# PARTICIPANT INFORMATION SHEET AND CONSENT FORM

## Participant Information Sheet- Part 1

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| **Title** | A phase 1b study to evaluate the blood stage antimalarial activity of a single oral dose of tafenoquine in healthy subjects experimentally infected with *Plasmodium falciparum*. |
| **Protocol Number** | CTM2002 |
| **Ethics Number** | P3646 |
| **Study Part** | Part 1 – Induced Blood Stage Malaria (IBSM) model |
| **Sponsor** | QIMR Berghofer Medical Research Institute |
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**Introduction**

You are invited to take part in this study because you are healthy, aged 18 to 55 years old, and have not been previously exposed to malaria. This study is investigating the safety and efficacy of a single oral dose of an anti-malarial drug called tafenoquine against the *Plasmodium falciparum* malaria parasite.

This Participant Information Sheet and Consent Form tells you about the study. It explains the tests and treatments involved and will help you decide if you want to take part in this study. Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local general practitioner (GP).

Participation in this study is voluntary. If you don't wish to take part, you don't have to. If you choose to be in the study and then change your mind, you are free to leave the study at any time, and you do not need to give a reason. Also, your participation in this study may be stopped at any time for any reason by the study doctor or the Sponsor for clinical or administrative reasons.

If you decide you want to take part in the study, you will be asked to sign the consent section before any study assessments are conducted. By signing it you are telling us that you:

- Understand what you have read.
- Consent to take part in the study.
- Consent to have the tests and treatments that are described.
- Consent to the use of your personal and health information as described.
- You will be given a copy of this Participant Information Sheet and Consent Form to keep.
- You will be asked to provide photo ID at each visit to the clinical trial site for this study.

**What is the purpose of this study?**

Malaria is an infectious disease caused by *Plasmodium* parasites. There are at least five *Plasmodium* parasites that can cause malaria in humans, and the parasite that will be used in this study is called *Plasmodium falciparum (P. falciparum)*. In natural infections, the malaria parasite is injected into the blood when an infected *Anopheles* mosquito bites its human victim. *Anopheles* mosquitoes are mostly found in hot and humid regions of the world, but they do not live in Brisbane.

Malaria is responsible for more deaths than other parasitic diseases in the world. Unfortunately, the malaria parasite is becoming resistant to commonly used antimalarial drugs, and so new drugs are needed. Anti-malarial drugs are usually tested in patients with malaria. However, this process can be lengthy and logistically difficult. One way of accelerating this process is to test the drugs in healthy volunteers who have been deliberately given malaria under experimental conditions. To do this, we infect healthy volunteer adults by injecting them with a very low dose of the malaria parasite. We call this process the Induced Blood Stage Malaria (IBSM) model.

In this study, we will use the IBSM model to investigate an anti-malarial drug called tafenoquine that is already registered and approved for two purposes in Australia by the Therapeutic Goods Administration (TGA), an organisation responsible for regulating medicines in Australia. The first purpose is the radical cure of a different malaria parasite (*Plasmodium vivax or P. vivax*). Unlike *P. falciparum*, *P. vivax* can persist in the liver, and the term "radical cure" refers to parasite elimination from both the blood and the liver. When used as a radical cure, a high dose of tafenoquine is given. The second purpose of Tafenoquine is to prevent malaria infection in humans caused by all five *Plasmodium* parasites. When used for this purpose, a higher dose is given followed by regular weekly doses.

This study has three parts; A Participant Information Sheet and a Consent Form have been prepared for each part. You are being invited to participate in Part 1 of the study. In this part, we are investigating whether a single low oral dose of tafenoquine is able to clear *P. falciparum* parasites from the blood.

It is expected that up to 28 male or female adults will be enrolled in Part 1 of the study and you may be eligible to be a participant in Part 1 if you meet all the requirements for the study.

Extra participants may be recruited and attend the clinical trial site on the day of malaria inoculation, but they may not end up participating. These participants are called reserves. Reserve participants will only take part if one or more participants are withdrawn by the study doctors or withdraw before they receive the malaria inoculation. You will be informed if you are a reserve participant on the day of malaria inoculation. All reserve participants are reimbursed for their time spent in the recruitment process, regardless of whether or not they end up in the study.

**Overview of what this study will involve**

During this study, your health will be monitored by study doctors who are experienced in conducting malaria infection studies in volunteers. After you are infected with malaria, we will follow the growth of the malaria parasite

in your blood using a very sensitive blood test called polymerase chain reaction (PCR). This PCR test will allow us to detect very low number of parasites in your blood, at levels that are much lower than those that make people sick.

The study doctors will monitor you for signs and symptoms of malaria infection which may include:

- Fever (oral temperature of ≥ 38°C)
- Rigors (shaking chills)
- Headache (moderate to severe)
- Malaise (general feeling of illness)
- Racing pulse
- Joint pain
- Neck ache
- Vomiting
- Diarrhoea
- Chills
- Sweats
- Dizziness
- Fatigue
- Insomnia
- Muscle pain
- Nausea
- Stomach/abdominal cramps

When the number of parasites in your blood reaches a level that could begin to cause early symptoms of malaria (like fever, aches and pains, headache), or when you reach the set day for tafenoquine treatment (Day 8), you will be admitted to the clinical trial site. You will be given tafenoquine and then your health will be monitored for up to 96 hours. Then if you are well you will be discharged home. After you are discharged, you will visit the clinical trial site approximately 18 times for medical examination and tests (blood and urine).

At the end of the study, or earlier if tafenoquine does not remove the malaria parasites as well as expected you will be treated with a registered, TGA-approved, commercially available, antimalarial drug (Riamet® which contains two active agents: artemether and lumefantrine). This treatment is compulsory to make sure that all malaria parasites are cleared from your body. Sometimes another antimalarial drug called primaquine (Primacin®) is also needed. Primacin® is a registered, TGA-approved, commercially available, antimalarial drug that clears the gametocytes from your body so that you cannot spread malaria to mosquitoes.

