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Participant ID: MMV_SMC_22_01_01_-I__I__I__I

Participant Information Sheet

Clinical 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.

Short title: Piperaquine granule formulation relative bioavailability and food effect study in healthy volunteers.

This clinical study is organized by MMV Medicines for Malaria Venture, Geneva, Switzerland, in collaboration with Ifakara Health Institute of Tanzania.

Protocol Number	MMV_SMC_22_01		
Version Number	2.0	**Document Date**	14.02.2023
Study Registration	**ClinicalTrials.gov: NCT05930782**		
Responsible Institution	Isabelle Borghini-or Stephan Chalon 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 P.O. Box 74, Bagamoyo, Tanzania		
Investigational Medicinal Product	Piperaquine (PQP)		

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Dear Sir or Madam,
We would like to invite you to take part in our clinical study investigating a new child-friendly, taste-masked dispersible granule formulation of PQP for the future potential prevention of malaria. PQP is a well-known antimalarial drug and already available for oral treatment under another formulation.

Your participation is entirely voluntary. Before you decide whether to participate, it is important that you understand why the study is being conducted and what is involved. In this participant information sheet, we explain what the study is about and what is involved in both a short version (summary) and a longer version with more details. Please take the time to read the following information carefully. If anything is not clear, or if you would like more information, please do not hesitate to ask us questions.

Thank you for your consideration and taking the time to read this information.

Summary:

1.	**Why is this clinical study needed? Aim and Selection** Malaria is still a major problem in the African Region, and about 80% of malaria deaths occur in children under five years of age. The WHO strongly recommends the use of medicines to prevent malaria infection and its effects (malaria chemoprevention) in infants, children under five years and pregnant women. Safe and well tolerated compounds are needed for these preventative medicines and new combinations need to be tested as malaria parasites become resistant to existing drugs. Piperaquine phosphate (PQP) combined with another antimalarial already in use is a potential option for malaria prevention as it has been in use for over 50 years. As the people to benefit from malaria prevention are mostly children, a child-friendly way of giving the medicine is needed. A new granule version of PQP has been developed which can be mixed with water and should have acceptable taste. To find out how well and how fast the new child-friendly PQP oral granule formulation is absorbed and eliminated in the human body when administered with different food conditions, we need to test it first in 60 healthy adult participants (male and female). The total study duration is 4 to 6 months. Each participant will be in the study for 37 to 75 days.
2.	**General information about the study** ● PQP is already available as part of a combination products e.g. an antimalarial known as D-ARTEPP® in Tanzania, for treatment of uncomplicated malaria. ● We would like to test a child-friendly PQP oral granule in adults to get preliminary information. ● Child-friendly PQP oral granules have not been tested in humans before. ● We would like to find out how the human body absorption is affected, when administered with different food conditions. The study doctor will let you know the type of food that you will be given. You can be given either high fat meal, low fat meal or milk or no food (fasting). You will not choose the type of food. ● We would like to find out how well tolerated the new child-friendly PQP oral granule is.
3.	**What are the procedures?**

	Taking part in the study will involve: ● Attending several hospital appointments to check that you are healthy and can participate in the study. ● After an overnight fast, taking the study medicine with or without food (see above), and staying in the hospital for three days, where we will closely follow you and do several tests to check your heart, your blood and vital signs. ● Samples of your blood will be checked to see how much of the study drug is in it at regular time points (Pharmacokinetics). ● Optional genetic testing of a liver enzyme (CYP450) from a blood sample. ● Attending follow-up checks for 30 days after you have taken the drug.
4.	**What are the benefits of participation?** There will be no direct benefit to you if you decide to participate. However, you may profit from a comprehensive health check and aid future malaria control efforts if the new PQP child-friendly formulation is shown to improve the amount of study drug in the body at a given time point (bioavailability) and this isn't affected by the type of food eaten.
5.	**Is it mandatory to participate in this study?** No, it is completely up to you. If you decide to take part you will be asked to sign a consent form. **What are my duties?** You will be asked to adhere to a certain lifestyle during the study and for women to follow contraception requirements.
6.	**What are the risks and burdens?** a) Risk of taking Piperaquine (PQP) PQP has been used extensively in many African and South East Asian countries. It's known to be well tolerated in children and adults in the treatment of uncomplicated malaria, when combined with another medicine for malaria called Dihydroartemisinin (DHA). Common side effects (that affect more than 1 in 100 people, but fewer than 1 in 10 people, who take the medicine) are: • a change in the heart's electrical system (called prolonged QTc interval), and increased heart rate (tachycardia), anaemia (reduced haemoglobin), fever, headache and feeling weak. Uncommon side effects (that affect more than 1 in 1000 people, but fewer than 1 in 100 people, who take the medicine) are: a slowing of heart rate (bradycardia), increases in the liver function enzymes (proteins that speed up chemical reactions in the body), dizziness, nausea and vomiting, abdominal pain, diarrhoea, skin changes such as inflammation, itchiness, rash or redness/dryness, muscle aches and joint pain, reduced appetite, cough, fever. Rare/ Very rare side effect (that affect fewer than 1 in 1000 people who take the medicine): convulsion (similar to an epileptic fit/seizure). PQP as a dispersible granule formulation has not been administered to human subjects yet. PQP in tablets form has been given to healthy participants in a Phase 1 study. The study participants were reported to have had temporary mild abnormal laboratory liver test results without being accompanied by clinical symptoms. These abnormal liver test results were considered rare.

