Participant Information and Consent Form

Alfred Project Number	125/21
Full Study Title:	A Phase 1b study to assess the safety, tolerability and antimalarial activity of MMV533 against *Plasmodium falciparum* 3D7 blood stage infection in healthy volunteers.
Protocol Number:	MMV_MMV533_20_01
Test Drug Code:	MMV533
International Sponsor:	Medicines for Malaria Venture (MMV)
Local Sponsor:	Southern Star Research Pty Ltd (SSR)
Coordinating Principal Investigator:	Dr Paul Griffin
Principal Investigator:	Dr Paul Griffin
Location:	Q-Pharm Pty Ltd, Level 5 Clive Berghofer Cancer Research Centre, (CBCRC) 300C Herston Rd, Herston QLD, 4006

PART 1 - What does my participation involve?

1. Introduction

You are invited to take part in this research study because you are a healthy male or female aged 18-55 years old who potentially meets the study participation requirements.

This project is testing the safety, tolerability, pharmacokinetics (PK, the amount of study drug in your blood) and pharmacodynamics (PD, how the study drug affects your body and, in our case, the malaria parasite) of a single oral dose of a new drug called MMV533. The study drug is being developed as a potential new treatment for acute uncomplicated malaria. You will be inoculated with *Plasmodium falciparum* 3D7 prior to receiving the study drug.

This Participant Information and Consent Form (PICF) tells you about the research study. It also explains the tests and treatments that will be completed during study participation. This information is given to you to help you decide if you want to take part in this research study. Please read this information carefully and ask the study doctor questions about anything that you don't understand or want to know more about before deciding whether or not you want to take part. If you wish to do so, please take the time to talk about it with a relative, friend or your local doctor before making a decision to participate.

Once you understand what the study is about and if you agree to take part in it, you will be asked to sign a Consent Form attached to this document. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research study.

Upon your confirmation, your information regarding participation in the study will be provided to your preferred doctor if you provide their contact details to study staff. It is desirable that your local doctor be advised of your decision to participate in this research study.

Participation in this research is voluntary. If you don't wish to take part, you don't have to.

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

- understand the information you have read;
- consent to take part in the research study;
- consent to follow the study requirements;
- consent to have the tests and treatments that are described;
- consent to follow the study requirements and to keep follow-up appointments that are described;
- consent to the use of your personal and health information as described.

A description of this clinical trial is available on https://clinicaltrials.gov/. This website will not include information that can identify you. At most, the website will include a summary of the results after the trial is completed. You can search this website at any time.

You will be given a signed copy of the Participant Information and Consent Form to keep.

2. What is the purpose of this research?

Malaria is an infectious disease caused by Plasmodium parasites that are carried by Anopheles mosquitoes. At least five types of Plasmodium parasites can cause malaria in humans. In natural infections, the malaria parasite is injected into the blood when an infected Anopheles mosquito bites its victim. Anopheles mosquitoes are mostly found in hot and humid regions of the world, but they do not live in Brisbane (however, they do live in far north Queensland).

Unfortunately, current approaches to controlling malaria in endemic areas (in regions where malaria is naturally present, for example South East Asia or Africa) are failing because the malaria parasites have become resistant or are becoming resistant to the antimalarial drugs we have available (this means the parasites are no longer killed by the drugs or they take longer to be killed by the drugs). Therefore, there is a need to develop and test new antimalarial drugs or combinations of drugs. One way of accelerating this process is to test the drugs in healthy volunteers who have been deliberately given malaria under well-controlled experimental conditions. To do this, we introduce, using controlled intravenous (directly into a vein) administration, very small quantities of parasite to healthy volunteer adults. We call this process the Induced Blood Stage Malaria (IBSM) model.

Medicines for Malaria Venture (MMV) is developing the study drug MMV533 as one such potential new oral treatment for the treatment of acute uncomplicated malaria. In this study, we will use the IBSM model to investigate whether MMV533 is able to eliminate the plasmodium parasite after single oral dose in healthy volunteers.

Medications, drugs and devices must be approved for use by the Australian Federal Government; the Therapeutic Goods Administration (TGA). MMV533 has not been approved for marketing by the TGA in Australia (and is not yet approved anywhere else in the world). Therefore, the use of MMV533 in this study is experimental.

MMV533 is being tested in humans in the ongoing First-in-Human (FIH) study investigating safety, tolerability and pharmacokinetics of MMV533 in healthy adult male and female volunteers. This study is also conducted in Australia (Melbourne). The six cohorts (5, 10, 20, 50, 100, and 160 mg) of the MMV533 FIH study have been completed (total of n=48 volunteers; 12 placebo and 36 study drug). No serious or severe adverse events were observed and the drug was associated with a good safety profile including the

highest dose of 160 mg. This study is blinded which means that we do not know yet who has received the active drug or a placebo.

In other studies, with drugs under development, some unexpected serious, life-threatening side effects have occurred following the administration of new experimental treatments. It is unknown, whether some unexpected, serious, life threatening side effects could occur with MMV533. Whilst these are considered unlikely, you will be monitored closely for them and treated if they occur.

This study is being conducted at Q-Pharm Pty Ltd. The Clinical Research Organisation involved in monitoring the study and acting as the local sponsor is Southern Star Research (SSR) and is sponsored by Medicines for Malaria Venture (hereafter referred to as MMV).

3. What does participation in this research involve?

Before you begin the study, you will be given detailed information about MMV533, the study, and any other relevant information by research staff. You are encouraged to ask questions until you are sure that you fully understand the nature of and requirements of the study.

If you decide to be assessed for inclusion in the study, you will be asked to visit Q-Pharm Pty Ltd. for an initial assessment visit (screening visit). Before any procedures are undertaken, you will be asked to sign a consent form. You will then have some tests to check that the study is suitable for you. The screening visit may take approximately 3 hours.

Participants deemed eligible after screening will be inoculated with the malaria challenge agent on Day -8 and first MMV533 dose will be given on Day 1. All safety checks will be performed during the study. Details of the study sequence and assessments in each visit are outlined below.

Approximately 12 participants in 1 cohort (group) will be enrolled. Participants will be tested and dosed in subgroups of 4 to 6. The doses that will be evaluated in this study have all been tested in the initial "First-In-Human" study (conducted in Melbourne) and have been be considered safe and well tolerated for human volunteers.

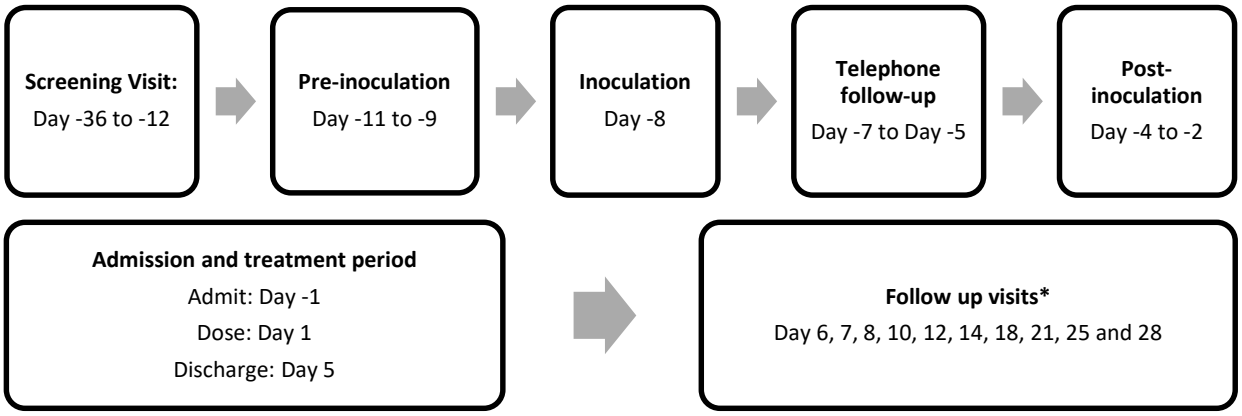
The dose levels planned for this study range from 10 mg to 160 mg. Preliminary data from the First In Human study have shown that 160 mg is well tolerated in healthy volunteers. You will be informed of the exact dose for your cohort when you check in to the clinical unit (Day -1).

