RPL ID Number: <INSERT VDB LABEL>
Screening Number:

Participant Information Sheet/Informed Consent Form

Clinical Trial Title:	A randomised, double-blind, placebo controlled, parallel group study in healthy adult volunteers to determine the safety and tolerability of pyronaridine (PYR) co-administered with piperaquine (PQP) under fasted conditions
Short Title	Safety and Tolerability of PYR co-administered with PQP (in fasted Healthy Volunteers
Protocol Number:	MMV_SMC_21_01
Clinical Trial Sponsor:	Medicines for Malaria Venture (MMV) ICC – Block G, 3rd Floor 20, Route de Pré-Bois PO Box 1826 1215 Geneva 15 Switzerland

Dear Volunteer,

We thank you for your interest and possible participation in this clinical trial in healthy adult volunteers.

Before you decide whether or not to take part, it is important for you to understand why the clinical trial is done, how we will use the information we collect about you and what the clinical trial involves. We also explain in this form possible risks and any discomfort you may feel during the clinical trial.

Please take time to read the following information carefully and discuss it with others if you like. Please ask us if there is anything that is not clear or if you would like more information. If you are currently participating in any other clinical trial or have participated in a clinical trial within 90 days prior to the scheduled dosing, you cannot take part in this clinical trial.

Once you have read this Participant Information Sheet, the Research Doctor will talk to you. The doctor will explain the clinical trial again and you can ask the doctor any questions you like.

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1. What is the purpose of this clinical trial?

We are inviting you to take part in a clinical trial involving two medicines, called piperaquine (PQP) and pyronaridine (PYR). Both of these medicines have been in clinical use for more than 20 years to treat acute episodes of malaria, but they have not been taken together before. This new combination will be explored for malaria prevention (i.e,. chemoprophylaxis) in Africa and more particularly for children living in areas where malaria is a risk. The volunteers in the trial will be healthy black male and female volunteers of Sub-Saharan African origin (defined as volunteers whose biological parents are both black and are of Sub-Saharan African origin).

Malaria is an infectious disease that causes symptoms including fever and headache, and in severe cases, can progress to coma and death. Malaria is caused by a parasite from the *Plasmodium* family that is transmitted to people via the bite of a certain type of mosquito (Anopheles mosquito). In some areas of the world, the current medicine combinations that are used to prevent malaria are not effective because some *Plasmodium* parasites have become resistant to them. Therefore, it is important to find new medication combinations that are safe and effective to prevent this disease. We hope that PQP and PYR might be an effective combination for malaria. If found to be safe and tolerable when taken in combination, the medicines may be investigated to prevent malaria in people living in areas where malaria is a risk.

The main aim of this trial is to find out how safe and well tolerated the investigational medicines, PQP and PYR, are in humans when taken alone and in combination and whether they affect the heart's electrical system. This trial also aims to calculate how much of the medicines reach the bloodstream after they are swallowed and how long they stay in the body (i.e., pharmacokinetics); as well as whether some peoples' bodies process the medicines differently if they have certain types of genes. Volunteers participating in this trial will have multiple blood tests and heart tracing tests (electrocardiograms [ECGs]) that will support the aims of the trial.

2. Summary of the clinical trial

We are conducting a clinical trial in 40 healthy, black, male and female volunteers, aged between 18 and 45 years whose biological parents are both black and are of Sub-Saharan African origin. The main aims of this clinical trial are as follows:

- To find out how safe and tolerable the investigational medicines are when they are taken together.
- After PQP and PYR tablets are swallowed, to find out how much of the investigational medicines reach the blood and how long the medicines (and the chemicals the body breaks them into; i.e. metabolites) stay in the body for, by taking blood tests. This process is called pharmacokinetics.
- To find out if, and in which ways, PQP alone or combined with PYR affects the heart's electrical system, by measuring the activity of the heart using an electrocardiograph.
- Some healthy people have different genes (called *CYP* gene variations) meaning that their livers process some medicines differently, as compared with other people. We will take blood tests to see which *CYP* gene variations you have,and may investigate whether your body reacts differently to the investigational medicines as a result.

The clinical trial will take up to approximately 52 days to complete, including the time before the clinical trial to determine if you are eligible to participate, the conduct of the clinical trial (comprising of an in-house period of eight days and a total of four outpatient visits if you are in the sentinel group (the first 10 volunteers to be dosed); or an in-house period of six days and five outpatient visits if you are in the non-sentinel group). The sentinel group contains the first volunteers to be dosed in each treatment arm, who will be dosed at least fifteen days before the non-sentinel group. As PQP and PYR have not been tested in combination before, the sentinel dosing strategy allows any safety concerns to be highlighted before giving the combination of PQP and PYR to a larger group of participants. This dosing strategy is done as an extra safety precaution in the event of any unexpected side effects and is a standard procedure for most studies. **NOTE: The shortened in-house period for the non-sentinel group will be confirmed following the review of safety and tolerability data from the sentinel group.**

If you are eligible to participate, you will be randomly assigned to one of four treatment groups. One of the treatment groups will take both PQP and PYR, another will take PQP and placebo (dummy medicine), another will take PYR and placebo and the final group will take two placebo medicines. The placebo medicines will be given in the same way and look similar to the active investigational medicines so that no volunteer, or clinical staff member, will know who is taking which treatments.

The clinical trial is made up of the following parts:

- **Screening visit:** You will be required to attend a screening visit scheduled within 22 days before the start of the clinical trial. Screening will take place over one day or may be divided into more than one day.

- **Treatment Period:** Participation requires an in-house period (which may vary depending upon whether you are in sentinel or non-sentinel group), outpatient visits and a final follow up visit. The planned period of your in-house stay may be extended, if necessary, for your safety.
    - The treatment period starts with admission to the unit on Day -1 (the day before you receive the investigational medicines) for additional safety checks.
    - You will receive the active investigational medicines and/or placebo on Days 1, 2 and 3. On these days we will also perform safety tests (described below) and take blood samples to measure the amount of each investigational medicine present in the blood.
    - Sentinel Group: On Days 4, 5, 6 and 7 you will not receive investigational medicines but will remain in the unit to continue to monitor your safety, side effects and we will monitor how much of the investigational medicines remain in your blood. Provided you feel well and there are no safety concerns, you will be discharged from the unit and allowed to go home on Day 7.
    - Non-Sentinel Group: On Days 4 and 5, you will not receive investigational medicines but will remain in the unit to continue to monitor your safety, side effects and we will monitor how much of the investigational medicines remain in your blood. Provided you feel well and there are no safety concerns, you will be discharged from the unit and allowed to go home on Day 5.

- **Outpatient visits**:
    - During the outpatient visits you will have further safety tests as described below and we will continue to take blood tests to monitor how much of the investigational medicines are still present in your blood.
    - Volunteers in the Sentinel Group will attend for four out-patient visits on Days 8, 15, 22 and a final follow-up visit on Day 30.
    - Volunteers who are not in the Sentinel Group will attend for five out-patient visits on Days, 6, 8, 15, 22 and a final follow-up visit on Day 30.

The standard safety tests that will be conducted during the clinical trial, include safety blood and urine laboratory tests, vital signs (pulse rate, blood pressure, respiratory rate and body temperature), physical examinations, ECG (electrocardiogram – electrical heart recording), telemetry (real-time electrical heart monitoring), blood samples for pharmacokinetics (measurement of medicine levels in the blood) and observations of any adverse events (side-effects).

The Research Doctor will be contactable 24 hours a day during the entire clinical trial in case you do not feel well or need any medical advice.

During your participation in this clinical trial including follow-up visits, you will be asked not to travel too far from London Bridge without our consent because we may need to get in touch with you to attend additional visits that may need to be done at short notice.

You will not receive any health benefits from taking PQP and PYR as these medicines are being given for research and development purposes only, but you will be compensated for your time. The Clinical Trial Plan can be found in Appendix 1.

Please note that you will be required to have a swab for COVID-19 at regular intervals and ad-hoc (as required) during your residential stay at the Richmond Pharmacology unit. Please also note Public Health England will be notified within 72 hours should you test positive for SARS-CoV-2, in line with our legal duty. By signing this consent, you are allowing us to also use your anonymised COVID-19 test results for Richmond Pharmacology Ltd ("RPL") research purposes.

The table of contents on page 2 may help you to read this consent form more easily, by breaking the information down into questions that you may have.