	There is also a risk of increased in absorption of PQP (and QTc effect) by the body in case it is taken together with some medications (antibiotics and herbal medication), that are strong 3A4 inhibitors. PQP is known to induce abnormal electrical conduction within the heart, which can lead to a change in the heart's electrical system (QTc prolongation) in human participants and possibly abnormal beats of the heart with a risk of loss of consciousness. Therefore, during this study, healthy participants with risk factors for abnormal electrical conduction within the heart will be excluded and enrolled participants will be monitored for the effects of PQP on electrical conduction within the heart through Electrocardiogram recording. b) <u>Risk associated with blood sampling and examinations</u> There may be a risk of infection, bruising or pain from the procedures. c) <u>Allergic reactions</u> Everyone reacts differently to different medicines. There are very rare cases of skin irritation after taking PQP. d) <u>Pregnancy risk and risk to foetus development</u> Current data are not sufficient to exclude any potential risk to unborn babies if you become pregnant during the study. Therefore, we ask you to follow strict contraception requirements. e) <u>Study burden</u> Attending all appointments and staying in the hospital for parts of the study period will require your time and dedication.
7.	**Will I know the results?** All information learned during the study and relevant to your health and decision to continue taking part in the study will be communicated to you in a timely manner. At the end of the study, we will share the study results with you.
8.	**Will my data and samples be kept confidential?** During this clinical study, certain data will be collected, such as your name, date of birth, gender, address, phone number, medical condition and history, medical images, biological samples, genetic sequence, race and ethnicity, etc. We call this "Personal Data" as this allows to identify you. Your Personal Data is collected and kept confidential by the clinical site. All persons involved in the collection of your Personal Data at the clinical site are subject to professional secrecy. The clinical site will replace your Personal Data with a code. We call this the "Personal Coded Data". The Sponsor will only receive the Personal Coded Data and will not be able to identify you. Only some of the Sponsor's employees, vendors or health agencies will be able to see the Personal Data when they check the quality and progress of the Study (monitoring). Since the objective of clinical studies is to advance science for obtaining new treatments, the Sponsor is required to combine your Personal Coded Data collected from the study with other participants´ Personal Coded Data. This is done in order to (i) assess the safety and efficacy of the study drug, (ii) submit the study drug to the competent health agencies for approval and generally (iii) support scientific research. In order to meet this objective, the following persons and organizations need to have access to your Personal Coded Data:

	• Sponsor's employees, collaborators or vendors (such as clinical research organizations); • Worldwide health agencies' employees and officers (i.e. Federal Drug Agency, European Medicine Agency, etc.); • Regulatory authority, Ethics Committees or Investigational Review Boards, as applicable; • Editors of scientific journals; • Insurers, as the case may be. They may be located in other countries but during the transfer, the Sponsor will ensure protection of the Personal Coded Data as required by law. The Sponsor and the clinical site have to keep all study data by law for several years in accordance with applicable law. If the results of the trial are published, you will not be named. You understand that it is not possible to erase the Personal Data as the study data needs to be complete, precise and available for regulatory purposes. **What will happen to my Samples?** You consent to the collection, processing and storage of your biological samples. The samples will be destroyed after completion of the clinical safety report or at the discretion of the sponsor and your study doctor. Should a regulatory authority request further testing, the Sponsor will proceed with such testing.
9.	**Can I withdraw from the study?** You are free to withdraw at any time, without giving a reason and this will not affect your right to receive any medical attention you require, but you might need to attend a follow-up control check for your own safety. Your Personal Data and samples provided until then in the study will still be analyzed and used in accordance with the section above.
10.	**Will I receive compensation?** Your participation is entirely free, and you will be compensated for your time by receiving TSH 25,000 per study visit. **Who owns the results of the study**? The Sponsor is the owner of the Study results and any intellectual property rights derived from the Study results. By signing this form, I agree to the use of the Personal Coded Data for the research as described above.
11.	**Is the study insured?** All participants will be insured for any harm caused by participation and in connection with the study.
12.	**How is the study funded?** This study is financed by the Sponsor, MMV Medicines for Malaria Venture (MMV).