**What is the duration of the study?**

The total duration of your participation in this study (Part 1) is approximately 2.5 months (80 days) from screening until the end of the study. In the unlikely event that you still have symptoms or laboratory abnormalities at the end of study, you may be asked to return to the clinical trial site a few times over the following two weeks. We will be contactable 24 hours a day during the study and we will be in regular contact with you.

**What does participation in this study involve?**

You will be injected with red blood cells infected with the *P. falciparum* malaria parasite. After the injection, you will visit the clinical trial site approximately seven times for medical examinations and blood tests to monitor the growth of the malaria parasite. When the number of the parasites in your blood grows to a level that will begin to cause early symptoms of malaria infection (like fever, aches and pains, headache) and/or you reach the allocated day to be given tafenoquine (Day 8), you will be admitted at the clinical trial site. You will be given tafenoquine and then your health will be monitored closely for up to 96 hours when you are discharged home. Once discharged, you will visit the clinical trial site approximately 18 times for medical examination and tests (including blood and urine).

The total duration of your participation in this study (Part 1) is approximately 2.5 months (80 days) from screening until the end of the study. During the entire study, your health will be monitored by study doctors who are experienced in conducting malaria volunteer infection studies. In the unlikely event that you still have symptoms or laboratory abnormalities at the end of study, you may be asked to return to the clinical trial site a few times over the following two weeks. We will be contactable 24 hours a day during the study and we will be in regular contact with you.

Typical procedures that will be performed during the study include:

- CANNULA: Insertion of a cannula into a vein in your forearm. This may cause minimal discomfort. A cannula is a small, flexible tube which will allow blood to be collected easily at some time points without the need for repeated needle insertions for each blood sample.
- INOCULATION: Inoculation with malaria parasites via injection into your veins using a cannula
- PHYSICAL: Medical physical examination
- MEDICATIONS: Checking of concurrent medications you may be taking
- WEIGHT: Body weight check
- VITALS: Measure of body temperature, heart rate, rate of breathing, and blood pressure
- BLOOD: Collection of blood samples (with a cannula or a needle) for medical tests (including hepatitis virus testing, HIV testing, haematology, biochemistry including iron and cholesterol, safety serum storage, red blood cell alloantibody testing, genetic testing (G6PD deficiency and looking at your CYP2D6 gene), and to check the number of parasites in your blood. Blood samples may also be collected for other study objectives.
- URINE: testing of your urine to assess your health e.g. kidney function and diabetes
- DRUG: Urine drug screen
- ALCOHOL: Alcohol breath test
- ECG: Electrocardiographs to record the electrical activity of your heart

The blood tests include screening tests for HIV and viral hepatitis. This is because the study doctors need to establish your health status. Please be aware that if you are found to have HIV or viral hepatitis, the laboratory conducting the test is required to inform the Queensland Health Department of these results in an anonymous manner as per *Queensland Public Health Act 2005*. If requested, the laboratory may disclose your name to the Chief Executive of the Queensland Health Department. If you are found to have HIV or viral hepatitis, you will be referred to appropriate counselling and/or medical services. If you are positive for HIV or Hepatitis you will be excluded from the study.

The study is divided into seven phases:

1. Screening and confirmation of eligibility
2. Malaria inoculation (Day 0)
3. Malaria monitoring follow-up days
4. Tafenoquine administration and confinement at the clinical trial site (for up to 96 hours from Day 8 to Day 12)
5. Outpatient visits to the clinical trial site
6. Treatment with malaria rescue medication (Day 48±2 or earlier)
7. End of study visit (Day 51±2)

<u>Phase 1: Screening and confirmation of eligibility</u>

Your screening visit may be up to 28 days before you are injected with the malaria parasite. You will be asked to fast for at least 8 hours (overnight) before your screening visit. Your screening visit will last approximately 2 to 3 hours. You will be provided with the Participant Information Sheet and Consent Form (this document) to read. This document should help you to understand the study, but please ask the study doctor questions about anything you

don't understand or want to know more about. It is very important that you understand what this study is about and what is expected from you. If you agree to participate in the study, you will be asked to sign the Consent Form (and you will be given a copy).

You will then be required to answer some questions to establish your medical history and have some tests to see if the study is suitable for you (PHYSICAL, MEDICATIONS, WEIGHT, VITALS, ALCOHOL, DRUG, ECG, URINE, and BLOOD). You will also be asked to fill in a questionnaire called the Beck Depression Inventory to help us determine if you may be suffering from depression.

One of the blood tests will be looking for a condition called Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency. G6PD deficiency is the most common genetic condition in humans. Some people with G6PD deficiency cannot use tafenoquine because it causes breakdown of red blood cells (haemolysis). If you have normal G6PD activity, you will be eligible for the study. If your G6PD activity is abnormal, you will be excluded. We will test your G6PD levels at other time points in the study to see if G6PD levels change with malaria infection.

Another blood test will be looking at one of your genes (CYP2D6 gene). This gene can be different in people. Scientists think that differences in our CYP2D6 gene may explain why people breakdown (metabolise) some medications differently, including tafenoquine.

Some of the screening tests may need to be repeated 1 to 3 days before injecting the malaria parasite if the screening was done earlier than 3 days before the planned inoculation date. This is to ensure that you remain suitable for participation in the study.

If any health conditions that affect your ability to participate in the study are detected during screening, these will be discussed with you. If necessary, you will be referred for follow-up tests with your GP or medical specialist.

If you are suitable to be included in the study and you decide to participate, you will be asked to arrive at clinical trial site on the morning of your inoculation day (approximately 7 am).

<u>Phase 2: Malaria inoculation (Day 0)</u>
This visit will take approximately 3 to 4 hours to complete. The following procedures will be performed: PHYSICAL, MEDICATIONS, VITALS, ALCOHOL, DRUG, ECG, CANNULA, BLOOD, and INOCULATION. You will not be injected with the malaria parasite if the results of alcohol test and/or drug screening are positive.

After receiving the injection of parasites, you must remain at the clinical trial site for at least one hour for observation. You will be given a thermometer and a diary card and you will be educated about the signs and symptoms of malaria (like fever, aches and pains, headache).