Study sequence:

Your total participation in the study will consist of approximately 10 weeks as follows;

- **Screening visit**: Will occur within 36 days of your first dose. You will undergo assessments to determine if you are eligible for the study.
- **Pre-inoculation:** You will be required to attend the study centre on a single occasion (Day -11, Day -10, or Day -9)
- **Inoculation:** You will be required to attend the study centre on a single occasion
- **Post-inoculation:** You will be required to attend the study centre on 3 separate occasions
- **Admission and treatment period**: You will be required to attend the study centre for a 5 night, in patient stay.
- **Follow up visits:** You will be required to attend the study centre on a maximum of 10 separate occasions following your discharge after Day 5.

Below is a schematic outlining the study schedule:



*Follow up visits on Day 8, 14, 21, 25, and 28 are mandatory. Additional follow-up visits on Day 6, 7, 10, 12, and 18 may be required by the study doctor. The study doctor will tell you which of these additional visits you will need to attend.

If you decide to be assessed for inclusion into the study, you will be asked to visit Q-Pharm Pty Ltd. for the screening visit.

Screening visit (between Day -36 to Day -12)

After reading this information sheet and if you agree to participate in the study, you will be asked to sign the attached consent form. The study doctor will perform a medical examination to ensure that it is appropriate for you to be part of the study. You will undergo the following assessments:

- You will be asked about your **current health status** and about your **medical/surgical history**, including all medications, over-the-counter and herbal medications that you have been, and are currently taking.
- You will be asked some personal details about yourself, including your date of birth.
- For your own health and for correct operation of the study, it is important that you are honest and complete with your answers. You may be asked about your use of tobacco (including e-cigarettes and other nicotine products), alcohol and other drugs. You will undergo an **alcohol breath test**.
- You will be asked to provide a **urine sample** to assess your general health and to test for substances/drugs of addiction as listed below:
  - to test for substances/drugs of addiction (such as amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine and tetrahydrocannabinol). This is a study requirement and the results will remain confidential. The tests may reveal that you have previously used legal or illegal substances. That information will be stored in a re-identifiable (or coded) format. If Q-Pharm Pty Ltd. is ordered by a court of law to disclose the information regarding the use of illegal medications or alcohol breath test levels, it may be used against you in legal proceedings or otherwise as the court directs. If you test positive for any of these substances, you will be excluded from further participation in this study.
  - to test for use of tricyclic antidepressants
- Your **vital signs** such as blood pressure, pulse rate and body temperature will be measured.
- You will have a full **physical examination** (PE), including measurement of your height and weight to determine your body mass index (BMI).

- **G6PD status testing:** Severe G6PD deficiency (a condition that may potentially have impact on your red blood cells during the study) diagnosed through a blood test at screening is an exclusion criteria due to increased risk in case of malaria infection.
- **Red blood cells antibodies:** It is possible that you could suffer a transfusion reaction after being inoculated with the malaria challenge agent, or develop alloantibodies to the donor red blood cells (RBCs) that may make blood transfusion more difficult for you in the future. The risk of developing such alloantibodies is considered extremely low as the donor blood used to produce the malaria challenge agent was blood group O Rh(D) negative which is generally considered to be a 'universal donor'.
  - As part of the safety monitoring for this study, you will be tested for RBC alloantibodies at screening and then at the end of the study, and will be monitored for signs and symptoms of transfusion reactions immediately after being inoculated with the malaria challenge agent.
- **Pregnancy test:** If you are a woman, your blood will be tested to check that you are not pregnant. If you are a woman of non-childbearing potential, your blood will be tested to confirm your postmenopausal status.
- You will have **electrocardiograms** (ECG) (recording of your heart's electrical activity and rhythm).
- **Safety Lab Test Blood sample** will be collected for screening for HIV (AIDS virus), and hepatitis B and C and general safety assessments. This is because the study doctors need to know about your general health and the health of your immune system.
  - You will receive information and counselling before the HIV and hepatitis tests. If a test shows you have HIV or hepatitis you will not be included in this study, but you will have follow-up counselling and medical advice. If your test results are positive, the researchers are required by law to notify the relevant state government. Signing the consent form means you agree to have this testing. It will not be done without your consent.
- **SARS-COV-2 (COVID-19) testing:** A swab will be inserted into your throat or nose to collect a sample for a COVID-19 test.
- **Questionnaire:** you will be asked questions by the site staff as part of a questionnaire called the Beck Depression inventory to assess your mental health. The purpose of this questionnaire is to ensure that participants do not have mood disorders while enrolled in the study.
- **Concomitant Medication (all medications, supplements and herbal preparations) review:** you will be asked if you have recently taken any medications as this may interact with the study drug.
- **Adverse Events:** You will be asked about how you are feeling (whether you feel alright, different from normal or unwell), please tell a study team member if you have any changes in your health or concerns.

If for any reason, the trial is found to not be suitable for you, staff from Q-Pharm Pty Ltd. will contact you.

Pre-inoculation Day (Three options: Day -11, Day -10 or Day -9)

- You will be asked about your **current health status** and about your **medical/surgical history**, including all medications, over-the-counter and herbal medications that you have been, and are currently taking.
- **Questionnaire:** you will be asked questions by the site staff as part of a questionnaire called the Beck Depression inventory to assess your mental health.
- **Physical Examination:** will be performed to assess your general health. This will include measuring your body weight.

- **Body Temperature:** your body temperature will be measured
- **Safety blood and urine samples:** a blood and urine sample will be collected to assess your general health. You will need to have fasted from all food and drink (except water) for at least 8 hours before providing blood samples.
- You will have **electrocardiograms** (ECG) (recording of your heart's electrical activity and rhythm).
- **Pregnancy test:** If you are a woman, your blood will be tested to check that you are not pregnant. If you are a woman of non-childbearing potential, your blood will be tested to confirm your postmenopausal status.
- **SARS-COV-2 (COVID-19) testing**: A swab will be inserted into your throat or nose to collect a sample for a COVID-19 test.
- **Concomitant Medication (all medications, supplements and herbal preparations) review:** you will be asked if you have recently taken any medications as this may interact with the study drug.
- **Adverse Events:** You will be asked about how you are feeling (whether you feel alright, different from normal or unwell), please tell a study team member if you have any changes in your health or concerns.

Inoculation (Day -8)

To ensure sufficient number of participants are available for inoculation Day -8, additional volunteers called 'alternates' will be recruited. If you are an alternate, you may be asked to participate in the study if someone is not included in the inoculation group. You will be informed if you are an alternate on Day -8 before being inoculated.