For further information please refer to our websites as below:

https://www.richmondpharmacology.com/
https://www.richmondresearchinstitute.org/

3. Do I have to take part?

No. Your participation in this clinical trial is voluntary, and you may withdraw your consent to take part at any time, without stating your reasons.

The Research Doctor may also decide to remove you from the clinical trial due to illness, side-effects, new information on the investigational medicines or if you are not following the clinical trial rules and restrictions. In addition, the Sponsor may end your participation in the clinical trial at any time without your consent. You are strongly advised to return to the unit for a follow-up visit if you decide not to continue with the clinical trial for any reason; this is for your safety.

By signing a separate General Practitioner (GP)/Medical Practitioner Consent Form, you will give RPL permission to contact your GP. This is so that your GP can tell RPL if there is any reason why you should not take part in this Medicines for Malaria Venture (MMV) sponsored clinical trial. By signing the form, you are also giving RPL permission to inform your GP of any abnormal results seen at screening or during the clinical trial. This is because your GP needs to be aware of any change in your health status. If you do not wish this to happen then you should not participate in this MMV or any other RPL sponsored or conducted clinical trial. With respect to any other RPL sponsored or conducted clinical trial that you may participate in, unless it is an MMV sponsored clinical trial, MMV shall have no responsibility or liability to you or RPL regarding contacting, obtaining medical records and information from, or otherwise communicating with your GP as set forth in the separate General Practitioner (GP)/Medical Practitioner Consent Form.

4. Why have I been invited?

You will be suitable for this clinical trial if you fulfil the following criteria:

1. You are a healthy male or female aged 18-45 years (inclusive).
2. Both of your biological parents are black and are of Sub-Saharan African origin.
3. You weigh more than 50 kg and your Body Mass Index (BMI) is between 18-28 kg/m^2, inclusive.
4. You are generally in good health based on medical history, physical examination, vital signs, laboratory blood and urine tests, and ECG performed at screening and/or prior to each investigational medicine administration.
5. You agree to not donate sperm or ova (eggs) from the time that you first take the investigational medicines until three months after the last day that you take the investigational medicines.
6. You agree to not donate blood from 90 days before the first day you are given the investigational medicines until three months after the last study visit.
7. You will receive standardised meals, served at scheduled times throughout your residential stay. **You agree to consume all your meals.** These meals may contain meat, and provision for diets that are either meat-free, or free from certain meats is not available as part of this research study.

Contraceptive criteria:

1. **If you are a female volunteer:**
    a. Women of non-childbearing potential do not require contraception. Non-childbearing potential is defined as physiologically incapable of becoming pregnant, e.g. post-menopausal (no menstrual periods for at least 12 consecutive months with no alternative medical cause) or permanently sterile (permanent sterilisation methods include hysterectomy, removal of both fallopian tubes and/or both ovaries). If you are post-menopausal, we will also confirm this with a blood test.

    b. Women of childbearing potential (if sexually active with a man) agree to use one or more forms of highly effective contraception as defined below, starting one complete menstrual cycle before the first day of taking the investigational medicines and continuing for 110 days (slightly less than 16 weeks) after the final day of taking the medicines. Highly effective contraceptive methods for females are as follows:

        i. Combined (oestrogen- and progesterone- containing) hormonal contraception associated with inhibition of ovulation as follows:
            1. Oral (tablet i.e., 'the combined pill')
            2. Intravaginal
            3. Transdermal
        ii. Progestogen-only hormonal contraception associated with inhibition of ovulation as follows:
            1. Oral (tablet i.e., 'the minipill')
            2. Injectable
            3. Implantable
        iii. Intrauterine device (IUD; also known as 'copper coils')
        iv. Intrauterine hormone-releasing system (IUS)
        v. Bilateral tubal occlusion (i.e., female sterilisation with fallopian tubes 'clipped')
        vi. Infertile male partner (e.g., after 'vasectomy' or surgical removal of both testicles, with documented evidence of azoospermia [no sperm] if possible)

    OR

    c. Women of childbearing potential agree to remain abstinent. If abstinence is your preferred and usual lifestyle prior to starting the study, and you will remain abstinent for from one complete menstrual cycle before the first day you take the investigational medicines, until 110 days (slightly less than 16 weeks) after the last day you take the investigational medicines, then you will be exempt from the contraception requirements. Abstinence is defined as not having any sexual intercourse with a male, and does <u>not</u> include having intercourse according to body temperature or lack of ovulation, using the 'pulling out' method, etc., or offering to be abstinent when this is not your usual lifestyle.

OR

2. **If you are a male volunteer:**
    a. If you are sexually active with a female partner of childbearing potential or a pregnant or breastfeeding partner, you must agree to use a male condom (with or without spermicide) from the first day of taking the investigational medicines and continue until 110 days (slightly less than 16 weeks) after the last day that you take the investigational medicines. If you are infertile (with documented evidence of azoospermia [no sperm] if possible) then you will be exempt from this contraception requirement.

    b. For male volunteers, abstinence from heterosexual intercourse from the first day you take the investigational medicines until 110 days (slightly less than 16 weeks) after the last day you take the investigational medicines is a permitted form of contraception.

The Research doctor will discuss your method of contraception or abstinence with you and decide whether this meets the study criteria.

A list of other inclusion criteria will be applied by the Research Doctor to assess your eligibility for the study. You can discuss these with the Research Doctor during the screening process.

You will NOT be suitable for this clinical trial if you meet any of the following exclusion criteria:

1. You have a current or recurrent disease that could affect the clinical or laboratory evaluations.
2. You are pregnant or breastfeeding.
3. You are not able to swallow up to eight tablets at the same time or consecutively.
4. You have a history of human immunodeficiency virus (HIV) antibody positivity, Hepatitis B or Hepatitis C or you test positive for any of these conditions at screening.
5. You have a history of photosensitivity.
6. You have a history of seizures or epilepsy.
7. A history of depression or suicidal ideation as per the Beck Depression Inventory.
8. You have documented evidence of retinopathy.
9. You have had malaria in the previous two years.
10. You have used tobacco in any form (e.g., smoking or chewing) or other nicotine-containing products (e.g., gum, patch, electronic cigarettes) in any form six months before the first day you take the investigational medicines.
11. You have positive test results for alcohol or drugs of abuse at screening or on admission or have a history of alcohol/drug abuse.
12. You have had a COVID-19 vaccine within four weeks before the first dose, or you plan to receive the vaccine within one week after trial completion.

A list of other exclusion criteria will be applied by the Research Doctor to assess your eligibility for the study.

5. What is the investigational medicine that is being tested?

The investigational medicines being tested are chemicals called piperaquine tetraphosphate (PQP) and pyronaridine tetraphosphate (PYR). These medicines which are registered in various countries have previously been tested in healthy volunteers and have been used (in different combinations) to treat acute malaria in patients for more than 20 years. They have not been tested for safety or tolerability when taken together.

How do they work?

The combination of the investigational medicines PQP and PYR is being developed as prevention of malaria infection. They are thought to work by stopping a malaria infection from taking hold in the red blood cells in the body.

What dose will I receive?

The investigational medicines will be in the form of tablets that you will swallow with a small glass (240 mL) of water. The three-day regimen and doses of both PQP and PYR are the recommended doses used to treat acute malaria. On Days 1, 2, and 3 of your in-house stay you will be dosed with the investigational medicines. The number of tablets that you will be given to swallow are described below.

- If you weigh between 50 kg and 64.99 kg, you will take on each day - 960 mg of PQP (three tablets) and 540 mg of PYR (three tablets) or placebo tablets.
- If you weigh between 65 kg and 74.99 kg, you will take on each day - 960 mg PQP (three tablets) and 720 mg PYR (four tablets) or placebo tablets.
- If you weigh 75 kg or more, you will take on each day - 1280 mg PQP (four tablets) and 720 mg PYR (four tablets) or placebo tablets.

The first ten volunteers in this trial will be the "sentinel dosing group", this means that the study will initially be conducted in these ten volunteers only. 15 days after their first dose, the data collected from all of the sentinel group's tests will be checked by a Safety Review Committee (SRC), before the remaining 30 volunteers are allowed to be enrolled into the non-sentinel group. The sentinel group will remain in-house until Day 7 to allow for additional safety monitoring. Following the review of the available safety and tolerability data, the SRC may decide to shorten the in-house period of non-sentinel group. You will be made aware of this, if such a decision is made. Sentinel dosing is an extra safety precaution and is a standard procedure for most early phase clinical trials.

6. What are the side effects of any treatment received when taking part?

The investigational medicines may cause some side effects. You may experience none, some or all of those described below.