It is important for your own safety that you return to the clinic trial site for all study visits.

<u>Phase 3: Malaria monitoring follow-up days</u>
During the first three days after the malaria inoculation, the malaria parasites will not be detectable in your blood. We will call you or send a text message daily to check how you are feeling. If you develop chills or feel feverish during this time, please take your temperature and record it on the diary card that was provided for this purpose. If you take any medication to reduce these symptoms (like ibuprofen), please also record it on the diary card. You must bring your diary with you to your clinic visits.

From Day 4 onwards, you must return to the clinical trial site to provide daily or twice daily blood samples (as requested by the study doctor) to measure the parasites in your blood. These visits will be between 6 - 11 am in the

morning and between 6 - 11 pm in the evening, preferably around 12 hours apart.

Phase 4: Confinement at the clinical trial site and tafenoquine administration

On the day you are to receive tafenoquine (Day 8 or earlier if advised by the study doctor) you will be required to come to the clinical trial site at approximately 7 am. You will have been asked to fast overnight for at least 8 hours before the following procedures will be performed: PHYSICAL, MEDICATIONS, VITALS, ALCOHOL, DRUG, ECG, CANNULA, and BLOOD. If the results of alcohol test and/or drug screening are positive, then you will excluded from the study and will not be administered tafenoquine.

If you are included in the study, then you will be fed a normal breakfast before being asked to swallow the tafenoquine tablets. The tafenoquine dose given to the first group of people will be 300 mg. The dose for other groups will be selected based on the information collected from earlier groups. The largest dose that may be given is 600 mg, and the smallest dose that may be given is 25 mg.

You will be admitted at the clinical trial site for up to 96 hours (four nights and four days) or longer if the study doctor thinks it is required for your safety. During your stay, you will be encouraged to drink water and other allowable drinks, and to consume all meals that will be provided. The following procedures may be performed once or several times during your stay: PHYSICAL, MEDS, VITALS, ALCOHOL, DRUG, ECG, URINE, PREG, CANNULA, and BLOOD. At the end of the planned confinement, if the study doctor thinks it is safe to do so, you will be allowed to leave the clinic. If the study doctor judges that it is not safe for you to be discharged, then you will be advised to stay in confinement until you are well.

Phase 5: Outpatient visits to the clinical trial site

You must return to the clinical trial site for clinical evaluation and blood sampling after discharge from the clinical trial site until the end of the study. You will visit the at least three times per week. During these visits, the following procedures may be performed: PHYSICAL, MEDICATIONS, VITALS, ECG, URINE, and BLOOD.

If you develop chills or feel feverish during this time, you will be asked to take your temperature and record it on a diary card that will be provided for this purpose. Any changes in mood, anxiety or difficulty to sleep should also be recorded in a diary card. You MUST contact the study staff at **any time** (even at night) if you develop a fever of 38°C or greater; feel the urge to harm yourself or others; or you are experiencing symptoms that are affecting your ability to complete activities you usually do.

Phase 6: Treatment with malarial rescue medication

On Day 48±2 (or earlier if advised by the study doctor), you will be required to come to the clinical trial site to begin a full treatment course of Riamet® to ensure that all parasites have been cleared from your body. The following procedures will be performed: PHYSICAL, MEDICATIONS, VITALS, ECG, and BLOOD.

Riamet® treatment comprises six doses of four tablets (total course of 24 tablets) given over a period of 3 days (60 hours). Some of these doses will be given to you at the clinical trial site, but you may also need to take some of the Riamet® doses at home. Instructions on taking Riamet® will be provided to you by the clinic staff. You will be contacted by phone on the days when you are taking the drug dose at home and on the day following the final dose to confirm completion of the final Riamet® dosing. If you experience an allergy or reaction to Riamet®, then another registered antimalarial, Malarone® will be administered. Malarone® treatment comprises three doses of four tablets (total course of 12 tablets) given over a period of three days. Some of these doses will be given to you at the clinic, but you may also need to take some of the Malarone® doses at home. Instructions on taking Malarone® will be provided to you by the clinic staff. You will be contacted by phone on the days when you are taking the drug dose at home and on the day following the final dose to confirm completion of the final Malarone® dosing.

You may also need to be treated with Primacin®, if we detect gametocytes in your blood, or if you withdraw from the study or at the study doctor's discretion. You will be notified if you require this additional treatment.

If you are not able to take Riamet® or Malarone® for any reason (e.g. vomiting), then intravenous artesunate may be administered.

Phase 7: End of study visit

On Day 51±2 (or earlier if advised by the study doctor), you will be required to come to the clinical trial site to an end of study visit. The following procedures will be performed: PHYSICAL, MEDICATIONS, VITALS, ECG, and BLOOD. If any of the test results are abnormal, follow-up visits may be required to repeat those tests. If this is the case, you will be told so by the clinical trial site staff.

A small sample of your blood taken at Day 0 (inoculation day) and Day 51±2 (end of study) will be stored indefinitely at QIMR Berghofer Medical Research Institute in case future confirmation of your safety results is required (safety serum storage).

**How will I be compensated for my time?**

If you are eligible to enter the study, you will be reimbursed $150.00 for the screening and follow-up visits, and at an hourly rate of $15.00 per hour for the in-clinic stay part of this study. The total reimbursement for participants who complete the entire study will be approximately $5,150.00 this includes a long-term follow-up reimbursement for participation in all study visits. Please note that this total may vary depending on the number of times your doctor requires you to come in for follow up assessments. If you are a reserve, and do not complete the entire study, you will receive a partial reimbursement of approximately $390.00.

Regardless of whether you withdraw early or complete the study, you will be reimbursed within 10 business days of the end of study visit via electronic funds transfer directly into your bank account. Should you withdraw from the study before the final visit you will receive a partial payment according to the number of visits you have attended.

Reimbursement compensates for your time, travel expenses, parking and inconvenience. This reimbursement is not made for undergoing risk nor is it to compensate you for any loss of earnings as a result of your participation. If you are dosed and then prematurely discontinue, or are withdrawn from the study, you will receive pro-rata reimbursement for both situations.