- You will be asked about your **current health status** and about your **medical/surgical history**, including all medications, over-the-counter and herbal medications that you have been, and are currently taking.
- **Physical Examination:** will be performed to assess your general health.
- You will be asked to provide a **urine sample** to test for substances/drugs of addiction and undergo an **alcohol breath test**
- Your **vital signs** such as blood pressure, pulse rate and body temperature will be measured.
- **12-Lead Electrocardiogram (ECG):** to assess your heart rhythm.
- **Serum Safety samples:** two blood samples will be taken for safety assessments related to the study drug and the malaria challenge agent.
- **SARS-COV-2 (COVID-19) testing:** A swab will be inserted into your throat or nose to collect a sample for a COVID-19 test.
- **Malaria clinical score:** The Malaria Clinical Score will be used to quantify any signs and symptoms of malaria after you have been inoculated with the malaria challenge agent. You will be asked to grade your signs/symptoms using a 4-point scale (absent 0; mild: 1; moderate: 2; severe: 3). The total score covers 14 possible symptoms/signs associated with malaria.
- **Pharmacodynamic (PD) blood samples also called "PCR samples":** will be collected to quantify the malaria parasite in your blood and measure the treatment effect. Blood samples will be collected at various times during the study visits (as shown in the schedule below).

- **IV malaria challenge agent:** The malaria challenge agent is composed of approximately 2800 viable human red blood cells infected with the *Plasmodium falciparum* 3D7 parasite, and is administered intravenously to the participant as part of the IBSM model of controlled infection to help study the effectiveness of the test drug (MMV533). This parasite is highly sensitive to commercially available treatments for malaria. These registered treatments (called "definitive medication") will be also administered at the end of the study (or earlier based on blood tests) to ensure full elimination of the parasites once the study is completed.
- **Diary card:** You will be given a diary card and thermometer to collect information during outpatient periods including daily oral temperature, adverse events (including any signs/symptoms of malaria), details of self-administered take home malaria definitive medication and concomitant medications. You will be required to fill the diary out every day and bring your diary cards to each visit to the clinical trial unit for review.
- **Concomitant Medication (all medications, supplements and herbal preparations) review:** you will be asked if you have recently taken any medications as this may interact with the study drug.
- **Adverse Events:** You will be asked about how you are feeling (whether you feel alright, different from normal or unwell), please tell a study team member if you have any changes in your health or concerns.

Telephone follow-up (Day -7 to Day -5)

On Days -7, -6, and -5, you will be telephoned by Q-Pharm Pty Ltd. The purpose of this call is to find out how you are feeling and whether you have had any changes in your health.

Post-inoculation (Day -4 to Day -2)

You will be required to attend the clinical unit for outpatient visits once (in the morning) on Day -4 and twice daily on Days -3 and -2 (separated by 12±2 hours on each day)

- **Physical Examination:** will be performed to assess your general health.
- Your **vital signs** such as blood pressure, pulse rate and body temperature will be measured.
- **SARS-COV-2 (COVID-19) testing:** A swab will be inserted into your throat or nose to collect a sample for a COVID-19 test.
- **Safety blood and urine samples (Day -3 only):** a blood and urine sample will be collected to assess your general health.
- **Diary card review:** You will be required to bring your diary cards to each visit to the clinical trial unit for review.
- **Malaria clinical score:** The Malaria Clinical Score will be used to quantify any signs and symptoms of malaria after you have been inoculated with the malaria challenge agent. You will be asked to grade your signs/symptoms using a 4-point scale (absent 0; mild: 1; moderate: 2; severe: 3).). The total score covers 14 possible symptoms/signs associated with malaria.
- **Pharmacodynamic (PD) blood samples:** will be collected to assess the effects against malaria parasite. Blood samples will be collected at various times during the study visits (as shown in the schedule below).

- **Concomitant Medication (all medications, supplements and herbal preparations) review:** you will be asked if you have recently taken any medications as this may interact with the study drug.
- **Adverse Events:** You will be asked about how you are feeling (whether you feel alright, different from normal or unwell), please tell a study team member if you have any changes in your health or concerns.

Admission and treatment period (Day -1 to Day 5)

You will be admitted to the clinical unit the day before the planned dosing day (Day -1). On Day -1 you will undergo a number of procedures to confirm your continued suitability for participation in the trial (see table below).

You will be required to stay in the clinical unit for 5 consecutive nights and discharged home on the last day of treatment period.

On your first day in the clinical unit Day -1, a cannula will be inserted into a vein in your arm. This is a small, tube which will allow blood to be collected easily throughout your unit stay and prevents the need for repeated needles to be inserted in your vein to collect each sample. The location of the cannula may need to be repositioned if required.

During your stay in the clinical unit, you will be provided meals. For Day -1 only, you will need to arrive fasted from all food and drink (except water) for at least 8 hours before providing blood samples.

You will undergo the following procedures at various times during the study:

- Your **vital signs** such as blood pressure, pulse rate and body temperature will be measured.
- **12-Lead Electrocardiogram (ECG):** to assess your heart rhythm.
- **Physical Examination:** to assess your general health.
- **Body weight and height:** Body weight (kg) will also be measured at eligibility visit between Days -11 to -9 and at EOS.
- **Safety blood and urine samples (Day -3 only):** a blood and urine sample will be collected to assess your general health.
- You will be asked to provide a **urine sample** to test for substances/drugs of addiction
- **Alcohol breath test:** You will undergo an alcohol breath test when you check into the clinical unit to see if you have been drinking any alcohol in the past 24 hours.
- **SARS-COV-2 (COVID-19) testing:** A swab will be inserted into your throat or nose to collect a sample for a COVID-19 test.
- **Study drug administration:** The study drug (MMV533) will be administered on Day 1 as an oral tablet with 240mL of water under fasting conditions (10 hrs overnight). You will be given a definitive medication on Day 21 (see page 8).
- **Pregnancy test:** If you are a woman, your urine will be tested to check that you are not pregnant.
- **Diary card:** You will be required to bring your diary cards to each visit to the clinical trial unit for review.
- **Malaria clinical score:** The Malaria Clinical Score will be used to quantify any signs and symptoms of malaria after you have been inoculated with the malaria challenge agent. You will be asked to grade your signs/symptoms using a 4-point scale (absent 0; mild: 1; moderate: 2; severe: 3). The total score covers 14 possible symptoms/signs associated with malaria.

- **Pharmacokinetic (PK) samples**: will be collected to measure the amount of MMV533 in your blood, the break down products and to assess the effect it has on your body. Blood samples will be collected at various time points during a study visit (as shown in the schedule below).
- **Pharmacodynamic (PD) blood samples:** will be collected to assess the effects against malaria parasite. Blood samples will be collected at various times during the study visits (as shown in the schedule below).
- **Concomitant Medication (all medications, supplements and herbal preparations) review:** you will be asked if you have recently taken any medications as this may interact with the study.
- **Adverse Events:** You will be asked about how you are feeling (whether you feel alright, different from normal or unwell) at regular intervals, please tell a study team member if you have any changes in your health or concerns.

You will be discharged from the clinical unit once all study procedures are complete and the clinical staff sees no changes in your health which would prevent your discharge from the clinical unit.