Side effects of piperaquine (PQP)

The following side effects (called adverse events) have been experienced after people took PQP in the past. You may or may not experience any of these side effects:

Common side effects (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 QT_c interval), and increased heart rate (tachycardia)
- anaemia (reduced haemoglobin)
- fever
- headache
- feeling weak

Uncommon side effects (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 effects (affect fewer than 1 in 1000 people who take the medicine):

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

Side effects of pyronaridine (PYR)

The main safety concern with PYR in healthy participants and in malaria patients consists of raised levels of liver enzymes (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), but without bilirubin changes (another liver chemical). This means that the indicators of liver function have been shown to become high after participants took PYR. This has been a temporary change without the presence of

symptoms. We will be vigilant towards any changes in the liver function tests and will stop the medication if we have any safety concerns.

The following side effects have been reported in people who took PYR, so you may or may not experience any of these side effects:

Common side effects (affect more than 1 in 100 people, but fewer than 1 in 10 people, who take the medicine):

- a slowing of heart rate (bradycardia)
- increases in the liver enzymes
- abdominal (tummy) pain
- nausea and vomiting
- changes in the number of some of the white blood cells (eosinophilia, neutropenia)
- increased number of blood clotting cells (platelet count)
- anaemia (reduced haemoglobin)
- headache
- feeling weak

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

- a change in the heart's electrical system (called prolonged QT_c interval) and extra heart beats (called ventricular extrasystole)
- sensation of heart palpitations
- diarrhoea
- constipation
- heartburn/ indigestion
- stomach inflammation (called gastritis)
- dizziness
- skin changes such as itchiness, redness/dryness and increased sweating
- altered sensation e.g., pins and needles
- insomnia
- muscle aches
- reduced appetite
- cough

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

- hypersensitivity reaction (a form of allergic reaction)
- heart rhythm and other heart electricity disturbances (called arrhythmia and first-degree atrioventricular block)
- high and low blood pressure
- hearing impaired and ringing in the ears
- reduction in multiple types of blood cells (which can cause dangerous infection and sepsis risk if undetected and untreated)
- increased bilirubin (a liver product which aids digestion).

The Research Doctor is aware of the possible side-effects of the investigational medicines and you will be monitored closely. Should side-effects arise, they will be treated appropriately. As PQP and PYR have not been taken together before, there is a risk that you will experience new (not previously noticed) side effects. In addition to this, as the investigational medicines PQP and PYR have some overlapping side effects there is the risk of worsening of known side effects.

If you have any side effects that involve the skin, you may be examined by a dermatologist (skin doctor) and/or you may have photographs taken of the area of interest. The photographs will, whenever possible, be taken in such a way as to prevent disclosure of your identity.

Could I have an allergic reaction?

Any medicine, including PQP and PYR, may cause allergic reactions. If you have a very bad allergic reaction, it could be life threatening. Signs and symptoms of an allergic reaction that could be life-threatening (anaphylaxis) are:

- rash
- hives (itchy raised rash)
- having difficulty breathing
- wheezing when you breathe
- sudden drop in blood pressure (feeling faint or dizzy)
- swelling around the face, mouth, lips, tongue, throat, or eyes
- fast pulse
- sweating.

Richmond Pharmacology Ltd is a specialist clinical trials unit that regularly conducts trials where investigational medicines are given to people for the first time. There are trained doctors and clinical staff on-site and procedures in place (approved by the authorities) to deal with any side effects, including allergic reactions, that arise.

Risks associated with clinical trial procedures

Investigational medicine risks: There are potential risks associated with taking the investigational medicines. Please read Section 6 carefully.

Investigational medicine administration: The investigational medicines will be given in the form of tablets that you will swallow with approximately 240 mL of water.

Blood pressure and pulse rate: These will be measured using an inflatable cuff which will be placed on your arm. You may experience mild discomfort in your arm whilst the cuff is inflated.

Blood sampling: On Days 1-3 a cannula (small plastic tube) will be placed in your arm using a small needle, the cannula will remain in place all day allowing us to take blood samples from you without having to insert a new needle into your vein every time. The cannula will be removed at night before you go to bed. On the other days in which blood tests are taken, blood will be drawn from the arm using a small needle. There is a small chance of infection by placing the cannula or needle in your arm, but every medical precaution will be taken to avoid an infection. You may experience a small bruise and/or soreness following these procedures. Very rarely, a blockage of a vein or a small nerve injury can occur, resulting in numbness and pain. If this occurs, it will resolve with time.

ECG (electrical heart recording): Before each ECG you will be asked to lie down for ten minutes. Areas where small sticky pads will be attached to the skin will be cleaned, and if necessary, any hair will be clipped or shaved. The small sticky pads will be placed on your chest, shoulder, and hips 30 minutes prior to the first ECG of the day, and an ECG machine will measure the electrical activity of your heart. Like Elastoplast®, these sticky pads may be uncomfortable to remove. ECGs will be carried out regularly during the clinical trial (at screening, at multiple times per day on dosing days, on each day after dosing during every outpatient visit and on the final follow-up visit).

Holter monitoring: You are required to wear a Holter monitor for 24 hours during the screening period. Similar to the ECG, small sticky pads will be placed on your chest and hips (twelve in total) and wires will connect the sticky pads to the Holter monitor. The Holter monitor is approximately the size of a large iPhone. You may experience some mild skin reactions such as slight redness, itchiness and irritation due to the sticky pads. If this occurs, it will resolve with time.

Telemetry: Your heart will be continuously monitored using a small device, about the size of an iPhone (telemetry). This will be attached to your body using sticky pads and you will wear the device for a period

of 24 hours on Days 1, 2 and 3. You may experience some mild skin reactions such as slight redness, itchiness and irritation due to the sticky pads. However, if this occurs, it will resolve with time.

Bed rest: Following dosing with the investigational medicines you may have to remain in a semi-lying down position for approximately four hours for your own safety.

If you have private medical insurance, you are advised to check with your insurance company whether participation in the clinical trial should be reported and to check if your participation will affect the medical insurance you receive.

7. What will happen to me if I take part?

What is done at the Screening Visit (Visit 1)?

The Informed Consent Form must be completed and signed before the start of any clinical trial-related procedures.

If you give informed consent, the following procedures will be performed:

- The Research Doctor will check if you meet the points listed in the Inclusion and Exclusion Criteria (eligibility check).
- Demographics (date of birth, sex and race or ethnic origin) will be recorded.
- You will be asked some questions about your medical history.
- You will be asked some questions about your smoking history, as well as your past and present medication use.
- You will be asked to complete the Beck Depression Inventory, a short questionnaire to screen for depression.
- The Research Doctor will perform a full physical examination.
- Your vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be measured.
- Your urine will be tested for drugs of abuse and to check your general health.
- Your breath will be tested for alcohol.
- Your height and body weight will be measured and your BMI (Body Mass Index) will be calculated.
- A 12-lead ECG will be recorded.
- A 24-hour Holter ECG will be attached.
- A needle will be used to draw blood from a vein in your arm for safety blood tests (haematology [checking the cells in your blood], coagulation [measures the time it takes for your blood to clot] and biochemistry [checking how your organs are working]), follicle stimulating hormone [FSH] [postmenopausal females only to confirm that you are post-menopausal] and pregnancy blood test [females only]).

You must also agree to an additional blood test being performed before the start of the clinical trial in order to test for HIV 1+2, Hepatitis B and Hepatitis C. We do this test for all volunteers, in order to reduce the risk to our staff in case they have an accidental 'needle-stick' injury. If the results of any of these tests are positive, you will be asked to return to the unit for a confidential appointment with a Research Doctor. He or she will provide you with advice, and depending on which test is positive, a repeat blood test may be done to confirm diagnosis. The Research Doctor will refer you to a specialist clinic depending on which test is positive. If you are found to be HIV positive, the Research Doctor will contact you and explain the results to you, and we will inform your GP. You will then be referred to an appropriate specialist clinic for further medical counselling and further investigation in the United Kingdom. Please note that you will not be able to participate in this clinical trial if you test positive for HIV, Hepatitis B or Hepatitis C or, if you refuse to allow collection of blood for these tests.

Screening will take place over one or more days. The results of these screening examinations, among other things, will determine whether or not you can take part in the clinical trial.

What is done during the Residential Visit?