These figures are calculated from a formula that provides for the reimbursement of time, the number of visits, and inconvenience. We will not make any deductions for any taxes from these payments — you are solely responsible for reporting this payment in your tax return and for the payment of any taxes due. To obtain valid clinical data and to follow up your safety, it is best that you complete the study where possible.

Your participation in this study does not entitle you to a payment or compensation for any commercialisation of the intellectual property associated with or discovered during the conduct of this study.

There are no additional costs associated with participating in this study. All medications, tests and medical care required as part of the study will be provided to you free of charge.

**What are my obligations and responsibilities during the study?**

For your safety, you will need to be contactable at all times by mobile phone and available for the duration of the study. It is a condition of this study that you do not live alone from the day you are inoculated with malaria until the

end of your antimalarial drug treatment (approximately 51 days). With their permission, we ask you to nominate a housemate, and provide their contact details during this period.

In order to provide maximum protection for your health, the study will be under the direct supervision of the Investigator and will be conducted by trained personnel. Please provide us with all the information about your current and past health (medical history) at the screening visit. We need this information to protect your health.

It is very important that you come to all the study visits at your scheduled time. Call the study staff immediately if you have a problem getting to the clinic on time. It is very important that you follow instructions from the study staff as you are at risk of developing malaria. Delaying treatment may lead to serious complications, including coma or death, if you are not treated.

You MUST contact the study staff at **any time** (even at night) if you develop a fever of 38°C or greater or you are experiencing symptoms that are moderate or severe or affecting your ability to complete activities you usually do. You must come to the clinic if the clinic staff ask you to for your own health and safety.

If you choose to participate in this study, you must also observe the following restrictions:

Medicines

- You must not take any other antimalarial or related drugs, or have any vaccination in the four weeks before the day you are inoculated with malaria, or during the study itself.
- You must not take prescription or non-prescription drugs or herbal supplements in the two weeks before the day you are inoculated with malaria or during the study itself unless approved by the study staff. If you take any other drug or herbal supplements (including St John's Wort) during the study, you may not be able to continue in the study due to possible interaction with the antimalarial drugs to be administered in the study. You must immediately contact the study staff at clinical trial site if you need to take any prescription or other medication not given to you by the study staff. You will be given a card with contact details at the start of the study.
- Recreational drug use is not permitted during the study. Urine testing for evidence of drug use will be undertaken during screening and on malaria inoculation day.
- If you are experiencing malaria symptoms after malaria inoculation and need a symptomatic treatment, you should preferably take ibuprofen (e.g. Nurofen) as treatment and avoid paracetamol (e.g. Panadol) unless agreed first with the study doctor. We are asking you to avoid paracetamol as it may worsen the liver inflammation that is sometimes observed with malaria infection.

Food and beverages

- Persons with specific dietary preferences may not be able to participate. Please discuss this with the study doctor if relevant. While in the clinical trial site, you must only consume the standard meals provided.
- You must not eat any food that contains poppy seeds in the 24 hours before the following time-points: screening visit, malaria inoculation day, and admission to the clinic for the confinement period.
- You must not drink or eat any beverages or food that contain alcohol (e.g., beer, wine, and mixed drinks) during confinement at the clinic and 24 hours prior to each alcohol breath test. You should not drink more than two standard drinks per day from 24 hours before inoculation until the end of the Riamet® treatment.
- You will be required to fast (have no food or drinks other than water) for at least 8 hours prior to the screening visit, eligibility confirmation visit, admission to the clinic for the confinement period, Days 15±2, 29±2 and end of study visit.
- You must not consume quinine containing foods/beverages (e.g. tonic water, lemon bitter) from malaria inoculation until the end of Riamet® treatment.
- You must not consume grapefruit or Seville orange or juices of these fruits until the end of the Riamet® treatment.
- You must not consume beverages that contain xanthine bases (e.g. Red Bull, coffee) during confinement at the clinical trial site. You should not consume more than 400 mg caffeine per day, equivalent to more than four cups of coffee, from malaria inoculation until the end of Riamet® treatment.

Activity

On your malaria inoculation day, you must remain at the clinical trial site for at least one hour after the dose of the inoculum. After that time, if your vital signs are normal, you will be free to leave the clinic site.

When you are confined in the clinic, you will not be allowed to do any activity that is more vigorous than walking. You should not increase your regular exercise activity during the study, especially after inoculation day and after being released from confinement at the clinic.

Tobacco use

Non-smokers and smokers who are considered social smokers may be eligible for this study. If you smoke fewer than five cigarettes per day you may be allowed to participate at the Investigator's discretion. Smoking will not be allowed during the confinement period.

Sexual activity and contraception

It is important that any participants involved in this study do not get pregnant or if male, get their female partners pregnant.

For males:

- If in a sexual relationship with a female, you must agree to use a double method of contraception including condom plus diaphragm, or condom plus intrauterine device, or condom plus stable oral/transdermal/injectable hormonal contraceptive by the female partner, from the time of informed consent through to 90 days after your last dose of Tafenoquine succinate (Kodatef®).
- If abstinent, you must agree to start a double method if you begin a sexual relationship with a female during the study, and through to 90 days after your last dose of Tafenoquine succinate (Kodatef®).
- You should not donate sperm or father a child from the time of informed consent until 90 days after inoculation with the malaria parasite.

For females:

- If of childbearing potential and in a sexual relationship with a male, you must agree to use an insertable, injectable, transdermal or combination oral contraceptive combined with a barrier contraceptive from the time of informed consent through to 90 days after your last dose of Tafenoquine succinate (Kodatef®).
- If abstinent, you must agree to start a double method if you start a sexual relationship with a male during the study, and through to 90 days after your last dose of Tafenoquine succinate (Kodatef®).
- You must not be planning *in vitro* fertilisation within the required contraception period.

Travelling

You should not travel to areas where *Anopheles* mosquitoes are present (which includes far north Queensland, and some areas of Africa, south-east Asia and South America) for the duration of the study. Please discuss any travel plans you may have with the study doctor.