Follow up visits (Day 5,+)

You will be required to attend follow-up visits on up to 10 days at Q-Pharm Pty Ltd. The follow-up visits on Day 8, 14, 21, 25 and 28 are mandatory. Additional follow-up visits on Day 6, 7, 10, 12, and 18 may be required by the study doctor. The study doctor will tell you which of these additional visits you will need to attend. These visits will take approximately 1-2 hours for a range of follow-up assessments as outlined above and in the table below.

- **Physical Examination:** to assess your general health.
- Your **vital signs** such as blood pressure, pulse rate and body temperature will be measured.
- **12-Lead Electrocardiogram (ECG):** to assess your heart rhythm.
- **Safety blood and urine samples:** blood and urine samples will be collected to assess your general health.
- **Pharmacokinetic (PK) samples**: will be collected to measure the amount of MMV533 in your blood, the break down products and to assess the effect it has on your body. Blood samples will be collected at various time points during a study visit (as shown in the schedule below).
- **Pharmacodynamic (PD) blood samples:** will be collected to assess the effects against malaria parasite. Blood samples will be collected at various times during the study visits (as shown in the schedule below).
- **SARS-COV-2 (COVID-19) testing:** A swab will be inserted into your throat or nose to collect a sample for a COVID-19 test.
- **Malaria clinical score:** The Malaria Clinical Score will be used to quantify any signs and symptoms of malaria after you have been inoculated with the malaria challenge agent. You will be asked to grade your signs/symptoms using a 4-point scale (absent 0; mild: 1; moderate: 2; severe: 3). The total score covers 14 possible symptoms/signs associated with malaria.
- **Parasite drug resistance samples:** One blood sample will be collected to investigate parasite drug resistance in the event there is a recurrence of infection with malaria detected through a blood test (i.e., “Pharmacodynamic blood sample”).

- **Definitive medication:** when your test results reach a certain value, you will be given a definitive medication against malaria as a preventative measure. This could be on any day within this follow up period. You will be required to consume 240 mL full-fat milk with each dose of definitive medication.

At your final follow up visit, blood samples will be collected to ensure that you are fully clear of malaria. If there is any follow up needed, this will be communicated to you by the study staff/ study doctor.

The study doctor will ask you to return to the research unit on these days and may ask you to return after this period, if he/she feels it is necessary. In the event it is necessary to further evaluate the safety or effects of the medication, it may be necessary to have access to additional information about your health status. Your study doctor may attempt to obtain study-related information about your health from you or from other sources, including your primary care physician. This may include contacting you again by phone or letter.

Total Blood Volume Collected Throughout Study

By consenting to take part in this study, you also consent to the collection and testing of your urine and blood samples and COVID tests (swabs/blood) for this research. The volume of blood to be collected during the study will not exceed 450mL. For comparison, a standard blood donation is approximately 470mL (approx. 2 cups).

The total volume does not account for a small amount of blood (approx. 2ml per collection) which is discarded (each time) when a cannula is used to collect the blood.
Please note that as per the Investigators discretion, additional blood samples may also be collected for safety reasons.

The table below outlines the assessments that will be performed during the study:

	Screening	Pre-inoculation	Inoculation	Post-inoculation Phase				Treatment and Posttreatment phase														EOS/ ET
Day	**D-36 to D-12**	**D-11 to D-9**	**D-8**	**D-4**	**D -3**	**D -2**	**D -1**	**D1**	**D 2**	**D 3**	**D 4**	**D 5**	***D 6***	***D 7***	**D8 ± 2**	***D10***	***D12***	**D14 ± 2**	***D18***	**D21 ± 3**	**D25 ± 3**	**D28 ± 3**
Informed consent	X																					
Confinement							X	X	X	X	X	X										
Discharge												X										
Outpatient visit at clinical site	X	X	X	X	X	X							*X*	*X*	X	*X*	*X*	X	*X*	X	X	X
Inclusion/exclusion criteria	X	X	X pre				X															
Medical/surgical history	X	X	X pre																			
BDI-II	X																					
Prior/concomitant medications	X	X	X pre	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study treatment administration																						
IV malaria challenge agent			X																			
MMV533 (IMP)								X														
Definitive medication																				Xa		
Safety																						
Physical exam - full	X																					X
Physical exam – symptom directed		X	X	X	X	X	X	X	X	X	X	X	*X*	*X*	X	*X*	*X*	X	*X*	X	X	
Height	X																					
Body weight	X	X																				X
G6PD status testing	X																					
Red blood cells antibodies	X																					X
Serology tests	X																					X
Urine drug screen, alcohol test	X		X pre				X															
Vital signs supine and standing	X																					X
Vital signs supine			X pre & post	X	X	X	X	*X*	X	X	X	X	*X*	*X*	X	*X*	*X*	X	*X*	X pre	X	
12-lead ECG	X	X	X pre				X	*X*	X	X	X	X			X			X		X pre	X	X
Body temperatur	X	X	X pre	X	X	X	X	X	X	X	X	X	*X*	*X*	X	*X*	*X*	X	*X*	X pre	X	X
Hematology, biochemistry	X	X			X		X	X	X	X	X	X			X			X		X pre	X	X
Urinalysis	X	X					X	X	X		X				X			X		X pre		X

	Screening	Pre-inoculation	Inoculation	Post-inoculation Phase				Treatment and Posttreatment phase														EOS/ ET
Day	**D-36 to D-12**	**D-11 to D-9**	**D-8**	**D-4**	**D -3**	**D -2**	**D -1**	**D1**	**D 2**	**D 3**	**D 4**	**D 5**	***D 6***	***D 7***	**D8 ± 2**	***D10***	***D12***	**D14 ± 2**	***D18***	**D21 ± 3**	**D25 ± 3**	**D28 ± 3**
Coagulation	X																					
Pregnancy Test/ FSH	X	X					X															X
SARS-CoV-2 Testing	X	X	X pre			X	X	X														
Serum Safety samples			X pre																			X**Error! Reference source not found.**
Diary card			X post	X	X	X	X						X	X	X	X	X	X	*X*	X pre	X	X
Malaria clinical score			X pre & post	X	X	X	X	X	X	X	X	X	*X*	*X*	*X*	*X*	*X*	*X*	*X*	X pre	X	X
Adverse event collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics																						
MMV533 + metabolites plasma samples								X	X	X	X	X			X			X		X		X
Pharmacodynamics																						
Parasitaemia by 18S qPCR			X pre	X	X	X	X	X	X	X	X	X	X	X	Xa	Xa	Xa	Xa	Xa	X	X	X
Gametocytaemia by qRT-PCR pfs25												X									X	X
Exploratory																						
Parasite drug resistance samples													X									

ABBREVIATIONS: BDI-II = Beck Depression Inventory; ECG = Electrocardiogram; EOS = End of study visit; ET = early termination visit; FSH = follicle stimulating hormone; IMP= Investigational Medicinal Product; qPCR =quantitative polymerase chain reaction; RT-PCR pfs25= gametocyte-specific mRNA transcript pfs25

4. What do I have to do?

It is important for your own safety that you inform the study doctor or staff of your complete medical history and all medications, supplements, and/or herbal preparations that you have taken within the past 6 months or are currently taking. If you have any health problems, please notify your study doctor immediately. As mentioned earlier in this document, if you notice any changes in your health or have concerns during your participation in the study, also inform your study doctor or study staff as soon as possible. You must always follow the instructions of the study doctor and staff.