13.	**Who do I contact if I have any concerns?** If you have any concerns or complaints about anything to do with the study, please contact: **Principal Investigator:** Dr Florence Aphida Milando, Tel: +255 712 935292 Email: fmilando@ihi.or.tz **Lead Physician:** Dr. Hussein Mbarak Tel: +255623397766 Email: hmbarak@ihi.or.tz **Community engagement personnel :** Bakari Mwalimu Tel: +255655680551 Email : bmwalimu@ihi.or.tz **For data privacy concerns** : Sylvie Fonteilles Drabek, General Counsel & EVP at MMV Medicines for Malaria Venture (E-mail: privacy@mmv.org)

What would taking part involve and detailed information?

1. **Why is this clinical study needed?**

Aim

Malaria is still a major problem in the world, with most of malaria deaths in children under five years of age in WHO (World Health Organization) Africa Region. There is strong benefit from using malaria medication to protect children by clearing existing infections and preventing malaria infections during the season of greatest risk (chemoprevention). Only two malaria medications,SP (Sulfadoxine-Pyrimethamine) and SPAQ (Sulfadoxine-Pyrimethamine and Amodiaquine) are currently recommended by WHO for chemoprevention, The efficacy of these medicine is currently threatened by increasing resistance to SP.

PQP is available as a fixed dose in combinations such as an antimalarial called Dihydroartemisinin (DHA) as D-ARTEPP in Tanzania, for treatment of uncomplicated malaria. The combination has been used extensively in many African and South East Asian countries. It is known to be well tolerated for the treatment of uncomplicated malaria in children and adults.
A new dispersible child-friendly granule formulation is being developed to improve the amount of PQP in the body at a given time point (bioavailability) and prevent it from being affected by the food eaten (food effect).

The aim of this pilot bioavailability/food effect study is to perform preliminary assessments on sixty (60) healthy adult participants (male and female) to evaluate the effects of different type of food regimen, including fasting condition, during the administration of a new child-friendly PQP oral granule formulation, as compared to a reference tablet formulation of PQP, on how well and how fast it is absorbed in the human body.

Selection

To participate in this study, we will check that:

- You have consented to participate in the study
- You are healthy
- You are between 18 years and 55 years of age at the time of consent
- You have a normal body weight
- You understand and agree to comply with the study visits and requirements
- You are willing to follow contraception
- You are willing to not donate sperm or ova.

In order to take part, you also **must not:**

- Be pregnant or breastfeeding (for female participants)
- Have a female partner(s) who is (are) pregnant or lactating (for male participants)
- Have milk intolerance
- Be unable or unwilling to follow the food requirement
- Currently use tobacco in any form
- Have donated blood or blood products (excluding plasma) within 90 days prior to the first day of dosing
- Have received or plan to receive a COVID-19 vaccination two weeks prior to dosing or one week after trial last visit.

- Have received PQP containing medication within 90 days or any other medications from 14 days prior to first planned dosing of investigational medicine. If a doctor has prescribed any medication for you or if you took herbal therapies, you must tell the Research Physician.

- Be unable to swallow tablets
- Have had any drug or alcohol abuse within the two years
- Have used any dietary supplements or herbal medicines within 30 days prior to the first day of dosing.
- Have ingested any poppy seeds within the 24 hours prior to screening or admission.

The medical doctors will ask questions about your health and your current medication. They will ask you about any previous diseases you might have suffered from, potential allergies, and conditions that may prevent you from taking part in the study.

They will also perform different examinations and several laboratory tests. You will be asked to give blood samples, urine to detect any potential infections such as malaria, HIV and hepatitis B or C. There may also be other reasons why you might not be suitable to take part in the study for your own safety. The doctor will discuss the test results with you.

2. General information about the study

This clinical trial is called "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"

What do these terms mean in more details?

a) Randomization means that participants are allocated to a treatment group at random, by chance. Therefore, it is a matter of chance whether a participant is assigned to five different treatment groups. By comparing these treatments groups, we can really see if the amount of drug in the blood after administration is the same or increased by chance or not.
b) Open label means that both the participant and the medical team will know which treatment has been assigned to whom.
c) A phase I is a study which determines if a test substance does not induce any important medical reaction in healthy participants. Phase 1 study usually also evaluate Pharmacokinetic (see below).
d) Pharmacokinetic tells how much there is test substance in your body over a period of time and how it is absorbed and then eliminated from your body. To know this, we need to take several blood samples at different times.

Where will the study be conducted?

The study will be conducted at Bagamoyo Clinical Trial Facility (BCTF) of Ifakara Health Institute located at Kingani Estate in Bagamoyo, which is part of the Ifakara Health Institute in the Bagamoyo district.

Who is responsible for the study?