Throughout the in-house stay at the clinical unit:

- You will be asked how you are feeling throughout the day and any medications, other than the investigational medicines you have taken will be recorded.
- Standardised meals will be served at scheduled mealtimes; all food must be eaten. The final meal on Day 7 for the sentinel group (after assessments are finished) will be optional. The final meal on Day 5 for the non-sentinel group (after assessments are finished) will be optional.

You will be admitted to the clinical unit on Day -1 (i.e., one day before the you receive the first dose of the investigational medicines) and will stay in the unit until Day 7 if in the sentinel group (i.e., eight days and seven nights in total) and the SRC may decide to shorten the in-house period of non-sentinel group in which case you will stay in the unit until Day 5 (i.e., six days and five nights in total). The break-down of all clinical trial procedures can be seen below:

Day -1:

The following procedures will be performed:

- The Research Doctor will check that you meet all of the requirements listed in the Inclusion and Exclusion Criteria (eligibility check).
- Your medical history will be updated.
- Your urine will be tested for drugs of abuse and to check your general health.
- Your breath will be tested for alcohol.
- If you are a female volunteer who has not had the menopause, you will have a blood test to confirm that you are not pregnant.
- Your vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be measured.
- A 12-lead ECG will be recorded.
- The Research Doctor will perform a physical examination.
- Your weight be measured to allow staff to calculate your BMI.
- Safety blood tests (haematology, coagulation and biochemistry) will be taken – a needle will be used to draw blood from a vein in your arm.

Day 1 - Day 3:

The following procedures will be performed:

- You will swallow between six and eight tablets of investigational medicines (depending on your body weight), at the same time or consecutively.
- You will not eat any food three hours before, and until four hours after, you take the investigational medicines. You will be allowed to drink water until one hour before taking the medicines, and from one hour after taking the medicines.
- Your vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be measured.
- 12-lead ECGs will be recorded at pre-determined timepoints.
- Real time ECG (telemetry) will be recorded from at least one hour before dosing on Day 1 until 24 hours after the final day of dosing on Day 3.
- The Research Doctor will perform a brief physical examination.
- Safety blood tests (haematology, coagulation and biochemistry on Day 1 only; liver function blood tests only on Days 2 and 3), blood tests to measure PQP and PYR levels (i.e,. pharmacokinetics), and a blood genetic test (Day 1 only) will be taken – a cannula or needle will be used to draw blood from a vein in your arm.
- On Day 1 and Day 3 only, your urine will be tested to check your general health.

Day 4-Day 5 for Non-Sentinel Group:

The following procedures will be performed:

- Your vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be measured.
- A 12-lead ECG will be recorded.
- The Research Doctor will perform a brief physical examination.
- Safety blood tests (haematology, coagulation and biochemistry) will be taken - a cannula or needle will be used to draw blood from a vein in your arm.
- On Day 4 only, your blood will be taken to measure the PQP and PYR levels (i.e., PK analysis) - a cannula or needle will be used to draw blood from a vein in your arm.
- On Day 5 only, your urine will be tested to check your general health.

Following completion of Day 5 (last day of residential stay) procedures, you will be allowed to leave the unit provided the Research Doctor considers it safe for you to do so. Please note that you still need to abide the restrictions described in this document (See Section 9: What will I have to do?). When you are discharged from the unit, you will be issued with a clinical trial participation card, which you will need to carry with you at all times and show to any health care professionals that you see up to and including the follow-up visit.

Day 4-Day 7 for Sentinel Group:

The following procedures will be performed:

- Your vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be measured.
- A 12-lead ECG will be recorded.
- The Research Doctor will perform a brief physical examination.
- On Days 4, 5, 6 and 7, safety blood tests (haematology, coagulation and biochemistry) will be taken - a cannula or needle will be used to draw blood from a vein in your arm.
- On Day 4 and 6, your blood will be taken to measure the PQP and PYR levels (i.e., PK analysis) - a cannula or needle will be used to draw blood from a vein in your arm.
- On Day 5 and 7 only, your urine will be tested to check your general health.

Following completion of procedures on Day 7 of the in-house stay you will be allowed to leave the unit provided the Research Doctor considers it safe for you to do so. Please note that you still need to abide the restrictions described in this document (See Section 9: What will I have to do?). When you are discharged from the unit, you will be issued with a clinical trial participation card, which you will need to carry with you at all times and show to any health care professionals that you see up to and including the follow-up visit.

You may be strongly advised to remain resident in the unit until resolution of any safety issues, after which you will be discharged from the unit.

<u>What is done at the Outpatient and Follow-up Visits?</u>

Day 1 is counted as the first day you take the investigational medicine, and the outpatient follow-up visits for the non-sentinel group will be on Day 6, Day 8, Day 15, Day 22 and approximately Day 30. Sentinel group volunteers will have outpatient follow-up visits on Day 8, Day 15 and Day 22 and approximately Day 30. These dates will be fixed for all volunteers in the group. The dates will be provided before you are admitted so that you can ensure you are available for them. Your participation in the clinical trial will last for up to approximately 52 days in total, however this may be reduced if the Research Doctor confirms that you can be released from the clinical trial at an earlier date.

Day 6 Non-Sentinel Group (Outpatient Visit):

The following procedures will be performed:

- The Research Doctor will ask about current and previous medication use.

- Your vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be measured.
- A 12-lead ECG will be recorded.
- The Research Doctor will perform a brief physical examination.
- Your blood will be taken for safety blood tests (haematology, coagulation and biochemistry) and to measure the PQP and PYR levels (i.e., PK analysis) - a needle will be used to draw blood from a vein in your arm.

Day 8 Sentinel and Non-Sentinel Group (Outpatient Visit):

The following procedures will be performed:

- The Research Doctor will ask about current and previous medication use.
- Your vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be measured.
- A 12-lead ECG will be recorded.
- The Research Doctor will perform a brief physical examination.
- Blood tests will be taken for safety (haematology, coagulation and biochemistry) and to measure the PQP and PYR levels (i.e., PK analysis) - a needle will be used to draw blood from a vein in your arm.
- Your urine will be tested to check your general health.

Day 15 Sentinel and Non-Sentinel Group (Outpatient Visit):

The following procedures will be performed:

- The Research Doctor will ask about current and previous medication use.
- Your vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be measured.
- A 12-lead ECG will be recorded.
- Blood tests will be taken for safety (haematology, coagulation and biochemistry) and to measure the PQP and PYR levels (i.e., PK analysis) - a needle will be used to draw blood from a vein in your arm.
- Your urine will be tested to check your general health.

Day 22 Sentinel and Non-Sentinel Group (Outpatient Visit):

The following procedures will be performed:

- The Research Doctor will ask about current and previous medication use.
- Your vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be measured.
- A 12-lead ECG will be recorded.
- Your blood will be taken for safety (haematology, coagulation and biochemistry) and to measure the PQP and PYR levels (i.e., PK analysis) - a needle will be used to draw blood from a vein in your arm.

Day 30 Sentinel and Non-Sentinel Group (Follow-up (Outpatient) Visit):

The following procedures will be performed:

- The Research Doctor will ask about current and previous medication use.
- Your vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be measured.
- A 12-lead ECG will be recorded.
- The Research Doctor will perform a brief physical examination.
- Safety blood tests (haematology, coagulation and biochemistry) will be taken - a needle will be used to draw blood from a vein in your arm.

- If you are a female volunteer who has not had the menopause, you will also have a blood test to confirm that you are not pregnant.
- Your urine will be tested to check your general health.

Blood volume

The total volume of blood that will be taken over the duration of the clinical trial will be less than the amount of a standard blood donation (470 mL). Additional blood samples and safety procedures/ measurements may be undertaken for safety reasons and to ensure the quality of the clinical trial data.

Wearing of face masks during your stay in the unit

Coronavirus (COVID-19) usually spreads by droplets from coughs, sneezes and speaking. These droplets can also be picked up from surfaces if you touch a surface and then your face without washing your hands first. This is why social distancing, regular hand hygiene, and covering coughs and sneezes is so important to control the spread of the virus.

The best available scientific evidence is that, when used correctly, wearing a face covering may reduce the spread of coronavirus droplets in certain circumstances, which helps to protect others.

During your time with us at Richmond Pharmacology you will be given face masks that must be worn at all times unless you are:

- taking medication
- eating or drinking
- showering
- washing or conducting other hygiene routines
- sleeping.

In line with UK Government recommendations, there are other situations where you also do not need to wear a face mask:

- where putting on, wearing or removing a face covering will cause you severe distress
- if you are speaking to or providing assistance to someone who relies on lip reading, clear sound or facial expressions to communicate
- to avoid harm or injury, or the risk of harm or injury, to yourself or others
- when interacting with police officers and other emergency workers.