Please note that in the days leading up to your admission to the clinical unit, there are a few things you must avoid to be included in the study:

- You should not have participated in any investigational product study within the 12 weeks preceding inoculation with the malaria challenge agent or 5 times the half-life of the Investigational product, whichever is longer. The half-life of a drug is the time it takes for the levels of the drug in your system to decrease by half. Your study doctor from your previous clinical trial should be able to tell you how long 5 half-lives would last
- You must not have any history of malaria or participation in a previous malaria challenge study or malaria vaccine trial
- You must not have received (or plan to receive) any vaccination (excluding COVID-19 vaccine) within 28 days of study drug dosing
- You MUST be fully vaccinated against COVID-19 including a booster shot (e.g. 3 doses of vaccine), with the most recent dose administered at least 14 days prior to inoculation of the malaria challenge agent.
- You must not have previously received a blood transfusion
- You must not have used antibiotics within 6 weeks of Screening
- You must not have used systemic therapies with antimalarial activity within 6 weeks of Screening. This includes (but not limited to) artemisinin, amodiaquine, atovaquone, chloroquine, mefloquine, mepacrine, primaquine, proguanil, quinine, sulfadoxine-pyrimethamine, benzodiazepine, flunarizine, fluoxetine, tetracycline, azithromycin, clindamycin, doxycycline, and tafenoquine.
- You must not have had any systemic administration (oral, pulmonary/nasal, IV) of corticosteroids, anti-inflammatory drugs (excluding commonly used over-the-counter anti-inflammatory drugs such as ibuprofen, acetylsalicylic acid, diclofenac), immunomodulators or anticoagulants within the past three months.
- You must not have had any topical administration (cutaneous, eye drops) of corticosteroids within the past 2 weeks.
- You must not currently be receiving or having previously received immunosuppressive therapy (including systemic steroids, adrenocorticotrophic hormone or inhaled steroids) at a dose or duration potentially associated with hypothalamic-pituitary-adrenal axis suppression within the past 12 months.
- You must not have donated any blood within one month before screening, or participation in any research study involving blood sampling (more than 450 mL/unit of blood)
- You must not consume any citrus fruits (grapefruit, Seville oranges, cranberry, pomegranate, star fruit, exotic fruits, pomelos, marmalade) or their juices, or herbal medications (such as St Johns wort) during the study and within 7 days prior to study drug administration (Day -1).
- You must not consume poppy seeds in the 24 hours prior to screening, day of admission, for confinement, for IMP administration (Day -1) and day of first dose of definitive medication.

- You must not consume food or beverages containing alcohol 24 hours prior to each alcohol breath test and for the entire period of confinement at the clinical unit
    - You should not drink more than 2 standard drinks per day and no more than 10 standard drinks per week from 24 hours prior to inoculation with the malaria challenge agent on Day -8, and after discharge from confinement until the end of treatment with definitive medication
- You must not consume food or beverages containing quinine, such as tonic water or lemon bitter, from the day of inoculation with the malaria challenge agent (Day -8) until after definitive medication has completed
- You must not consume beverages containing xanthine bases (eg, Red Bull, coffee) during the entire period of confinement. You should not consume more than 400 mg caffeine per day (equivalent to more than 4 cups of coffee) from inoculation with the malaria challenge agent on Day -8 until admission for confinement at the clinical unit (Day -1), and after being released from confinement at the clinical unit on Day 5 until the end of treatment with definitive medication
- You must not use tobacco during confinement at the clinical unit for IMP administration (Day -1 to Day 5). You should not smoke more than 5 cigarettes (or equivalent) per day until Day -1 and after being discharged from confinement at the clinical unit on Day 5 until the end of treatment definitive medication.
- You must abstain from strenuous exercise sessions for 4 days prior to study drug administration until Day 14.
- You must not use any illicit substances for the entire study period

All meals and beverages during your stay at the study centre will be provided. You must not consume any other food or beverage whilst in the study centre unless directed by study staff.

Please note that you will not be allowed to smoke while at the study centre.

In case of emergency, you must be easily contactable by phone and/or email. You will be given a Participant Wallet Card which contains emergency contact information and information about your study commitments. You must carry the Participant Wallet Card with you at all times until the end of the study.

5. Other relevant information about the research study

This study is being conducted at Q-Pharm Pty Ltd. in Australia. Researchers from Nucleus Network Pty Ltd (located in Melbourne, Victoria) and Q-Pharm Pty Ltd (located in Queensland), both Nucleus Network companies, will be working in collaboration. A malaria expert (Dr Bridget Barber / QIMR - Brisbane) will be also supporting this study.

A representative of MMV (study sponsor) may be present for inspections in the unit during the study.

6. Do I have to take part in this research study?

Participation in any research study is voluntary. If you do not wish to take part, you don't have to. If you decide to take part and later change your mind, you are free to withdraw from the study at any time without providing any reason. Your study doctor may ask you the reason for your withdrawal; you can answer or not.

Your decision whether to take part or not, or to take part and then withdraw, will not affect your relationship with Q-Pharm Pty Ltd. and will not involve any penalty or loss of benefits to which you would be otherwise entitled. 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.

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research study. You can ask for any information you want. Sign the Consent Form only if you agree to participate and only after you have had a chance to ask your questions and have received satisfactory answers.

7. What are the alternatives to participation?

Since this study is intended only to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of MMV533, the alternative to being a participant in this study is to choose not to participate in the study.

8. What are the possible benefits of taking part?

If you agree to take part in this study, there will be no direct benefit to you. However, your participation in this study may help develop important scientific knowledge that could contribute to the development of a treatment for Malaria. We hope the information learned from this study will benefit others in the future.

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

MMV533 is an experimental medication which has been evaluated in a small number of healthy volunteers (less than 50), therefore the risks to human participants have not been fully evaluated.

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with a study doctor. Your study doctor and study staff will also be watching you closely for side effects.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your involvement in the study. Tell your study doctor or site staff if you notice any changes in your health or have concerns. Your study doctor will discuss the best way of managing any side effects with you.

There may also be side effects that are not expected or are not known that may be serious. Tell your study doctor immediately about any new or unusual symptoms or changes in your health that you become aware of. The treatment of the side effects will depend on the type and severity of the symptom(s).

If during screening or participation in this research study a previously unknown medical condition is discovered the study doctor will discuss:

- whether you are eligible for study participation
- if you require referral to your usual doctor or to a specialist

Risks of Malaria Inoculation

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 401 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 100% cleared by the standard antimalarial medications that you will receive after administration with MMV533. The strain of parasite you will be given has been used in 401 participants in 30 malaria studies, most of which were conducted at the clinical trial site and QIMR Berghofer.

Also, the number of parasites administered to 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 as 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.

Among the 401 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.

One case of severe transient neutropenia (a decrease in a specific subset of White Blood Cell called neutrophils) has been also reported after malaria inoculation in one healthy participant. During the study and particularly after malaria inoculation, your blood cell count will be monitored at periodic intervals. Should this adverse event be observed, hospitalization for further monitoring could be considered due to a risk for further infections.

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 definitive 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 definitive treatment for the malaria. The abnormal heart rhythm went back into a normal heart rhythm after treatment.

It was felt 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 and have a cardiologist available on call 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.

