Data Protection Act, 1998, which requires data to be anonymized as soon as it is practical to do so.

13.6 Storage of biological material and related health data

The data and remaining biological materials related to the trial will be stored at the IHI archive and laboratories in Bagamoyo. All study data will be archived for a minimum of 25 years after study termination or premature termination of the clinical trial. The samples will be destroyed after the specified period. Participants will be asked for their consent to allow institutional ethics review boards to use anonymized data and aliquots of the samples for assessments of other markers of infectious disease or protection.

13.7 Safety Review Committee (SRC)

A formal Safety Review Committee (SRC) will be established by the sponsor to oversee the study.

The SRC will evaluate the data at the interim analysis and provide recommendations to the Sponsor with regard to continuation of the study (more details are provided in the SRC charter).

The SRC's composition, responsibilities and procedures will be pre-specified in details by a safety monitoring charter. The members of the SRC are responsible for decisions related to the safety of participants and the continuation of the study. The SRC will assess all preliminary safety and available PK data whenever indicated as a result of safety concerns. They will decide on the appropriateness of subsequent cohorts and the continuation of the study.

At the minimum, the SRC will include the following members (more details are provided in the SRC charter):

- the principal investigator or delegate
- the medical monitor or delegate
- the medical director or delegate
- the independent local safety monitor

14 FUNDING

The study will be funded by the sponsor (Medicines for Malaria Venture (MMV)). The Sponsor, the Principal Investigator and supporting organizations / institutions declare to have no conflict of interest.

The Investigators, including the Principal Investigator and/or any sub-Investigators, directly involved in the treatment or evaluation of participants may be requested to provide a financial disclosure. All relevant documentation will be filed in the Trial Master File.

15 DISSEMINATION OF RESULTS AND PUBLICATION POLICY

15.1 Dissemination to scientific community; incl. lead in publications

All data and results generated in the study will be owned by the Sponsor, who may utilize them in various ways, such as for submission to the regulatory authorities.

The Sponsor will make the results derived from the study freely publicly available through appropriate open access databases, repositories and similar tools. The Sponsor will not specifically protect them as intellectual property, i.e. not to file any patent application, or otherwise protect, assert or take any action to enforce any rights on such results.

The Investigators will be involved in writing and/or reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Apart from obvious flaws to the conduct of the study, which may preclude data publication, safety and efficacy data will be published under the supervision, review and formal authorization of the Sponsor.

Authorship follows the International Committee of Medical Journal Editors (ICMJE) principles, publications will follow CONSORT statement.

Authorship for publication in scientific journals will be offered to each party that has substantially contributed to the work reported in the publication. It is expected that authorship of such publications will be led by the Sponsor.

The final clinical study report will be the responsibility of the Sponsor and will be submitted to the regulatory authorities and ethics committee(s), if required by these bodies when available.

The Sponsor encourages the communication and/or publication of the results, in accordance with the terms of the Clinical Trial Agreement.

15.2 Information of community and policy makers

Study outcomes will be disseminated to study communities and local authorities at the end of the study. A final safety report will be submitted to all ethics committees and regulatory authorities.

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