A face covering should:

- cover your nose and mouth while allowing you to breathe comfortably
- fit comfortably but securely against the side of the face
- be secured to the head with ties or ear loops.

When wearing a face covering you should:

- wash your hands thoroughly with soap and water for 20 seconds or use hand sanitiser before putting a face covering on
- avoid wearing the face mask on your neck or forehead
- avoid touching the part of the face mask in contact with your mouth and nose, as it could be contaminated with the virus
- change the face mask if it becomes damp or if you've touched it
- avoid taking the face mask off and putting it back on a lot in quick succession.

When removing a face mask:

- wash your hands thoroughly with soap and water for 20 seconds or use hand sanitiser before removing the mask
- only handle the straps, ties or clips of the face mask
- do not give your face mask to someone else to use
- dispose of the face mask carefully in the clinical waste bin
- wash your hands thoroughly with soap and water for 20 seconds or use hand sanitiser once you remove your face mask.

Possible changes

The Covid-19 pandemic is an ongoing global healthcare crisis and Richmond Pharmacology are constantly adapting our health and safety measures in line with the latest scientific evidence and Government advice. You will be fully informed of any changes to our health and safety policy, including the requirement to wear face masks and other personal protective equipment as soon as practically possible.

Source:
https://www.gov.uk/government/publications/face-coverings-when-to-wear-one-and-how-to-make-your-own/face-coverings-when-to-wear-one-and-how-to-make-your-own

8. Expenses and payments

Volunteer payment

In recognition of the time and effort involved in taking part in this clinical trial, you will be paid £1,152 (if you are in the sentinel group) or £1,088 (if you are in the non-sentinel group and discharged on Day 5) on completion of the clinical trial, once follow-up results are confirmed, checked by the Research Doctor and confirmed there are no safety issues. i.e., the Research Doctor considers your participation in the clinical trial to be completed.

We want you to cooperate with us to achieve the objectives of the clinical trial, so if you are dosed, we will give you a compliance payment of £580 (if you are in the sentinel group) or £544 (if you are in the non-sentinel group) for your satisfactory compliance with this document (Participant Information/Informed Consent Form), the Richmond Pharmacology Volunteer Charter and all unit rules (unit regulations). However, the compliance payment is issued at the discretion of RPL, meaning RPL may not pay these monies if there is a justified reason not to do so within the terms of the contract with you the volunteer.

The total amount that you could be paid for the clinical trial is £1,732 if you are in the sentinel group, or £1,632 if you are in the non-sentinel group. Payment will be paid to you up to 21 working days after completion of the clinical trial.

You will be paid for the time you give up for the clinical trial site and this payment is only for time and NOT linked to risk or inconvenience. Therefore, payment is proportional to the time you spend on the clinical trial i.e., payment may be reduced or increased depending on your duration in the clinical trial (if you are required to attend the unit for fewer or more days than stated in the Clinical Trial Plan). You should not view participation in this clinical trial as equivalent to employment and under no circumstances should you participate in more than one clinical trial at a time. You will also be paid £20 for travel expenses to attend the screening visit, and £120 for travel expenses in the clinic/ follow-up stage of the trial.

You will receive payment for your participation in this clinical trial as described in Table 1 below, depending on the number of follow-up visits you are requested to attend.

If you are dosed with the investigational medicine and are required to attend the unit for a repeat test (outside of scheduled or requested visits prolonging your participation in the clinical trial) you will be paid £80 for a day visit or £100 for an overnight visit plus a contribution towards your travel expenses of £20. This is applicable for each visit (i.e., in addition to the visits above) that you are required to attend.

Table 1

REASON for WITHDRAWAL	RE-IMBURSEMENT	COMPLIANCE PAYMENT
Clinical trial or investigational medicine related side effects*	Pro-rata**	Full
Non clinical trial or investigational medicine related side effects*	Pro-rata**	Full
Entire clinical trial stopped	Pro-rata**	Full
Non-compliance or voluntary withdrawal	None	None

*As judged by the Research Doctor.
**Calculated according to the actual time spent in the clinical trial in relation to the total clinical trial period.

For admission and in order to make sure that we start the clinical trial with the right number of volunteers, we will book more volunteers than will be dosed. The decision as to who is included on Day 1 of the clinical trial will be decided by the Research Doctor who will take into account your past medical history and the availability and quality of your medical history. The amount you will be paid if you are admitted but not dosed is £150.

Should you not wish to receive payment for this clinical trial, then we suggest that you nominate a charity of your choice and we will arrange for a donation of the amounts that would otherwise be due to you.

It is your responsibility to manage your own tax affairs. Information on how the clinical trial payments may impact your tax responsibilities can be found on the following website: www.hmrc.gov.uk/manuals/eimanual/eim71105.htm. For any further information, please contact your local tax office.

9. What will I have to do?

You must be willing to adhere to the restrictions stated below and be able to attend the scheduled visits. You must be prepared to attend and remain in the unit (in-house visit) for up to eight days and seven nights (depending upon whether you are in the sentinel or non-sentinel group as described earlier in this document), attend unit on various outpatient visits and attend a final follow up visit in the unit. Not including the screening period, the trial will take place over a period of approximately 31 days. You may need to attend additional follow up visits until the Research Doctor confirms that you are no longer required to do so. You will also be required not to leave the country for two weeks after you have completed the clinical trial as you may need to return for additional blood samples.

It is important that you tell our clinical staff about any other medication you are taking before and during the clinical trial. The Research Doctor must be told immediately if you or your partner becomes pregnant within three months after taking the investigational medicines.

If you have a medical need to take any medications and your GP/another Doctor prescribes or advises you to take them, you should follow the medical advice but please inform the Research Doctor as soon as possible afterwards using the contact details on the Subject ID card that you will be given, or the contact information in Section 20 (Further information and contact details) of this document. You should not stop taking any medication that has been prescribed by your GP/another Doctor. The requirement to take any new medication or change your existing medication may affect your continued participation in the clinical trial.

Participation in the clinical trial will restrict your normal lifestyle as follows:

Items you must not use / Things you must not do:	**When you must stop taking it / doing it from:**	**How long you must not use these items / not do this for:**
Tobacco in any form (e.g., smoking or chewing) or other nicotine-containing products in any form (e.g., gum, patch, electronic cigarettes)	You must abstain from tobacco or nicotine-containing products from six months before the planned first day of dosing.	Until the end of the trial (after final Follow-up visit).
Medication – Any prescription medications or over-the-counter medications (including corticosteroids, aspirin, ibuprofen or other NSAIDs, decongestants, and antihistamines or herbal supplements)	You will not be eligible for the trial if you take any medications from 14 days prior to first planned dosing of investigational medicine. If a doctor has prescribed any medication for you, you must tell the Research Physician.	Until the end of the trial (after final Follow-up visit) unless medically necessary.
Any herbal medications/ remedy or dietary supplements	You must not take any herbal medicines/remedies or dietary supplements containing herbal remedies from 30 days before first planned dosing of the investigational medicines.	Until the end of the trial (after final Follow-up visit).
Alcohol	You must not consume alcohol within 48 hours before the planned first investigational medicine 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.	Until the end of the trial (after final Follow-up visit).
Energy drinks or drinks containing taurine, glucuronolactone (e.g., Red Bull)	You must not consume any energy drinks containing taurine or glucuronolactone (e.g., Red Bull) within 48 hours before the planned first investigational medicine administration	Until the end of the trial (after final Follow-up visit).
Caffeine and Xanthine-containing products (e.g,. coffee, tea, colas and chocolates)	You are not allowed to consume caffeine or xanthine-containing products for 48 hours before the planned first investigational medicine administration	Until the end of the trial (after final Follow-up visit).
Food or drink products containing cranberry, pomegranate, grapefruit, star fruit, grapefruit, pomelos, exotic citrus fruits or Seville oranges (including marmalade and juices made from these fruits)	You must not consume any of these products for 30 days before the planned first investigational medicine administration.	Until the end of the trial (after final Follow-up visit).
Recreational drugs	Under no circumstances are you allowed to take drugs of abuse for the duration of the clinical trial. This could lead to unpredictable risks, which can seriously damage your health.	Until the end of the trial (after final Follow-up visit).
Poppy seeds	You must not consume poppy-seed containing food within 24 hours before the screening visit because this can lead to a positive result of your urine test for drugs of abuse.	Until the end of the trial (after final Follow-up visit).