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

Risks of Study Drugs:

1. Risks of MMV533

A. Risks of the study drug (MMV533) based on related drugs and animal studies

The mechanism of action of MMV533 against the malaria parasite is unknown and there are no other licensed medications on the market that act in a similar way. To assess the potential risk of treating humans with MMV533, non-clinical (i.e. animal) studies were conducted in two species (rats and dogs).

In these animal studies, some unexpected serious side effects have occurred following the administration of MMV533 at drug levels that are higher than levels that will be reached in this current human study. These side effects observed in rats and dogs are considered unlikely to occur in humans; however, you will be monitored closely for all side effects and treated if they occur.

Studies were conducted with repeated dose of MMV533. In these studies where animals were treated for 2 weeks, there were some transient changes in blood tests (liver enzymes and bile acids) without symptoms. There were minor changes seen in the bile ducts of dogs receiving MMV533 (called hyperplasia) which where reversible when the drug was stopped.

MMV533 may have side effects in humans, including side effects which are currently unknown.

Based on the animal observations, the following effects may occur after single dose administration of MMV533:

- Elevated liver enzymes and bile acids in your blood,
- Temporary changes in liver tissue (a consequence of increased levels of bile acids),
- Changes in cardiac activity on electrocardiograms (called “QTc prolongation”), a condition which may lead to irregular heart beat (cardiac arrythmia). Your heart activity will be monitored closely during the study for any adverse cardiac activity.

As a further precaution you will not be included on the study if you have any conditions that may put you at an increased risk of developing any of these effects. We will monitor these risks through regular blood samples and recordings of your cardiac activity.

B. Risks of the study drug (MMV533) based on preliminary human data

Single dose administration of MMV533 was recently evaluated in the First-in-Human study MMV_MMV533_19_01 in Melbourne, Australia. Six dose levels, 5, 10, 20, 50, 100, and 160 mg MMV533, have been fully evaluated in six cohorts of 8 healthy volunteers (6 active drug/2 placebo). Although safety observations are still blinded (i.e. we do not know who received placebo and who received the drug), preliminary data did not show serious or severe adverse events nor any clinically concerning events from electrocardiograms, vital signs (blood pressure/heart rate, body temperature) and safety laboratory tests. At this time in point, reported adverse events after MMV553/placebo observed in these first 48 volunteers (i.e. with 5, 10, 20, 50, 100 and 160 mg) and considered as "drug-related" are: mild transient elevation of total bile acids (blood tests changes, no symptoms), headache, palpitations and contact dermatitis.

2. Risks of Malaria Definitive Medication

As previously indicated, all the study participants inoculated with malaria will receive a final treatment against malaria with a registered medication. This definitive medication will be given regardless of the efficacy profile of MMV533 observed in the study.

For this specific study, the recommended first-line definitive medication is Malarone® (oral treatment). In case of intolerance or allergy to Malarone®, Riamet® (oral treatment) is the second-line medication.

Risks associated with antimalarial drugs

- **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.
- **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. If you are administered MMV533 and later prescribed Riamet® as definitive medication for malaria in this study, additional electrocardiograms (ECG) will be performed on the last day of Riamet® treatment. The purpose of this ECG is to ensure that lumefantrine is not associated with an asymptomatic but clinically relevant change called "QTc prolongation". If detected, further monitoring of this transient effect on your ECG might be requested.
- **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. If this is required, you may be transferred to the hospital for treatment there. 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 401 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 study site or at the nearby Emergency Department at the Royal Brisbane and Women's 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.

Possible allergic reactions

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.

Blood Draw/Cannula Insertion Risks:

During the study, you may have pain or bruising at the site where blood is drawn or a cannula (a temporary small plastic tube) is inserted. Insertion of the cannula or the drawing of blood may be associated with some pain. Possible side effects from blood drawing include feeling faint, inflammation of the vein, pain, bruising or bleeding at the site of puncture. These will normally disappear a few days after the procedure.

Other blood collection risks include:

1) there is a risk of a blood clot developing in the vein where the cannula was inserted. Usually this does not require any specific treatment. Rarely the clot can extend to a larger section of the vein or may even reach the deeper veins, in which case blood thinning (anticoagulant) medication may be recommended.

2) there is a small risk of temporary damage (risk of permanent damage is very small) to the nerves next to where the IV site is inserted.

3) there is a risk of developing an infection at the cannula site (rarely this could be serious) which may require antibiotics.

Study staff will monitor the cannula site on a regular basis and if any concerns are noted the canula may be re-sited or removed.

Blood Pressure Measurement Risks:

There is no risk to your health when having your blood pressure tested. You may experience some feeling of discomfort as the cuff inflates and squeezes your arm, but it should only last a few seconds. Sometimes, there are tiny red spots that appear after the test just below the location of the cuff, they should be painless.

Electrocardiogram (ECG) risks:

The ECG test is a recording of the electrical activity of your heart. The sticky pads used may be cold when applied and sometimes cause some discomfort (irritation) such as redness or itching. If there is hair in the area where patches need to be applied, this area may need to be shaved in order to complete the ECG. Shaving may result in irritation.

Allergic Reaction Risks:

There is a risk of allergic reaction. If you have a very serious allergic reaction, you may be at risk of death.

In general, most symptoms are manageable and are mild to moderate in severity. But life-threatening reactions may occur at any drug dose. If you believe you are having a serious allergic reaction after you have been discharged, you should seek emergency medical assistance immediately by calling the emergency services on 000.

Please notify the study doctor immediately if you experience any of these symptoms:

- Rash
- Wheezing and difficulty breathing
- Dizziness and fainting
- Swelling around the mouth, throat or eyes
- Fast pulse
- Sweating
- Abdominal pain
- Vomiting
- Diarrhoea

You will be monitored very carefully for any signs or symptoms that you may be having an allergic reaction and appropriate care will be taken by the study doctor and nursing staff.
If you do not understand what some of these side effects or risks mean, ask the study doctor or the study staff to explain them to you.

Pregnancy Risk:

The effects of MMV533 on the unborn child and on the newborn baby are not known at this stage of the development Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the research study. You must not participate in the research if you are pregnant, or believe you may be pregnant, or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the study.

Female Participants

Heterosexual **women of childbearing potential (WOCBP**) must agree to the use of a highly effective method of birth control (see below) combined with a barrier contraceptive from the screening visit until 60 days after the last dose of the study drug (covering a full menstrual cycle of 30 days starting after 5 half-lives of last dose of study drug) and have a negative result on urine pregnancy test performed before inoculation with the malaria challenge agent.

Note:

a) *Highly effective birth control methods include: combined (oestrogen and progestogen containing) oral/intravaginal/transdermal/implantable hormonal contraception associated with inhibition of ovulation, progestogen-only oral/injectable/implantable hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, or sexual abstinence or same sex relationship.*

b) *Female participants who are abstinent (from penile-vaginal intercourse) must agree to start a double method if they start a sexual relationship with a male during the study. Female participants must not be planning in vitro fertilisation within the required contraception period.*

Male Participants

Males who have, or may have female sexual partners of child bearing potential during the course of the study 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/implantable hormonal contraceptive by the female partner, from the time of informed consent through to 90 days (covering a spermatogenesis cycle) after the last dose of the study drug.

Abstinent males must agree to start a double method if they begin sexual relationship with a female during the study and up to 90 days after the last dose of study drug. Males with female partners of child-bearing potential that are surgically sterile, or males who have undergone sterilisation and have had testing to confirm the success of the sterilisation, will not be required to use above described methods of contraception.