The institution responsible for the conduct of the study is MMV Medicines for Malaria Venture (MMV). They are called the Sponsor. We are conducting this study in accordance with Tanzania's laws and internationally recognized guidelines. The Ifakara Health Institute Independent Review Board and the National Institute for Medical Research, the competent and independent ethics committees in Tanzania, have reviewed and approved this study. As well, Tanzanian Medicines and Medical Devices Authority has also reviewed the study and information about this medicine and has approved the study to take place.

How does the study work?

A total of sixty (60) healthy adult participants (male and female) will be enrolled: 24 in part 1 and 36 in part 2.

Healthy adult participants (male and female) will be randomly allocated (one after the other) to one of the 5 treatment groups as follows:

Part of the study	Treatment Groups	Number of Participants	Conditions for treatment administration.	Treatment /dosage
Part 1	1	12	Fasting for at 10 hours before treatment	PQP hard tablet (320 mg)
	2	12	Fasting for at 10 hours before Treatment	PQP dispersible granule (320 mg)
Part 2	3	12	Fast for at least 10 hours before feeding with a high-fat meal (feeding will happen at least 30 minutes before treatment).	PQP dispersible granule (320 mg)
	4	12	Fast for at least 10 hours before feeding with a Low-fat meal representative of the African diet (feeding will happen at least 30 minutes before treatment).	PQP dispersible granule (320 mg)
	5	12	Fast for at least 10 hours before feeding with 250 ml of whole milk (feeding will happen at least 30 minutes before treatment).	PQP dispersible granule (320 mg)

The study doctor will let you know the fasting conditions required and the type of food that you will be given. You can be given either high fat meal, low fat meal or milk, or being dosed in fasting condition. You will not choose the type of food.

3. What are the procedures?

Participating in the study involves coming to the clinical trial facility for several appointments. The total study duration is 4 to 6 months; each participant will be in the study for 37 to 75 days.

Screening period (D-45 to D-2)

You will come to the facility and you will be screened. First, we will explain the study to you. After you have signed the informed consent and agreed to take part in the study, we will ask you questions about your health, recent illnesses, and medications. If you seem suitable, we will:

- Give you a medical examination. This includes taking your vital signs, an electrocardiogram (a painless test that records the rhythm of the heart) to check that you are healthy.
- Measure your height, and weight.
- Do a blood pregnancy test on women of childbearing potential.
- Discuss and consult you on contraception requirements
- Test your urine and blood for different health conditions and infections.
- Test your blood for malaria
- Test your blood for the hepatitis viruses B and C (viruses that can damage the liver) and HIV (the AIDS virus).

If any of the tests are positive, we will treat you on site or refer you to the National Health System or the clinic at the Bagamoyo District Hospital. This will be for counselling, follow-up and referral if needed. A positive HIV or hepatitis test means that you are at risk of developing a serious disease in the future, and you might need to take medications to prevent it.

During this first visit, we will take your passport size picture to make a study identification card, so that we can easily identify you when you come for subsequent study visits. You must keep this card with you all the time, so that you have contact numbers for the study team available in case of a medical emergency in case you are enrolled into the study.

If any of the screening tests need repeating, or if we cannot do all the tests at your first visit, we will ask you to come back for a repeat tests or do the remaining tests.

Admission to the facility (Day -1)

You will be admitted to the ward of the Bagamoyo Clinical Trial Unit on the day before receiving the treatment.

Please do not bring any food or drink from home as well as any recreational drugs, cigarettes, alcohol and medicines. This is for your safety and ensures you are at the best health.

At the ward we will:

- ask you about your health since your last visit and do an examination
- check your vital signs and heart
- take some blood to check you are healthy
- do a blood pregnancy test on women of childbearing potential .

We will ask you to fast for at least 10 hours before receiving the trial medication.

Study procedures (Day 1 to Day 3)

You will stay on the ward for two (2) days and three (3) nights in a row. We will ask you to come back after discharge for the follow-up visits on days 5,8,15,22 and 30.

The following procedures and assessment will be done on the day when you receive your treatment, during the observation days and at the follow-up visit.