Blood Donation

By participating in this study, you will experience a mild malaria infection. The Australian Red Cross Blood Service (Blood Service) excludes people with previous malaria infection from donating blood for a minimum of six months after malaria infection. Blood donation services in other countries may have even longer exclusionary periods. Therefore, if you choose to participate in the study you will be ineligible to donate blood for a minimum of six months following the end of study visit. If this is important to you, you should consider not taking part in this study.

**Is there any benefit for me to participate in the study?**

You will receive no direct personal benefit from the study, except for information about your general state of health. Participating in this study will not protect you from developing malaria in the future if you travel to a country where malaria is common. You should follow recommendations from your health care provider to prevent malaria when you travel.

Information collected during the study will increase our knowledge about tafenoquine and may be useful for treating malaria in the future.

**What are the risks and disadvantages of taking part in with this study?**

The study involves you being injected with malaria parasites that are contained in human red blood cells. These red blood cells were collected from a volunteer who got malaria when they were bitten by an infected mosquito. This raises several possible risks:

Potential risks of receiving red blood cells from a donor

- The risk of infection with viruses or organisms (other than malaria) from the very small quantity of blood injected into you in this study is much smaller than the risk of infection from a blood transfusion for reasons described:
  - The volume of blood used to transmit the malaria in this study is many thousands of times smaller than what would be used in a whole blood transfusion and so the risk is reduced.
  - The blood cells have been washed and the white cells have been removed, both of which lower the risk of infection due to transfusion.
  - Before this initial volunteer donor was infected with malaria, the volunteer was screened for a wide range of blood borne diseases. After the malaria-infected blood was collected, it was frozen for over a year so that the donor could be observed and retested for any infections. During this time the donor remained healthy, and repeat testing after one year did not reveal any new infections. This last point is significant as this indicated that the volunteer's malaria infected blood did not contain any low-level infections with viruses or other organisms at the time of collection that did not show up on the initial tests. This is especially important in reducing the risk of transfusion associated infection.
  - Over 350 people have received this malaria parasite and none have developed a blood-borne infection because of it.
- The risk of a transfusion reaction (similar to an allergic reaction) is unlikely because of the extremely small quantity of donor blood in the inoculum, and because the white cells have been removed from the donor blood. Nevertheless, you will be monitored closely for one hour after you are given the malaria parasite dose.
- The risk that you could develop antibodies (a protein that can protect the body from foreign organisms, such as bacteria and viruses) to the donor red cells is also very small because the donor of the red cells was blood group O and Rh negative. People with blood group O blood are considered 'universal donors', as people who receive even large volumes of blood from them are unlikely to develop red cell antibodies. Nevertheless, as a precaution, you will be tested for red cell antibodies before and after the study. Women of childbearing potential have a small additional risk of developing red cell antibodies that could cause problems during pregnancy. Women of childbearing potential have participated in several malaria challenge studies with *P. falciparum* 3D7 with no known issues to date. If you are a woman of childbearing potential, you will be required to comply with strict contraception requirements during the study.

The risk of malaria

**Untreated *P. falciparum* malaria infection can be fatal.** In this study, to ensure your safety, blood samples will be taken to monitor the number of parasites in your blood after you receive the malaria inoculum. You will be closely monitored for any early symptoms of malaria (like fever, aches and pains, headache).

The parasites you will receive are known to be cleared by the standard antimalarial medications that you will receive after administration with tafenoquine. The strain of parasite you will be given has been used in >350 participants in >25 malaria studies.

Also, the number of parasites used to infect participants in the study is much lower than the number of parasites that reach the blood after the bite of a single malaria-infected mosquito. Most previous participants have no or only mild symptoms due to the low number of parasites. Some people do however experience flu-like symptoms prior to antimalarial treatment, or a brief fever after the antimalarial treatment once the malaria parasite is killed and the immune system is activated. These episodes may require treatment, for example a medication for fever, in which case ibuprofen is preferred to paracetamol.

Adverse effects observed during previous studies (where malaria is inoculated via infected red blood cells or via

mosquito bites)

Temporary changes in blood tests are regularly observed during malaria challenge studies. These include decreased white blood cells and platelets, which always return to normal by the end of these studies. These blood test changes are also seen in natural malaria infection.

In one study, one healthy participant experienced a severe drop in their neutrophil count. Neutrophils are a type of white blood cell that help protect you from developing infections. This was considered a severe adverse reaction that was likely a consequence of the malaria infection itself. Because this participant's neutrophil count was so low they were admitted to the hospital and given a treatment to increase the amount of neutrophils. The participant's neutrophil count recovered after treatment and he was discharged from the hospital.

Among the 379 healthy participants who have received the *P. falciparum* inoculum (3D7 strain) in drug studies, a small portion (less than 5%) have shown moderate or severe elevations of liver enzymes a few days after antimalarial treatment. Although some of these elevations have reached values in the range 5-10 times the normal levels (i.e., severe elevations), they have not been caused any symptoms, and results have returned to normal before the end of the study without any specific treatment.

It is unclear why some participants show these biological changes: a contribution of the malaria, of paracetamol and/or the drugs tested cannot be excluded. Liver experts have reviewed the data and believe that the changes are most likely due to the response to the malaria infection rather than being caused by the drug. These changes are also seen in naturally acquired malaria and return to normal in these situations too. We will closely monitor your liver function tests during this study. If such elevations occur during the study, we will monitor your blood until these parameters are back to normal values.

There have been three unexpected cardiac serious adverse events in healthy participants infected in malaria challenge studies, using mosquito malaria inoculum (a slight variation to the blood stage malaria challenge in this study) that occurred in the Netherlands:

- The first participant experienced an episode of chest pain, diagnosed as acute coronary syndrome (decreased blood flow to part of the heart muscle). This occurred two days after completion of malaria treatment. It is uncertain what caused the blood flow to be decreased. This could be due to the heart artery spasm or blockage, or cardiac inflammation. This participant was also found to be suffering with a viral upper respiratory tract infection (common cold virus) at the time. The individual was treated accordingly, with full recovery reported.
- The second participant was found to have an abnormal blood test suggesting cardiac inflammation. The individual subsequently suffered a very short episode of chest pain and was diagnosed with cardiac inflammation. This participant was also found to be suffering with a viral upper respiratory tract infection (common cold virus) at the time. Again, this second individual made a full recovery.
- More recently, a third participant also had an abnormal blood test suggesting mild cardiac inflammation. This participant also fully recovered.