Strenuous physical activity	You may not participate in any of these activities for 48 hours before screening, admission and the out-patient/follow-up visits. Strenuous exercise means more than your normal exercise regime at the time of screening but you can discuss this further with the Research Doctor if you are unsure about what this means.	Until the end of the trial (after final Follow-up visit).
Activity	You will be requested to remain in a semi-lying down position for the first four hours after investigational medicine administration each day, except to use the bathroom. You may then walk around but should not engage in strenuous activities and should rest in a semi-lying down position for at least five minutes prior to any Vital Signs measurements or at least ten minutes prior to ECG measurements.	Until the end of the trial (after final Follow-up visit).
Blood donation	You are not allowed to donate blood within 90 days before the planned first investigational medicine administration.	Three months after the end of the trial (after final Follow-up visit).
Clinical trial	You are not allowed to participate in this clinical trial if you have participated in another clinical trial within 90 days prior to screening or have participated in more than three clinical trials within one year prior to screening.	Until the end of the trial (after final Follow-up visit).
You must not have a COVID-19 vaccination	You are not allowed to have a COVID-19 vaccination from four weeks before the first investigational medicine administration.	Until seven days after the end of the trial (after final Follow-up visit).

Items you must use/ Things you must do:	**When you must start taking it / or doing it from:**	**How long you must use these items / or do this for:**
Acceptable methods of Contraception	Will be discussed with you by the Research Doctor, please refer to Section 4.	Will be discussed with you by the Research Doctor, please refer to Section 4.
Meals	You will receive standardised meals, served at scheduled times throughout your residential stay. You are required to consume all your meals. These meals may contain meat, and provision for diets that are either meat-free, or free from certain meats is not available as part of this clinical trial.	Throughout your residential stay.
Fasting and water consumption	On dosing days you will be required to fast for three hours before, and four hours after, taking the investigational medicine. You will be allowed to drink water until one hour before dosing, and from one hour after dosing.	On Day 1, Day 2 and Day 3 of the trial.
Unit Rules	You will be required to observe and adhere to the unit rules during your in-house stays as stated in the Volunteer Charter and unit Rules (unit regulations).	Throughout the clinical trial.
Avoid excessive UV radiation exposure.	From Admission (Day-1) you should use sun protective measures (such as a hat, sunglasses, protective clothing, and sunscreen SPF ≥30) and limit exposure to natural sunlight (including occupational exposure to the sun or sunbathing) and avoid artificial sunlight (tanning beds or phototherapy). Ideally, outdoor activities should	You can resume usual sun exposure 110 days (slightly less than 16 weeks) after the last dose of the investigational medicine.

	be scheduled outside the hours that ultraviolet radiation is most intense or should be performed in the shade.	

10. Adaptive Changes allowed by the clinical trial protocol

The following changes can be made within pre-defined limits of the protocol:

1. The in-house stay or outpatient/follow-up period may be extended for your safety. Based on the available safety and tolerability data from the sentinel group, the members of safety review committee may decide to shorten the in-house period for the non-sentinel group.
2. Additional or fewer blood and urine samples may be taken (e.g., for safety or PK assessment) but the maximum blood volume stated in Section 7 (What will happen to me if I take part?) will not be exceeded.
3. Additional safety tests such as vital signs and ECGs may be done.
4. The timing of blood samples and other safety tests such as vital signs and ECGs may be adjusted.
5. You may have to undergo additional safety investigations (e.g., you could be referred to a specialist) if required.
6. One or more of the treatment arms may be removed, and/or treatment groups may be split into sub-groups.

We will inform you about any changes at the time we decide to introduce them by issuing you with a 'Notification of changes made to this Participant Information/ Informed Consent Form', the template can be found in Appendix 4.

11. What are the possible benefits of taking part?

The investigational medicine you will receive is being given to you purely for research purposes – it is not intended that you will receive any benefit from it.

Ultimately, it will be populations in malaria-endemic countries requiring malaria prevention treatments that may benefit from these studies. New, more effective and convenient medicines can only be developed by performing research and we would like to thank you for considering to participate in this clinical trial.

12. What are the possible disadvantages and risks of taking part?

The possible disadvantages are explained in Section 6 above.

13. What happens when the clinical trial stops or if I stop participating in the clinical trial early?

If the clinical trial stops or if you decide to withdraw from the clinical trial early, you understand that we will keep the information about you that we have already obtained and that we can process this information in accordance with the clinical trial protocol and this Informed Consent Form.

Please refer to Appendix 3 for more information.

14. What if there is a problem?

Any complaint about the way you have been treated during the clinical trial or any possible harm you may suffer will be addressed. Please see Section 20 below for contact details. Reimbursement will be available for any injury attributable to administration of the investigational medicine or any clinical intervention or procedure within the clinical trial.

The detailed information is given in Appendix 2.

15. What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment/investigational medicine that is being studied. If this happens, the Research Doctor will tell you about it and discuss with you whether you want to continue in the clinical trial. If you decide to withdraw, the Research Doctor will make arrangements to continue your care if this proves necessary. If you decide to continue in the clinical trial, you will be asked to sign an updated consent form. There is a possibility that on receiving new information, the Research Doctor might consider it to be in your best interests to withdraw you from the clinical trial.

If new information emerges during the trial, Richmond Pharmacology and the Sponsor reserve the right to terminate your participation in the clinical trial, at any time without your consent.

16. Will my taking part in the clinical trial be kept confidential?

Yes. By signing this form, you consent to the Research Doctor and his/her staff, the Sponsor (MMV), regulatory authorities and Ethics Committee collecting, storing, transferring and processing your personal data, including the following: your date of birth, your sex, your race or ethnic origin, personal data on your physical or mental health or condition and any other personal data obtained during your participation in the clinical trial or as a result of any follow-up assessments.

Your personal data is processed in observance of confidentiality obligations. All persons involved in the processing of your personal data are subject to professional secrecy.

Please refer to Appendix 3 for more information.

17. What will happen to any samples I give?

What happens to the different samples we collect from you is explained in the table below:

Samples	Processing and Analysis	Retention
Blood and urine (safety)	Processed and analysed by a laboratory within the UK on an ongoing basis during the clinical trial. These samples will not have your personal details on them, however they will be coded in a way that is linked to you (see Appendix 3).	These samples will be retained for a maximum of three months to perform all tests described in the clinical trial protocol, after which they will be destroyed.
Blood for pharmacokinetics	Processed and analysed by a laboratory in Switzerland on an ongoing basis during the clinical trial. These samples will not have your personal details on them, however they will be coded in a way that is linked to you (see Appendix 3).	These samples will be retained until the clinical trial has been closed to perform all tests described in the clinical trial protocol, after which they will be destroyed. Back-up samples may be stored for up to 12 months after the clinical trial has been closed to measure the chemicals of the investigational drug PQP produced by the body (i.e.,metabolites), if a process for analysis becomes available.
Blood for pharmacogenomics	Processed and analysed by a laboratory in the UK or within the EU on an ongoing basis during the clinical trial. These samples will not have your personal details on them, however they will be coded in a way that is linked to you (see Appendix 3).	These samples will be retained until the clinical trial has been closed to perform all tests described in the clinical trial protocol, after which they will be destroyed.

The samples will not be used for any other research that you have not consented to on this form.

Please contact the Research Doctor at any time, if you require more detailed explanations about this. Further detailed information about each visit/day and the precise schedule for the clinical trial will be distributed if you agree to participate in this clinical trial.

18. Who is organising and funding the clinical trial?

This clinical trial will be conducted in the UK and will be run by Richmond Pharmacology Ltd. (RPL) and funded by MMV (the sponsor for the clinical trial) which is a not-for-profit organization based in Switzerland. Richmond Pharmacology Ltd. is an independent clinical research unit, which performs clinical trials mostly on behalf of the pharmaceutical industry. Richmond Pharmacology Ltd. is located at London Bridge in London and St George's University of London in Tooting.