Please ask your study doctor if you have any questions regarding the forms of birth control that must be used while participating in this study.

If you or your partner becomes pregnant during the study or up to 60 days (female participants) or 90 days (female partners of male participants) after last dose of study drug, please tell your study doctor or staff immediately as we would like to request permission to follow this pregnancy and its outcome. The study doctor will also report the pregnancy to the Human Research Ethics Committee and to the study Sponsor.

Allowing the pregnancy and outcome to be followed is optional. If you or your partner agrees to have this pregnancy followed, then she will be asked to sign a separate Pregnancy Follow-Up Participant Information and Consent Form. The information collected is similar to that which would be routinely collected during a typical pregnancy consultation. The consultation will be done in person at Q-Pharm Pty Ltd., and/or by telephone.

In addition, she will be asked to notify the study doctor about the outcome of the pregnancy. If she forgets, she will be contacted to obtain this information. This outcome data collected includes: pregnancy complications and outcome, birth weight, birth defects (if any), and additional factors that may have had an impact on the outcome of the pregnancy (drugs, infections, family history etc.).

The study doctor may also need to contact the obstetrician/gynaecologist of you or your partner.

10. What will happen to my test samples?

The blood and urine samples collected for the assessment of your health status (e.g. liver and kidney function tests), G6PD status and red blood cells antibodies will be processed by a local pathology laboratory. These samples will be labelled with your unique study participant number, your initials and date of birth, and will not be provided to anyone outside the study site and the pathology laboratory. These samples will be destroyed following analysis.

Blood samples collected for pharmacokinetics and pharmacodynamics analysis will be sent to various Sponsor-approved laboratories in Switzerland. These samples will be labelled with your unique study participant number and will not contain any information that can identify you personally. These samples will be stored during the study at a secure premise and the samples will be destroyed following analysis at the end of the study.

Serum Safety samples collected for safety assessments related to the study drug will be stored at Nucleus Network. If the sample is not used, it will be destroyed at the end of the study. Serum Safety samples collected for safety assessments related to the malaria challenge agent will be retained for at least 15 years from the completion of the study at the QIMR Berghofer Institute.

Parasite drug resistance samples may be shipped to a national or international reference laboratory for phenotypic assessment and parasite gene sequencing analysis

11. What if new information arises during this research study?

Sometimes during a research study, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research study. If you decide to continue in the research study, you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research study. If this happens, he/she will explain the reasons and arrange for your regular health care to continue.

Sometimes this information becomes available after you have completed the study. If the Investigator and Sponsor believe it to be relevant for your health, you may be contacted by Q-Pharm Pty Ltd., even beyond the end of the study.

12. Can I have other treatments during this research study?

The proposed study implies that you will receive two types of drugs as part of the research after malaria inoculation: the drug under development for treatment of acute uncomplicated malaria (MMV533, single dose) and a full treatment with a registered antimalarial (Malarone® oral treatment as first-line definitive medication) to ensure that remaining parasites in your body are fully eliminated. Whilst you are participating in this research study, you are not able to take any medications or treatments other than those agreed upon at the start of your participation in the study, unless medically required. It is important to tell your study doctor and the study staff, at each clinic visit, about any treatments or medications you may have taken, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments.

Sometimes it is necessary for you to receive treatment for a medical problem whilst on study (e.g. an infection). It is preferable, where possible, to discuss this with the study doctor, including by phone or additional follow up visits.

13. What if I withdraw from this research study?

If you decide to withdraw from the study, please notify your study doctor or staff before you withdraw. This notice will allow the study doctor to discuss any health risks or special requirements linked to withdrawing.
If you do withdraw your consent during the research study, any information collected on you up to the point of withdrawal will be used.

<u>Data collected after your withdrawal, if any, may be used:</u>

- If you have any on-going medical issues at the time of the withdrawal, we would like the option to continue to follow you until its resolution. If you do not agree to participate in follow up visits at the study centre, we can provide a referral letter for your GP to provide follow-up and treatment if necessary. You may also contact your study doctor if you experience a new adverse event.

- If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project

Biological Samples collected prior to your withdrawal:

- If you withdraw your consent, all your biological sample(s) already sent to sponsor approved laboratories will be used for analysis. You should be aware that your biological samples collected by the sponsor up to the time you withdraw will form part of the research project results. This is to ensure that the results can be measured properly. If you do not want them to do this, you must tell them before you join the research project.

14. Could this research be stopped unexpectedly?

This research study or your participation in the study may be stopped unexpectedly for the reasons listed below.

- Unacceptable side effects
- The drug being shown not to be safe
- Decisions made in the commercial interests of the sponsor or by local regulatory/health authorities
- If you don't follow the instructions of the clinical unit staff; or
- If the study doctor decides it is in the best interest of your health and welfare to stop.

15. What will happen when the research study ends?

The study data will be analysed, and a final report provided to the study doctor, who will share the results with you when requested. The disclosure and/or any published results will be available to you when requested. It is usual for a number of years to elapse before definitive results of this type of study are available. These may be published in medical journals that are available to the public. You should feel free to ask the study staff about this.

Part 2 - How is this study being conducted?

16. What will happen to information about me?

Any information and data obtained/retained in connection with this research study that can identify you will remain confidential and will only be used for this research study and future research related to the pathophysiology of malaria and/or mechanism of action of the drug (MMV533) under evaluation.

Information about you may be obtained from your health records held at other health services for the purpose of this research. By signing the consent form you agree to the study team, including Sponsor

delegates, accessing health records if they are relevant to your participation in this research study to ensure data accuracy. Whilst every effort will be made to keep your personal information confidential, the data gathered for this study will also be reviewed by a Sponsor delegate. This delegate will have access to your medical records, without violating your confidentiality to the extent permitted by local laws and regulations, to verify the data are correct and complete.

The data collected as part of this research study may be reviewed by representatives of the international sponsor, MMV, its affiliated companies and/or subcontractors, the local sponsor, Southern Star Research (SSR), the Alfred Hospital Ethics Committee, by authorised representatives of the Australian Therapeutic Goods Administration or other regulatory agencies. Information may be transferred to parties in countries (and regions) other than Australia including the US, and Europe for these purposes. Southern Star Research (SSR), MMV representatives, collaborators and contracted agencies comply with internal procedures to protect personal information even in countries whose data privacy laws are less strict than those of this country. In all cases when dealing with your personal (coded) information. MMV, and any of their agents will comply with the Privacy Act 1988. If you have any concerns on how your information is handled, please feel free to ask a member of the study team for more information.

By signing the consent section, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

Study Medical Records

Data from your study medical record will be identifiable and stored in secured offices at Q-Pharm Pty Ltd. Only research team members and authorised representatives from the Sponsor, the Ethics Committee or regulatory agencies will have access to your medical records.

In accordance with relevant Australian and/or Queensland privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.
Information about your participation in this research study will be recorded in your study records at Q-Pharm Pty Ltd.

Case Report Form (CRF)

Information you provide us will be recorded in electronic case report forms (CRF). Your information will be coded by your unique study number, your gender and birth date only and thus will be considered re-identifiable. The recorded data will be kept in an electronic database which will be managed throughout the study by Southern Star Research (SSR). Information from these CRFs will form part of the study results, which may be published. This data base will form part of the study results, which may be published.