It is unclear at this stage whether these events were related to i) the experimental malaria vaccine the participants received, ii) the malaria infection, or iii) the malaria treatment, or were caused by something unrelated.

In a recent trial at the clinical trial site, two participants developed cardiac adverse events:

- The first participant had an abnormal ECG prior to the antimalarial rescue drug. The participant did not have any symptoms at the time the abnormally fast heart rhythm with extra beats was noticed. Subsequent investigations did not find a significant cause of the abnormal heart rhythm.
- The second participant had an abnormal fast rhythm with extra beats at the same time point as the first

participant. The participant had a temperature and required rescue treatment for the malaria. The abnormal heart rhythm went back into a normal heart rhythm after treatment.

It was determined by an independent cardiologist and the study safety review team that the malaria infection had unmasked the unknown cardiac conditions that these subjects had prior to enrolment in the study. It was felt that these conditions would not have been picked up in the screening process. Nonetheless, as a precaution, we will exclude people at significant risk of heart disease from participating in this study. We will also monitor your heart using ECG at regular intervals throughout the study and have a cardiologist available if a problem arises.

There is no risk of developing malaria again from this study, as the final antimalarial drug treatment you will be given will completely cure you and these infections do not occur with *P. falciparum* malaria, which is the type of malaria parasite used in this study.

Blood collection

There is some risk of pain, local bruising, and infection at the site where blood is drawn for laboratory tests. This is particularly the case where multiple blood samples will need to be collected. The study doctor and clinical trial site staff are very skilled in blood collection, but this study is not suitable for people afraid of needles or of having their blood collected.

There is also a small risk of a fainting episode, which can occur as a reaction to donating blood. We will ensure that the maximum amount of blood drawn over any consecutive 30 day period does not exceed 450 mL, which is similar to the amount drawn in blood donation to the Blood Service.

Other monitoring procedures

We will also be measuring your blood pressure and taking your pulse at regular intervals as well as conducting ECGs to check the activity of your heart. ECGs record the electrical activity of your heart by placing electrodes (adhesive tabs attached to wires) on the skin of your chest. Occasionally, there may be some minor skin irritation from the electrodes and hair-pulling when the electrodes are removed.

Risks associated with antimalarial drugs

- Tafenoquine succinate (Kodatef®) is a registered, commercially available drug for the prevention for malaria and a radical cure treatment for *P. vivax* malaria, not *P. falciparum* malaria. The dose of tafenoquine that you receive will not be the standard dose. The most significant concern with tafenoquine is the risk of severe haemolytic anaemia in subjects with G6PD deficiency. You will be tested for this deficiency at screening to ensure you are eligible for this study. Common side effects associated with tafenoquine include headache, diarrhoea, dizziness, nausea, anxiety, insomnia, and abnormal dreams. Most of these side effects have been mild and have not lasted very long. A very small proportion of people experience depression/depressed mood (0.3%) or attempt suicide (0.1%). Your history of psychiatric disorders will be examined during the screening process to determine your eligibility for this study.
- Riamet® is a registered, commercially available drug that is recognised as a treatment for malaria. It contains two drugs (artemether and lumefantrine) that work together to kill the malaria parasite. The dose of Riamet® that you will receive is the recommended standard daily dose of the drug. However, side effects from taking this antimalarial drug may occur. You may experience some side effects such as stomach pain, diarrhoea, dizziness, aching muscles/joints, sore throat/cough, nausea/vomiting, headache, difficulty sleeping, tingling, and fever/shivering. Most of these side effects have been mild and have not lasted very long.
- Malarone® is a registered, commercially available drug that is recognised as a treatment for malaria. It contains two drugs (atovaquone and proguanil hydrochloride) that work together to kill the malaria parasite. The dose of

Malarone® that you will receive is the recommended standard daily dose of the drug. However, side effects from taking this antimalarial drug may occur. You may experience some side effects such as loss of appetite, nausea, vomiting, stomach pain, diarrhoea, mouth ulcers, rash or itching, headache, difficulty sleeping or strange dreams, dizziness, tiredness, cough, fever and elevated liver function tests. Most of these side effects have been mild and have not lasted very long.

- Primacin® is a registered and commercially available antimalarial drug containing primaquine phosphate, which is recognised as a treatment for the sexual gametocyte stage of malaria to prevent transmission to other humans (via *Anopheles* mosquito bite). Generally, side effects of Primacin® are few and the most common ones are abdominal cramps and pains, nausea, vomiting, dizziness, and headache. Effects on red blood cells may occur in susceptible individuals; a test will be done at screening to determine if you are at risk of this effect and to ensure your safety.
- If you are not able to take Riamet® and Malarone® for any reason (e.g., vomiting) then intravenous artesunate may be administered to you as a replacement. Intravenous artesunate is not a registered product in Australia. However, the World Health Organisation (WHO) recommend intravenous artesunate as the treatment of choice for adults with severe malaria. In the 379 participants in the challenge studies who have been inoculated with *P. falciparum* malaria (3D7 strain), only one participant has required intravenous artesunate treatment.
- The lists of side effects above are not complete. The study medications, like many medicines, can cause other side effects, some very severe or life-threatening, but rare. However, it is hard to predict if these side effects could occur in your case. Side effects may occur almost immediately after the drug is administered, or days later. Tell the clinical trial site doctor or nurse right away about any change in your health.
- You will be monitored closely during this study, so in the rare event that you experience a severe side-effect, you will receive rapid care at the clinical trial site or at the nearby Emergency Department at Caboolture Hospital so that your safety is ensured.
- The Consumer Medicines Information leaflets for Kodatef®, Riamet®, Malarone® and Primacin® containing the full list of side effects will be provided at your initial medical screening visit. Please read these leaflets for more details about these drugs.