Study Day	Procedures and assessments
Treatment day Day 1 in the ward	Early in the morning, we will review your medical history and medications and ask if you are still willing to participate in the study. You will be allocated at random, by chance to the treatment group. Neither you nor the Doctor will know in advance to which treatment group you will be allocated. Before and after your treatment we will do the following: ● check your vital signs ● take blood at 7 different time points (this will correspond to a total of 21 ml = 4 teaspoons of blood) ● Do electrocardiogram at 5 different time points ● Within 10 minutes after receiving the study compound, you will be asked to complete a questionnaire on the taste of the compound. ● No food will be allowed for 4 hours after having received the study compound. After that period, you will receive standardized meals at regular times during your stay in the ward. ● Water will not be permitted 1 hour before and 1 hour after dosing. Otherwise, you may drink water at your own convenience.
Observation days Day 2	On day 2, we will do the following: ● check your vital signs and examine you in case of any symptoms ● take blood samples (3 ml = less than a teaspoon of blood) ● do Electrocardiogram once
Observation days Day 3	On 3 days, we will do the following: ● check your vital signs and examine you in case of any symptoms ● take blood samples (6 ml = a teaspoon of blood) ● do Electrocardiogram once In the afternoon of day 3, you will be discharged.
Follow-up visits Days 5,8,15,22 and 30	On days 5,8,15,22 and 30 you will come back to the facility for a medical examination. We will do the following: ● check your vital signs ● take blood samples (3 ml = less than a teaspoon on day 5 and 22; 6 ml = a teaspoon of blood on days 8 and 15; and 5 ml = a teaspoon of blood on day 30). ● examine you in case of any unusual symptoms ● do a blood pregnancy test on women of childbearing potential on Day 30 ● check for malaria on day 30 ● do Electrocardiograms

During the whole study, you will be asked to give a total of 67 ml (about 14 teaspoons) of blood.

CYP450 is an enzymatic system (proteins) involved in causing chemical changes of a drug in your body and that occurs differently from one individual to the others. It causes each individual to handle PQP differently. In this study, to find out how different forms of CYP450 influence the biotransformation of PQP we would like to do a genetic testing of CYP450 from a single sample of

your blood. You can opt out of this genetic test if you wish, without any effect on your participation in the study.

4. What are the benefits?

You will not have a direct benefit if you participate in this study.

You may benefit from a comprehensive health check. The screening tests might be of benefit to you if we find an important medical problem. If any of the tests are positive, we will treat you on site or refer you to the National Health System or the clinic at the Bagamoyo District Hospital. This will be for counselling, follow-up and referral if needed.

You will be closely monitored and you will receive free medical attention for illness or injury related to study participation during the entire study period. Routine medical or dental care and illness or injury not related to the study will not be compensated.

If you participate, you may be helping malaria control efforts in the future if a new PQP formulation improves the amount of study drug in the body at a given time point (bioavailability) and is minimally affected by the food eaten.

5. Do I have to participate?

Your participation is voluntary. If you do not want to take part or later change your mind, you do not have to justify this.

Duties if you decide to participate in the study:

You must:

- Not use tobacco in any form (e.g. smoking or chewing) or other nicotine-containing products in any form (e.g. gum, patch, electronic cigarettes)
- Not consume 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 before the first planned trial drug administration.
- Not exercise very hard (anything that might make your muscles ache – for example, manual work, running, cycling, gym workouts, weightlifting), 48 hours before screening, admission and outpatient / follow-up visit.
- Not have any food or drinks containing xanthine (e.g. chocolate, tea, coffee or cola drinks), 48 hours before the planned first trial drug administration and each out-patient/ follow-up visit.
- Not drink energy drinks or drinks containing taurine, glucuronolactone (e.g. Red Bull and Mo energy) 48 hours before the planned first trial drug administration and each out-patient/ follow-up visit.
- Not consume alcohol 48 hours before the first planned trial drug administration and each outpatient / follow-up visit. On other days: less than 14 units a week and less than three units in one day is permitted.

- Remain in a semi-supine position for the first four hours after dosing each day, except to use the bathroom.

- Fast overnight (no food or drink, except water) for at least 10 hours each time before getting treatment and to remain fasting for four hours afterwards if you are in treatment groups 1 and 2.

- Not take any other medicines (prescribed, non-prescribed, dietary supplements, herbal remedies) from now until the end of the study. If another doctor advises you in the meantime to take a medicine, please let us know as soon as possible and inform your doctor that you are taking part in this study.
- Not donate blood and plasma 90 days before the planned first trial drug administration.
- Notify the medical team of any new symptoms or any concerns or injuries to your person during the study
- Not take COVID-19 vaccination two weeks before the planned drug administration or one week after trial last visit.
- Be willing to follow the contraception requirements of the study, which are detailed below;

Contraception and risks

If you are a **woman** of childbearing potential, you have to use a highly effective contraception.

Personnel qualified in family planning (e.g., a nurse or a doctor) will counsel you on the options and what is best in your case.

1) Options of highly effective contraceptives:
- Hormones (taking tablets by mouth, injected or implanted under the skin)
- Intrauterine device (T-shaped device that is placed inside the womb) to prevent pregnancy either by releasing hormones or not
- Vasectomized partner (surgical procedure for male sterilization or permanent contraception)
- Bilateral tubal occlusion (a long-life form of birth control, sterilization)
- Abstinence from having sex.

Contraceptives must be started at least **30** days prior to the first dose and need to be continued up to **16 weeks** after the last dosage of PQP. If you become pregnant within 4 months after receiving the trial medication, you must inform the study doctor at Ifakara Health Institute as soon as possible.