19. Who has reviewed this clinical trial?

The protocol has been reviewed and approved by MMV and reviewed by members of the scientific review board at Richmond Pharmacology Ltd. This clinical trial has been approved by the **M**edicines and **H**ealthcare products **R**egulatory **A**gency (MHRA) which is the regulatory authority in the UK. To protect your interests

the clinical trial has been looked at by an independent group of people called a Research Ethics Committee. This clinical trial has been reviewed and given favourable opinion by NRES Committee South Central – Berkshire B (IRAS ID 307070). This clinical trial is regulated by both national and international guidelines. Richmond Pharmacology Ltd is under the inspection of the MHRA ensuring that the quality of our clinical trial is to acceptable standards. According to Good Clinical Practice (GCP) guidelines, UK law and other relevant legal, regulatory and scientific guidelines your clinical trial data must be stored and made accessible for at least 25 years after either medicine development stops OR after the last approval of a marketing authorisation in a country where GCP applies.

20. Further information and contact details

The Research Doctor and his/her staff will be pleased to help if you have any further questions about this clinical trial. Should you have any questions or experience a side effect, a member of staff is contactable on one of the telephone numbers below 24 hours a day.

A side effect is any illness, symptom or discomfort you develop at any time during the clinical trial. The illness/symptom might be related to the clinical trial or it might be something completely unrelated like a cold or a headache or an injury. However, **you must let us know about all of these events, even if you think that they might not be serious or important**. While you are in the unit we will ask you frequently whether you have experienced any side effects.

Prior to leaving the unit after you have been dosed, you will be provided with a Participant ID Card. You should carry this card at all times while you are involved in the clinical trial. The Participant ID Card contains your details (RPL ID, forename, surname and date of birth along with the clinical trial code C21007 and the following information (in italics):

I am currently participating in a medical trial. I may be taking an investigational medicine. In case of an emergency please contact Richmond Pharmacology:

Richmond Pharmacology Ltd *1A Newcomen Street* *London Bridge* *London* *SE1 1YR*	*0207 042 5800* *Monday-Friday: 08h00-19h00* *079 7942 2946* *24-hour Medical Emergency (for any medical concerns)*

www.richmondpharmacology.com
www.trials4us.com
www.trials4patients.com

The medically responsible person at Richmond Pharmacology is Dr Ulrike Lorch (RPL Medical Director) whose contact details are:

Dr Ulrike Lorch

Email: u.lorch@richmondpharmacology.com Telephone: 0207 042 5800

Thank you for considering taking part in this clinical trial.

RPL Number: <INSERT VDB LABEL>
Screening Number:

Informed Consent Form

Clinical Trial Title: A randomised, double-blind, placebo controlled, parallel group study in healthy adult volunteers to determine the tolerability and safety of pyronaridine (PYR) co-administered with piperaquine (PQP) under fasted conditions

Please read the following statements and put your short signature in the box to show that you have read and understood them and that you agree with them.		**Please provide short signature in each box**
1	I confirm that I have received verbal information on the above clinical trial and I understand and have read the Participant Information dated 07/Feb/2022, Version 4.0 and have had the opportunity to ask questions and any questions I asked have been answered to my satisfaction.	☐
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. I am aware of any risks associated with withdrawal from clinical trial before end.	☐
3	I understand that sections of any of my medical notes and clinical trial-specific records may be looked at by responsible individuals from the sponsor or from regulatory authorities where it is relevant to my taking part in clinical trial. I give permission for these individuals to have access to my records.	☐
4	By signing this consent form, I agree that my personal data, including photographs (this would only be applicable when monitoring possible side effects and will be taken in such a way as to prevent disclosure of your identity) and data relating to my physical or mental health or condition, and race or ethnic origin, may be collected and processed as described in the information sheet for the clinical trial.	☐
5	I agree that some of my samples may be sent outside the UK for analysis; where they have data protection laws which may be different than what is found in the UK; and I accept that the transferred samples will not be covered under the Human Tissue Act (i.e., the laws that govern and protect the collection, storage, use and disposal of human tissue in the UK).	☐

RPL Number: <INSERT VDB LABEL>
Screening Number:

6	I give my consent for my General Practitioner (GP) to be contacted and informed of my participation on the clinical trial and of any significant, abnormal results seen at screening or during the clinical trial.	☐
7	I understand I will receive a copy of this Participant Information/Informed Consent Form.	☐
8	I understand that I have the option of being informed about the general outcome and results of the clinical trial, once available.	☐
9	I confirm that I voluntarily agree to take part in this clinical trial.	☐

RPL Number: <INSERT VDB LABEL>
Screening Number:

Volunteer:

The Research Doctor supervising this clinical trial has given me an explanation of the nature, purpose and likely duration of the clinical trial, and what I will be expected to do. I have also been advised about any possible discomfort and ill effects on my health or well-being which may result from my participation.

I understand that if I withdraw from the clinical trial at any time and for any reason, the information that I have provided will be kept and will continue to be used, transferred and processed.

I have been given the opportunity to question the Research Doctor on all aspects of the clinical trial and have understood the advice and information given to me. I understand that the information for volunteers in its current **version number 4.0 dated 07/FEB/2022** which has been handed out to me forms part of this written informed consent.

Signature of Volunteer	Full Name	Date (DD/MMM/YYYY)	Time (24 HOUR CLOCK)
_____	_____	|__|__|.|__|__|__|.|__|__|__|__|	|__|__|.|__|__|

Observer:
Observer to signature of the volunteer and to the fact that they have read the document and freely given their consent.

Signature of Observer	Full Name	Date (DD/MMM/YYYY)	Time (24 HOUR CLOCK)
_____	_____	|__|__|.|__|__|__|.|__|__|__|__|	|__|__|.|__|__|

Research Doctor:
I confirm that I have explained to the volunteer the nature, purpose and possible hazards of these procedures, and therefore sign on behalf of RPL.

Signature of Research Doctor	Full Name	Date (DD/MMM/YYYY)	Time (24 HOUR CLOCK)
_____	_____	|__|__|.|__|__|__|.|__|__|__|__|	|__|__|.|__|__|

Richmond Pharmacology Limited | 1a Newcomen Street| London Bridge | London | SE1 1YR | Tel: 020 7042 5800

Appendix 1 – Clinical Trial Plan

Clinical Trial Plan - The timing of assessments may be adjusted following review of ongoing clinical trial data.

Table 1 from Clinical Study Protocol v3.0, 07 Feb2022: Schedule of Assessments

Procedure	Screening (D-22 to D-2)	D-1	D1	D2	D3	D4	D5	D6	D7 Sentinel Group only	D8	D15	D22	Last visit D30 (±1)
In-house stay		X	X	X	X	X	X	X	X				
Outpatient visit								X		X	X	X	X
Informed consent	X												
Eligibility check	X	X											
Medical history/ demographics	X	X											
Previous & current medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking history and current	X												
Beck depression inventory questionnaire	X												
Urine drugs of abuse screen	X	X											
Alcohol breath test	X	X											
Blood test for HIV 1&2, Hepatitis B&C	X												
Blood pregnancy test (females)	X	X											X
FSH (post-menopausal females)	X												
Investigational medicines administration			X	X	X								
Meals		X	X	X	X	X	X	X	X				
Safety and tolerability:													
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Screening (D-22 to D-2)	D-1	D1	D2	D3	D4	D5	D6	D7 Sentinel Group only	D8	D15	D22	Last visit D30 (±1)
24-hour Holter ECG	X												
Telemetry			X	X	X								
Height, weight and BMI calculation	X	X											
Physical examination	X	X	X	X	X	X	X	X	X	X			X
Safety blood tests (Biochemistry, Haematology, Coagulation)	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X		X		X		X	X	X		X
Pharmacokinetics blood tests			X	X	X	X		X		X	X	X	
CYP genetic blood test			X										

Depending on whether volunteers are included in the sentinel or non-sentinel group, they may be discharged on Day 7 or Day 5.
Volunteers in the sentinel group will attend the outpatient visits on days 8, 15 and 22.
Volunteers in the non-sentinel group will attend the outpatient visits on days 6, 8, 15 and 22, provided they are discharged on Day 5.

Appendix 2 – What to do if there is a problem

1. If you suffer any side effects or injury, notify the Research Doctor immediately so that you can receive appropriate medical treatment.

2. If you suffer injury caused directly by participation in the clinical trial, the sponsoring company MMV will pay you reimbursement in accordance with the Association of British Pharmaceutical Industry Clinical Trial Compensation Guidelines 2014 [*http://abpi.org.uk/media/1607/compensation_guidelines_2014.pdf*]. A copy can be provided to you.

3. Any dispute or disagreement as to the application of clause 2 and above shall be referred to an arbitrator to be agreed between yourself and the sponsor. If you and the Sponsor cannot agree on the identity of an arbitrator, the President of the Royal College of Physicians of London will be invited to appoint an arbitrator with the power to consult a barrister of 10 years standing on any issue of law including the amount of damages to be paid.