<u>Possible allergic reactions</u>

It is important to understand that any medication, including the medication that you will be taking in this study, could possibly cause a serious life threatening or fatal allergic reaction. Allergic reactions may result in swelling of the face, lips, tongue, throat, and vocal cords, difficulty breathing, skin rashes, seizures, loss of consciousness, shock, and death may result from heart and lung failure in very rare cases. Any symptoms and signs of allergic reaction will be closely monitored. As a precaution, a management plan for possible allergic reactions has been developed by the study doctors.

Finally, although we consider that this study involves minimal risk, we cannot completely rule out the possibility of unforeseen side effects.

**<u>What will happen to my test samples?</u>**

Samples of your blood and urine, obtained for the purposes described in this clinical study, will be transferred to the Sponsor's nominated national or international laboratory for testing. These samples will not identify you by name, but only by your study number (code), initials, and perhaps your date of birth. These coded samples will be stored according to the laboratories' testing requirements, for the duration required to complete the tests, and then they will be destroyed as per the laboratories' procedures.

A small sample of your blood taken at Day 0 (inoculation day) and at the end of the study will be stored indefinitely

at QIMR Berghofer Medical Research Institute in case future confirmation of your safety results is required (safety serum storage).

You may also be asked if you are willing for your unused blood samples to be used for future research via the Consent Form for Blood Storage: Blood Sample Specimen Storage for Use in Future Research. Your decision about the use of your samples for future research will not affect your participation in this study or other studies.

**What happens if new information arises during this research study?**

As any new information becomes available, you will be informed of any newly identified risks to which you may be exposed and that may affect your willingness to participate in this study. If you should decide to continue with the study, you may be asked under certain circumstances to sign an updated Participant Information Sheet and Consent Form.

**What if I withdraw from this research project?**

Your participation is voluntary. However, if after receiving the malaria parasite you wish to withdraw from the study, it is important to stress that to safely withdraw from the study you **must** return to the clinical trial site to receive an appropriate antimalarial treatment, as untreated malaria can be fatal. This is for your own safety.

If you withdraw during the study, any data collected up to the point you withdraw from the study may still be used in the analyses for this study.

**What will happen to information about me?**

The Australian Government requires that companies and organisations that collect personal information about you must show that information to you if you wish to see it. Below we tell you how to request a copy of your personal information. Please read this carefully. If you have any questions, please ask the study doctor.

This study is being conducted under the Australian regulatory agency, the Therapeutic Goods Administration (TGA). All records are kept for a minimum of 15 years. All information obtained during this study, including clinic and hospital records, personal information and research data, will be kept confidential. Your personal information specifically relating to your health before, during your participation and when you finish the study is recorded on special forms by the study doctor and clinical trial site staff.

The clinical trial site keeps all forms on which your personal information is recorded. If you wish to see these forms, you may ask clinical trial site staff to show them to you. The clinical trial site does not forward any study records showing your personal details to the Sponsor Company; only information taken from your records (which will be coded by your study identification number and in some cases your initials, sex, and date of birth) are sent by the clinical trial site to the Sponsor. However, you may contact the Sponsor if you wish to see what information they hold about you in relation to this study. If you wish to do this, please contact the clinical trial site staff.

The forms containing your name may be inspected by Sponsor representatives, and the QIMR Berghofer Human Research Ethics Committee to ensure study conformity with the TGA requirements. However, such records will only be accessible at the clinical trial site and cannot leave the site. The representatives of these organisations all comply with privacy standards.

A description of this study will be available in the public clinical trial registry http://www.anzctr.org.au. This website will not include information that can identify you. At most, the website will include a summary of the results. You

can search this website at any time. A report of the study may be submitted to government agencies (including the TGA) and perhaps for publication. Only your study identification number (and in some cases your initials, sex, and age) will be included in such reports.

If you have a local GP, we strongly recommend that you inform them of your participation in this research study. We will give you a letter to give to your GP or to another treating doctor that you may consult in the future.

**What happens if I become sick or if I am injured during the study?**

Your health is our primary concern. If you suffer any injuries or complications as a result of this study, the study doctor or your GP will provide the usual, customary, or hospitalised medical care. If this occurs, you should contact the study staff as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital

In the event of loss or injury as a result of the proper conduct of the study, the parties agree to be bound by the "Medicines Australia Guidelines for Compensation of Injury Resulting from Participation in a Company-Sponsored Clinical Trial". You will receive a copy of these Guidelines. You do not give up any legal rights to compensation by participating in this study, including any rights to take legal action as a result of injuries or loss not covered by the Guidelines. The Sponsor has adequate insurance in place.

You may be able to seek compensation through the courts. It is the recommendation of the independent ethics committee responsible for the review of this study that you seek independent legal advice before taking any steps towards compensation for injury.

**Who is organising and funding the research?**

The research study is funded by the Bill and Melinda Gates Foundation and is locally sponsored by QIMR Berghofer Medical Research Institute. The Sponsor is paying the clinical trial site to conduct the study.

No member of the research team will receive a personal financial benefit from your involvement in this study (other than their ordinary wages).

**Who has reviewed the research study?**

The study has been reviewed and approved by the QIMR Berghofer Human Research Ethics Committee (HREC number EC00278), in accordance with the *National Statement on Ethical Conduct in Human Research* (2007), incorporating all updates. The *National Statement* has been developed to protect the interests and safety of people who participate in human research studies.

**Who should I contact if I have questions?**

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the Principal Investigator Bridget Barber on 0424 737 153 or the clinic contact person listed below:

**General contact details**

| | |
|---|---|
| During Business Hours | (07) 5430 2956 |
| After Hours | 0401 226 709 |

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

**Complaints contact person**

| | |
|---|---|
| Phone | (07) 5459 4759 |

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

**Reviewing HREC approving this research and HREC Executive Officer details**

| | |
|---|---|
| Reviewing HREC name | QIMR Berghofer HREC |
| Telephone | 07 3362 0117 |
| Email | HREC.Secretariat@qimrberghofer.edu.au |

In the event of a severe medical emergency please call **000**.