6. What are the risks and burdens?

In any clinical study, there is a risk of an unexpected and serious reaction to the test substance, which could be life-threatening.

a) Risk of taking the test substance (PQP)

PQP as a dispersible granule formulation is a new formulation which has not been administered yet. PQP as tablets have been administered to healthy subject in phase 1 clinical study, participants (who were given PQP in tablets) were reported to have had temporary mild abnormal laboratory liver test results without being accompanied by clinical symptoms. These abnormal liver test results were considered rare (less than 1 in 1000 people).

Side effects of piperaquine in (PQP); The following side effects (called adverse events) have been experienced after people took PQP in combination with another antimalarial substance called Dihydroartemisinin (DHA) in the past. You may or may not experience any of these side effects: Common side effects (that affect more than 1 in 100 people, but fewer than 1 in 10 people, who take the medicine):

• a change in the heart's electrical system (called prolonged QTc interval), and increased heart rate (tachycardia)

• anaemia (reduced haemoglobin)

- fever
- headache
- feeling weak

Uncommon side effects (that affect more than 1 in 1000 people, but fewer than 1 in 100 people, who take the medicine):

- a slowing of heart rate (bradycardia)
- increases in the liver function enzymes (proteins that speed up chemical reactions in your body)
- dizziness
- nausea and vomiting
- abdominal pain
- diarrhoea
- skin changes such as inflammation, itchiness, rash or redness/dryness
- muscle aches and joint pain
- reduced appetite
- cough
- fever

Rare/ Very rare side effect (that affect fewer than 1 in 1000 people who take the medicine):

- convulsion (similar to an epileptic fit/seizure).

During this study, healthy participants with risk factors for abnormal electrical conduction within the heart will be excluded and enrolled participants will be monitored for the effects of PQP on electrical conduction within the heart through ECG recording (simple or triplicate ECGs recording depending on the time point). Also, biochemistry and hematology measurements (from blood samples) will be done periodically as part of clinical monitoring.

You will remain in the facility under medical supervision until 48 hours following the drug administration and will be followed up to Day 30 (+/-1 day).
The medical team will check you frequently for symptoms or side effects and provide treatment accordingly, if necessary.

b) Risk associated with blood sampling and examinations

All medical procedures involve some risk of injury such as a risk of infection, bruising, or pain from the procedures. Blood will need to be taken from you. This will be done with a cannula (a small tube inserted into your vein) or a needle.

The pads we stick to your chest to monitor your heart may irritate your skin and cause itching and redness. We may have to shave you to make sure they stick correctly.

All reasonable precautions will be taken to avoid these associated risks.

c) Allergic reactions

Everyone reacts differently to different medicines. There are very rare cases of skin irritation after taking PQP.

d) Pregnancy risk and risk to foetus development

There is a potential risk to unborn babies if you become pregnant during the study. Therefore, it is necessary to avoid getting pregnant during the study or within 4 months after receiving the trial medication and follow strict safety and contraception requirements. If you or your partner (for male participants), becomes pregnant during this time period, you must inform the study doctor immediately and you will be asked to provide information on the course and outcome of the pregnancy. The study doctor will discuss these steps with you.

In addition, three pregnancy tests are carried out in all women participating in the study of childbearing potential : one at the screening, one on the day of admission and one at the last follow-up visit.

e) Study burden

Attending all appointments and staying in the hospital for parts of the study period will require your time and dedication.

7. Results

During the study, the study doctors will inform you orally and in writing of any new results and findings that are important to you personally and to decide whether you want to continue participating in the study.

"Incidental findings", for example, results that were not specifically researched for, but found by chance during a test (such as blood sample for example), will be communicated to you if these findings are relevant to your health and well-being. This means that you may also be informed about an unknown disease if this is detected by chance. If you do not want to be informed about this, please inform your study doctor.

At the end of the study, your study doctor will receive the study results and will share them with you.

8. Will my data and samples be kept confidential?

The steps taken to ensure your confidentiality are detailed below:

a) Identifier- anonymity

If you agree to participate in the study, certain data will be collected, such as name, date of birth gender, address, phone number, medical condition and history, images, biological samples, genetic sequence, race and ethnicity, etc. We call this “Personal Data” as this allows to identify you..

Your samples and other medical data will not include any personal identification details. Your data will be stored using a unique patient identification number. This process is called coded data. The study doctors are responsible for maintaining the code list that links your assigned participant identification number to your name. This code list will be kept in a safe place at the Ifakara Health Institute and will allow you to be identified and contacted in case of emergency.

b) Access to your information by Sponsor’s employees and external people

The information that we collect may be reviewed by study sponsor’s employees and sponsor’s representatives (collaborators or vendors, such as clinical research organizations), authorized members from the government or regulatory health authorities, worldwide health agencies’ employees and officers (i.e. Federal Drug Agency, European Medicine Agency, etc.), independent ethics committees or institutional review boards’ members as part of their responsibility with

regards to the supervision of this study, editors of scientific journals, insurers, as the case may be. All of these must also maintain confidentiality of your records within the limits of the law. They may be located in other countries but during the transfer, the Sponsor will ensure protection of the Personal Coded Data as required by law.