4. The agreement to pay reimbursement shall be construed in accordance with English law and subject to the clause 3 above, the English courts shall have sole jurisdiction over any dispute which may arise out of it.

5. You are not being asked to give up any of your legal rights by agreeing to take part in this clinical trial.

Both Richmond Pharmacology and MMV have insurance policies in place for insuring against claims for their alleged liability.

Appendix 3 – Use of Personal Data

The results of this clinical trial will be used for the further development of the new treatment and the other purposes described in this Participant Information/Informed Consent Form. The data from this clinical trial may be published. However, it is important for you to know that you will never be personally identified in any reports or publications produced following this clinical trial. Richmond Pharmacology will keep your name and contact details (i.e. your address, phone number, passport number and other data allowing us to contact you) confidential and will not pass this information to MMV or any other organisations involved in this clinical trial. Richmond Pharmacology will use this information as needed, to contact you about the clinical trial, and make sure that relevant information about the clinical trial is recorded for your care, and to oversee the quality of the clinical trial. Certain individuals from MMV and regulatory organisations may look at your medical and research records to check the accuracy of the clinical trial either on site or remotely. MMV will only receive information without any identifying information. The people outside Richmond Pharmacology who analyse the information will not be able to identify you and will not be able to find out your name or contact details. We will keep identifiable information about you from this clinical trial for at least 25 years after either medicine development stops OR after the last approval of a marketing authorisation in a country where GCP applies.

Your personal information will not be removed or copied to be taken outside the Richmond Pharmacology premises or off-site secure archiving within the United Kingdom other than for the purpose of routine computer back-ups and in any case be stored in a secure access-controlled environment. In addition, the information may be disclosed on a strict need to know basis in case of medical emergencies. Otherwise, your identifying personal data will solely be accessible by authorised members of Richmond Pharmacology's staff.

MMV, who is based in Switzerland, is the sponsor for this clinical trial. RPL will be processing information from you and/or your medical records in order to undertake this clinical trial and will act as the data controller of the personal data you provide to us for the purpose of the clinical trial. This means that we are responsible for looking after your information and using it properly. MMV will be a data controller of the Clinical Trial Data (as defined below).

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If the clinical trial stops or if you withdraw from the clinical trial early, you agree that we will keep the information about you that we have already obtained and continue to use it as outlined in this document, but will stop collecting new information. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at http://www.trials4us.co.uk/privacy-policy.php.

Your personal data is held for your future identification related to this clinical trial for as long as is necessary to comply with currently applicable Good Clinical Practice guidelines, UK law and other relevant legal, regulatory and scientific requirements, which may be at least for the time the medicine investigated in this clinical trial is under research and/or on the market anywhere in the world. Richmond Pharmacology also permanently retains your identifying personal data on their Volunteer Database and as paper records, to be able to contact you at a later date either by e-mail, mail or telephone to supply or receive information including information about future studies in which you may want to participate. You may instruct Richmond Pharmacology not to contact you regarding future studies.

Some of your identifying personal data (National Insurance Number or passport number) is also entered onto a UK register named TOPS-check so that other research units such as us can ensure you are not participating in more than one clinical trial at the same time. It is important to note however that this data can only be obtained by authorised users of the TOPS-check system who have your details already.

The Research Doctor will use your "Clinical Trial Data" (the coded/anonymised information, i.e. your date of birth and a subject number, not your full name) to conduct the clinical trial, research and statistical analysis. The Sponsor may also use your Clinical Trial Data to conduct the clinical trial, to support applications for approval of the investigational medicine and for research related to the development of pharmaceutical products, diagnostics or medical aids. Your Clinical Trial Data shared with the Sponsor does not include your name or address. Instead the Research Doctor assigns a code number to the Clinical Trial Data sent to the Sponsor. Only the Research Doctor and his/her staff have access to the code key with which it is possible to connect your Clinical Trial Data to you. However, any of your personal data, which is

available to the Research Doctor, may be reviewed, subject to strict controls, at the Research Doctor's site by the Sponsor and/or its representatives, its contractors, regulatory authorities, the Ethics Committee or other supervisory bodies.

The Sponsor may share your Clinical Trial Data with other companies within its group, with its service providers, its contractors and with other research institutions who will use your anonymised Clinical Trial Data only for the purposes described above.

The Sponsor may transfer your Clinical Trial Data to countries outside of the UK and European Union (EU) for the purposes described in this document. Please be aware that the laws in such countries may not provide the same level of data protection as in the UK and may not stop your Clinical Trial Data from being shared with others. However, all data that is transferred will be coded and you will not be identified.

You have the right to request information about your Clinical Trial Data held by the Research Doctor and Sponsor. You also have the right to request that any inaccuracies in such data be corrected. If you wish to make a request, then please contact the Research Doctor, who can help you contact the Sponsor if necessary.

Richmond Pharmacology and the Sponsor are each responsible for their handling of your Clinical Trial Data in accordance with applicable Data Protection law(s). Your consent to the collection, storage, access, use and transfer of your Clinical Trial Data does not have a specific expiration date.

To process your data lawfully we need to rely on one or more valid legal grounds. Our legitimate interest (except where your interests or fundamental rights override these) and your consent are the primary legal grounds for our processing of your personal information. There may be circumstances where we also rely on other valid legal grounds, such as our compliance with a legal obligation to which Richmond Pharmacology is subject to (for example, we have a regulatory duty to investigate and respond to complaints and may need to process your data as part of such investigation).

Please note that if you fail to provide personal information when requested, we may be prevented from complying with our legal obligation (such as to ensure your health and safety).

We suggest that you contact us via email DPO@richmondpharmacology.com about any questions or if you have a complaint in relation to how we process your personal data. However, you do have the right to contact the relevant supervisory authority directly. To contact the Information Commissioner's Office in the United Kingdom, please visit the https://ico.org.uk/global/contact-us/ for instructions.

"Applicable Data Protection Law" shall mean (a) the Data Protection Act 2018; (b), the UK GDPR (as defined in Section 3(10) of the Data Protection Act 2018) and/or (c) General Data Protection Regulation ((EU) 2016/679), as applicable, and any other applicable privacy or data protection legislation applicable in the UK from time to time.

Appendix 4 – Template for the Notification of changes made to this Participant Information/ Informed Consent Form

This is a template of the form to notify and explain to volunteers any changes made to the clinical trial. The changes we may make are listed in Section 10. You do not have to sign this form now, it is just here for your information should changes be made to the clinical trial in the future.

Template for the Notification of changes made to this Participant Information/ Informed Consent Form (Number X)

This form is to notify you of the changes which may be implemented from Section 10 (Adaptive Changes allowed by the protocol) of this Participant Information Sheet.

Change 1	
Summary of what is changing	We will provide a summary sentence of what has changed. We will indicate which number in the list in Section 10 of the original ICF this change refers to.
Details of change	We will highlight which parts of the original ICF you signed this change applies to.
Impact on you	The effect on you will be explained (i.e. attendance of additional clinical trial days, additional or fewer samples taken, adjusting the time of sample collection or safety tests etc.).
Impact on payment	Any payment changes will be stated, if applicable.

Change 2 – Additional tables will be added depending on the number of changes	
Summary of what is changing	We will provide a summary sentence of what has changed. We will indicate which number in the list in Section 10 of the original ICF this change refers to.
Details of change	We will highlight which parts of the original ICF you signed this change applies to.
Impact on you	The effect on you will be explained (i.e. attendance of additional clinical trial days, additional or fewer samples taken, adjusting the time of sample collection or safety tests etc.).
Impact on payment	Any payment changes will be stated, if applicable.

RPL Number: <INSERT VDB LABEL>
Screening Number:

Volunteer:

This notification form has been provided to you for your information and we require you to sign to acknowledge receipt of this form and that you understand the changes being made. You have previously consented to such changes as part of the original informed consent process, but should you have any questions, you should ask the Research Doctor to further explain anything that you may not understand. If you are not happy with these changes, you have the right to withdraw consent. If you are happy with the changes and would like to continue in the clinical trial, you will be required to sign and date two copies: one will be provided to you and one for RPL records.

TEMPLATE ONLY – DO NOT SIGN

_____	_____	|__|__|.|__|__|__|.|__|__|__|__|	|__|__|.|__|__|
Signature of Volunteer	Full Name	Date (DD/MMM/YYYY)	Time (24 HOUR CLOCK)

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