## INFORMED CONSENT FOR STUDY PARTICIPATION

| | |
|---|---|
| Protocol Number: | CTM2002 |
| Ethics Number : | P3646 |
| Study Title: | A phase 1b study to evaluate the blood stage antimalarial activity of a single oral dose of tafenoquine in healthy subjects experimentally infected with *Plasmodium falciparum*. |
| Study Part: | Part 1 |

I have read this Participant Information Sheet or someone has read it to me in a language I understand. I understand the purpose of the study, the study requirements and the risks of participating in the study. I have had the opportunity to ask questions and my questions have been answered. I hereby give my informed consent to be a participant in this study.

I understand that potential adverse reactions could be caused by the malaria challenge agent, the investigational medicinal product (tafenoquine) and the antimalarial rescue treatments (Riamet®, Primacin® (if required), Malarone® (if required) and intravenous artesunate (if required)). I have been given copies of the Consumer Medicines Information leaflet for Kodatef®, Riamet®, Malarone® and Primacin®.

I am aware that I will receive a copy of this fully signed Informed Consent. I agree to provide a photo ID at each visit to clinical trial site for this study.

I understand that I must be contactable and not live alone, and that I must provide contact details of my housemate (with his/her permission), from the time of malaria inoculation until I have completed taking the antimalarial drugs.

I understand that when I sign this consent form, I authorise representatives of the Sponsor and members of the Human Research Ethics Committee or regulatory authorities to access my study-related medical records. They may need to access my records to verify the clinical study procedures and/or data.

I agree that if I have a General Practitioner that he/she may be informed about my study participation.

I also realise that the information obtained from this study, including the results of all tests upon myself, will be held in both computerised and manual filing systems. The case report form for this study will not identify me by name. These anonymised records may be used for product registration purposes and thus may be made available to Health Authorities worldwide, and they may be sent overseas for processing by either Sponsor personnel or a third party.

I understand that I am free to withdraw from the study:

- at any time,
- without having to give a reason for withdrawing,
- and without affecting my future medical care.

However, as untreated malaria is a potentially fatal illness, I understand that if I wish to withdraw after the malaria challenge agent, I will need to be treated with appropriate antimalarial drugs. **I understand that for my protection I MUST take the full course of antimalarial drugs to clear the malaria parasites.**

I understand that I am free to discuss my participation in this study with project staff (Study Doctor: Bridget Barber). I also understand that if I have any concerns and/or complaints about the study, I may contact the Chairperson of the QIMR Berghofer-HREC via the Secretary (07 3362 0117).

**Participant:**

| Full name | Signature | Date | Time |
|---|---|---|---|
| | | | |

**I, the undersigned, have fully explained the relevant details of this study to the participant named above, and I believe that the participant has understood that explanation.**

**Investigator or delegate:**

| Full name | Signature | Date | Time |
|---|---|---|---|
| | | | |

***Reminder: A copy of this signed consent form must be given to the participant.***

***Each party signing the consent form must date their own signature.***

The QIMR Berghofer Medical Research Institute - Human Research Ethics Committee, in accordance with the National Health and Medical Research Council's guidelines, has approved this study.

## INFORMED CONSENT FOR BLOOD STORAGE

## BLOOD SAMPLE SPECIMEN STORAGE FOR USE IN FUTURE RESEARCH

| | |
|---|---|
| Protocol Number: | CTM2002 |
| Ethics Number : | P3636 |
| Study Title: | A phase 1b study to evaluate the blood stage antimalarial activity of a single oral dose of tafenoquine in healthy subjects experimentally infected with *Plasmodium falciparum*. |
| Study Part: | Part 1 |

As part of this study, we are obtaining blood samples from you. If you agree, we will store these samples so that we can study them in the future. These samples may be used to test for malaria antibodies or to investigate the immune response to malaria. The Investigator's Human Research Ethics Committee, a special committee that oversees medical research to protect the rights and welfare of the human volunteers, will review any additional research studies beyond the current study. The samples collected from you will not be sold or used directly for production of any commercial product.

For this study, each blood sample will be labelled only with a code that serves as a unique tracking number. No personally identifying information will be included on the tube, to protect your confidentiality. Personnel at the testing lab will not know your identity, or the subject ID code assigned to you.

There are no direct benefits to you in the collection, storage and subsequent use of specimens. Reports about future research done with your samples will NOT be kept in your health records. You can decide if you want your code-identified unused samples to be used for future research, have your unused samples re-labelled at the end of the study and used for future research, or have your unused samples destroyed. Your decision can be changed at any time prior to the end of the study by notifying the study doctors or nurses. However, if you originally consented to the future use of your blood for research purposes, and some of your blood has already been used for research purposes, the information from that research may still be used.

Your decision about your samples will not affect your participation in this study or other studies.

Please initial your decision about granting permission for the storage and future use of your samples for research purposes below (**indicate only ONE option**):

☐ _____YES, you may store my unused, code-identified samples for an indefinite period for future research as described above.

☐ _____YES, you may store my unused samples for an indefinite period for future research as described above, but you must remove the code label that could link the sample to me or identify it as my sample. The sample will be re-labelled only with study number, malaria strain, and visit.

☐ _____NO, you may not use my samples for other future research. Destroy my unused samples at the end of this study.

**Future studies involvement**

As being part of this study, we would like to contact you regarding the possibility of your involvement in future malaria research projects that develop from this study or in a new aspect of this study.

Please **initial** your decision about granting permission to us to contact you for possible involvement in future studies (**indicate only ONE option**):

☐ _____YES, you may contact me for possible involvement in future research.

☐ _____NO, you may not contact me for involvement in future research.

Agreeing to be contacted for future studies does not obligate you to participate in any of our future studies and a separate consent document would be signed for future studies.

**Participant:**

| Full name | Signature | Date | Time |
|---|---|---|---|
| | | | |

**Investigator or delegate:**

| Full name | Signature | Date | Time |
|---|---|---|---|
| | | | |

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