If the results of the trial are published, your identity will remain confidential.

c) Transfer and storage of data and blood samples

Your coded data will be transferred to Switzerland, the UK and the European Union; therefore, your data will be protected and follow applicable laws.

Several blood samples collected for specific analysis, which cannot be done in Tanzania will be coded and shipped to Switzerland and the UK. They will be destroyed after the clinical safety report has been completed or at the discretion of the sponsor and PI.

The Personal Data will be stored for a period of time in accordance with applicable laws.

The code list and your medical data will be kept in a safe place at the Ifakara Health Institute for a period of 20 years after the end of the study.

9. Can I withdraw from the study?

You are free to stop and withdraw from the study at any time without giving a reason. Your withdrawal from the study will not affect your general medical care. If you decide to stop participating in the research study, we might ask you to do a final safety follow-up assessment.

Your data and samples collected until then will still be evaluated in coded form.

Please note that the medical team can remove you from the study by the medical team for any of the following reasons:

- If you experience a significant reaction to the test substance
- If you develop a medical condition for which continuing would pose a risk to you or interfere with the analysis of the study result
- If you cannot comply with visits or assessments
- If the study is terminated for any reason
- If the investigator believes that it is in your best interest to remove you from the study,

10. Will I receive compensation?

If you participate in this study, you will not be paid for your participation. However, we will compensate for your time lost during the period of clinic visits and admission only. This amount is 25,000 TSH per study visit. For outpatient visits, you will be paid at the end of the visit before returning home. For the stay on the ward, you will be paid on the day of discharge for the number of days you stayed on the ward. In addition, meals and beverages will be provided during your admission to the hospital and the transportation fare incurred when returning to the hospital will be reimbursed.

11. Is the study insured?

MMV Medicines for Malaria Venture is responsible and liable for any damages you may incur in connection with the study product or the research procedures (e.g. examinations). MMV Medicines for Malaria Venture has taken out insurance for this purpose. The conditions and procedure are regulated by law.

12. How is the study funded?

All of the costs of the study are financed by MMV Medicines for Malaria Venture, Geneva, Switzerland.

13. Who do I contact if I have any concerns?

The Ifakara Health Institute Institutional Review Board (IRB) secretary and the MRCC (Medical Research Coordinating Committee) chair and Tanzania Medicines and Medical Devices Authority (TMDA) representative may be contacted in case of any question or need of clarification related to this study or to your participation at any time before signing the consent form and during the study period. You can also contact these individuals in the event of an injury resulting from your participation in this study:

Secretary of Ifakara Health Institute IRB:

Dr. Mwifadhi Mrisho

Ifakara Health Institute, Plot 463, Kiko Avenue Mikocheni, P.O. Box 78 373 - Dar es Salaam

Tel: +255 222 774 756 or +255 655 766 675

Email: enquiries@Ifakara Health Institute.or.tz

Chair of the MRCC (NIMR).

Medical Research Coordinating Committee (MRCC), National Health Research Ethics Review Committee, National Institute for Medical Research (NIMR), 2448 Ocean Road, P.O.Box 9653, Dar es Salaam, Tanzania

Tel +255 22 2121400

Email: info@nimr.or.tz

TMDA Representative:

Tanzania Medicines and Medical Devices Authority (TMDA), P. O. Box 77150, Dar es Salaam, Tanzania

Tel +255 22 2450512,

Email: info@tmda.or.tz

Principal Investigator (Medical team):
Dr. Florence Aphida Milando
Ifakara Health Institute
P.O. Box 74, Bagamoyo, Tanzania
Tel: +255 712 935292
Email: fmilando@ihi.or.tz

Co-Investigators (Medical team):
Dr. Hussein Mbarak Tel: +255623 397766 Email: hmbarak@ihi.or.tz

Dr. Mohammed Ally Rashid Tel: +255673837063 Email: mrashid@ihi.or.tz

Community engagement personnel:
Dr. Bakari Mwalimu Tel: +255655680551 Email: bmwalimu@ihi.or.tz

The Sponsor, directly or through insurance coverage, will only pay for study related injuries in accordance with applicable laws.

You have the right to contact the sponsor MMV Medicines for Malaria Venture to obtain information about your stored personal data.

Contact person for any questions relating to data privacy/personal data of MMV Medicines for Malaria Venture:

MMV Medicines for Malaria Venture, ICC – Block G, 3rd floor, 20 route de Pré-Bois, P O Box 1826, 1215 Geneva 15, Switzerland
Sylvie Fonteilles Drabek, General Counsel & EVP
E-mail: privacy@mmv.org

Informed Consent Form

Please read this form carefully.

Please ask if you do not understand or want to know something.

Your written consent is required for participation in the study.

Study Information:

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"
Responsible institution:	MMV Medicines for Malaria Venture ICC – Block G, 3rd floor, 20 route de Pré-Bois P O Box 1826, 1215 Geneva 15, Switzerland
Site of study conduct:	Ifakara Health Institute P.O. Box 74, Bagamoyo, Tanzania
Principal Investigator:	Dr. Florence Milando P.O. Box 74, Bagamoyo, Tanzania

Participant Information:

First name, middle name and last name (in capital letters)		
Date of birth (dd.mm.yyyy)		
Sex	□ Female	□ Male

- I was informed verbally and in writing by the undersigned study doctor/ clinician/nurse about the purpose, the course of the project, possible advantages and disadvantages and possible risks.
- I voluntarily participate in this study and accept the content of the written information provided. I had enough time to make my decision.
- My questions regarding participation in this study have been answered. I retain the written information and receive a copy of my signed informed consent.

- I agree that the responsible experts of the sponsor, the responsible ethics committees and the drug regulatory agencies may inspect my uncoded data for review and control purposes, but with strict maintenance of confidentiality.
- I will be informed of the results of the study and incidental findings that directly affect my health. If I do not wish this, I will inform the study doctor/ clinician.
- I know that my health-related and personal data (and samples) can only be passed on in coded form for research purposes for this study abroad. The sponsor is responsible for ensuring that the same standards as in Switzerland/Europe/Tanzania laws are respected.
- I can withdraw from the study at any time and without giving reasons. The data and samples collected up to the time of withdrawal will be used for the evaluation of the study.
- I am informed that an insurance policy covers damages that are attributable to the study
- I am aware that the obligations stated in the participant information must be complied with. In the interest of my health, the study doctor may exclude me from the study at any time.

Date (dd.mm.yyyy) and **time** (hh: mm)	**Participant's signature:**

Confirmation of the person taking the consent:

I hereby confirm that I have explained the nature, meaning and scope of the study to this participant. I assure that I will fulfil all my obligations in connection with this study in accordance with applicable law. If, at any time during the conduct of the study, I become aware of any aspect that may affect the participant's willingness to participate in the study, I will inform the participant immediately.

First name, middle name and last name of the person taking the consent: (in capital letters)		
Role in the study: (in capital letters)		
Date (dd.mm.yyyy) and **time** (hh: mm)		**Signature of the person taking the consent:**

Participant ID: MMV_SMC_22_01_01_-I__I__I__I

ONLY FOR THOSE WHO CONSENT

Do you agree your blood to be used for genetic testing of CYP450 system? ☐ Yes ☐ No

Date (dd.mm.yyyy) and **time** (hh: mm)	**Participant's signature:**

First name, middle name and last name of the person taking the consent: (in capital letters)		
Role in the study: (in capital letters)		
Date (dd.mm.yyyy) and time (hh: mm)		**Signature of the person taking the consent:**

APPENDIX: Optional Consent for Future Research

During or after the clinical study, the Sponsor (MMV) may want to use the Personal Coded Data for additional research projects. The Personal Coded Data includes your year of birth, gender, a special code that identifies you, study information, and biological samples as explained in the Section 8 “Will my data and samples be kept confidential?”.

Wherever permitted by law or requested by the authorities, this additional research may include studies to get more information on (Malaria or other diseases with similar mechanism of action). It may be used to design or improve methods for analyzing, comparing, or combining your study data with data from subjects treated with other drugs. It may involve new approaches or biological markers of Malaria and other aspects of Malaria. Researchers may study the benefits and risks of (paediatric) PQP and compare the data from (paediatric) PQP with other drugs. This will allow MMV and other researchers to better understand Malaria, how (paediatric) PQP works and to be able to find the best way to treat subjects with Malaria (or other diseases with a similar mechanism of action).

The information under section 8 “Will my data and samples be kept confidential?” is applicable to this optional consent.

You will not own any data and discoveries generated from the additional research studies. The data will not become part of your medical record.

If you choose to give consent for additional research, you can change your mind at any time. If you decide you no longer want MMV to use the Personal Coded Data for additional research, this is possible. You can continue to be in the main study. Please notify the study doctor if this is the case.

By signing below, I agree to the use of the Personal Coded Data for additional research as described above.

This consent is valid unless and until I withdraw it.

Participant Name (First name, middle name and last name).	
Date (dd.mm.yyyy)	**Participant signature:**

Name of presenter who presented/explained the document. (First name, middle name and last name).	
Date (dd.mm.yyyy)	**Signature of presenter who presented/explained the document:**