A copy of the database entries and your medical record will be kept securely in accordance with ICH GCP requirements with all other study related documents.

This information will be reviewed by authorised individuals from the contract research organisation, MMV or affiliates, contractors and/or Health Authorities or Government Agencies (including the Therapeutic Goods Administration, as well as health authorities in USA and other countries) and delegates of the Ethics Committee for confirming the accuracy of the research study data.

By signing the consent section, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

Publications

A report of the study results may be submitted for publication. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. If you want to know more about Q-Pharm Pty Ltd. approach to privacy or access any of your information held by Q-Pharm Pty Ltd., you can contact the privacy officer at privacyofficer@nucleusnetwork.com.au.

17. Complaints and compensation

If you suffer any injuries or complications because of this research study, you should contact the study doctor or study team 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.

If you are not eligible for Medicare, the Sponsor and/or the Q-Pharm Pty Ltd. (Nucleus Network Pty Ltd) will cover the cost of any and all health care service costs incurred by you in respect of any injury or complication that has been independently determined to have been incurred as a result of the study drug or study procedure.

There are two avenues that may be available to you for seeking compensation if you suffer an injury because of your participation in this research study:

- The pharmaceutical industry has set up a compensation process, with which the local sponsor of this research study, Southern Star Research (SSR), has agreed to comply. Details of this process and conditions are set out in the Medicines Australia Guidelines for Compensation for Injury Resulting from Participation in a Company-Sponsored Clinical Trial. In accordance with these Guidelines, the sponsor will determine whether to pay compensation to you, and if so, how much. The research staff can give you a copy of the Guidelines together with this Participant Information and Consent Form or it can be accessed online;
- https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2010/09/Clnical-Trials-Compensation-Guidelines-1.pdf. If you have any questions about the Guidelines, please contact Paul Griffin on p.griffin@nucleusnetwork.com.au.
- You may be able to seek compensation through the courts.

If you are not satisfied with how your personal information has been handled (as laid out in the Privacy Act, 1988), then you can make a complaint to the Office of the Australian Information Commissioner (OAIC). It is free to lodge a complaint and you do not need a lawyer, however if you do decide to hire a lawyer, you must pay for the lawyer yourself. You can choose to withdraw your complaint at any time. Please refer to http://www.oaic.gov.au/privacy/privacy-complaints for more information.

18 Who is organising and funding the research?

This research is being conducted by Medicines for Malaria Venture (MMV) based in Geneva and sponsored in Australia by Southern Star Research. MMV may benefit financially from this research study if, for example, the study assists to obtain approval for a new drug.

By taking part in this research study you agree that samples of your blood (or data generated from analysis of these materials) may be provided to MMV.

MMV may directly or indirectly benefit financially from your samples or from knowledge acquired through analysis of your samples.

If knowledge acquired through this research leads to discoveries that are of commercial value to MMV, the study doctor or their institutions, there will be no financial benefit to you or your family from these discoveries.

MMV, other researchers, or research companies may patent or sell discoveries that result from this research. Neither MMV nor the study doctor will compensate you if this happens.

Contractors engaged by MMV will receive a payment from MMV for undertaking this research study.

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

19. Will I be reimbursed to take part in this research study?

If you are eligible and enrolled in the study, you will be reimbursed $150.00 for the screening and follow-up visits, at a daily rate of $480.00 per day for the in-clinic stay part of this study, and $50.00 for each follow-up phone call. Please note that admission and discharge days will be reimbursed at half-day rates. For this study, you may be required to attend additional follow-up visits at the discretion of the study doctor, so we ask you to be readily contactable and available to attend visits at any time as required throughout the study period. We recognise that this is an increased level of commitment compared to other studies, so you will be reimbursed $55.00 per day from Day -7 to Day 28 (except during the in-clinic stay**,** in total $1650 for the increase level of commitment) as compensation for your availability and flexibility. You will also be reimbursed $150.00 for each follow-up visit you attend, including any additional visits required by the study doctor.

The total reimbursement for participants who complete the entire study will be approximately $6,450.00, depending on the number of outpatient visits attended. This reimbursement rate includes compensation for your time, travel expenses, parking and inconvenience across the entire study period.

If you are an alternate, and do not get dosed, you will receive a partial reimbursement of $450.00.

If you are deemed to be ineligible after your screening visit due to a medical result that is independent from your direct actions, you will be reimbursed $150.00 for your screening visit. This payment will be made within a month of your screening appointment. Screening visit will not be reimbursed if your ineligibility is due to a positive drug of abuse or alcohol testing.

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 reimbursement 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.

It is not anticipated that participation in this research study will result in any additional cost to you.

20. Who has reviewed the research study?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC) who make sure that the rights, safety and well-being of participants in a study are protected. The ethical aspects of this research study have been approved by the Alfred Hospital Ethics Committee.

This study will be carried out according to the National Statement on Ethical Conduct in Human Research (March 2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

21. Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this study, please contact the below;

General Enquiries:	**(07) 3707 2700**
After hours contact:	0451 515 440 (urgent medical enquiries only)

If you have any medical questions/problems which may be related to your involvement in the study (for example, any side effects), you can contact the principal study doctor (Dr Paul Griffin on p.griffin@nucleusnetwork.com.au. Please also refer to your participant card with your study specific contact numbers.

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

Position	Complaints Officer
Email	complaintsofficer@nucleusnetwork.com.au

Privacy contact person

Position	Privacy Officer
Email	privacyofficer@nucleusnetwork.com.au

If you have any complaints about any aspect of the study, 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	Alfred Hospital Ethics Committee
Position	Governance Officer, Ethics and Research Governance, Alfred Health
Telephone	(03) 9076 3619
Email	research@alfred.org.au

Please reference the following Alfred project number: 125/21

CONSENT

Alfred Project Number	125/21
Full Study Title:	A Phase 1b study to assess the safety, tolerability and antimalarial activity of MMV533 against *Plasmodium falciparum* 3D7 blood stage infection in healthy volunteers.
Protocol Number:	MMV_MMV533_20_01
Test Drug Code:	MMV533
International Sponsor:	Medicines for Malaria Venture (MMV)
Local Sponsor:	Southern Star Research Pty Ltd (SSR)
Coordinating Principal Investigator:	Dr Paul Griffin
Principal Investigator:	Dr Paul Griffin
Location:	Q-Pharm Pty Ltd, Level 5 Clive Berghofer Cancer Research Centre, (CBCRC) 300C Herston Rd, Herston QLD, 4006

- I have read the Participant Information Sheet, or someone has read it to me in a language that I understand.
- I have had an opportunity to ask questions and I am satisfied with the answers I have received.
- I understand the purposes, procedures and risks of the research described for this study.
- I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Q-Pharm Pty Ltd. for the purposes of this study. I understand that such information will remain confidential.
- I freely agree to participate in this research study as described and understand that I am free to withdraw at any stage during the study without affecting my future health care
- I understand that I will be given a signed copy of this document to keep.

Participant's First Name (printed) ……Middle Initial……Surname…….

Signature

Date _____/_____/_____ Time _____:_____

Declaration by Study Doctor/Senior Researcher

I have given a verbal explanation of the research study; its procedures and risks and I believe that the participant has understood that explanation.

Study Doctor/Researcher's First Name (printed) ……Middle Initial……..Surname……..

Signature

Date _____/_____/_____ Time _____:_____

A senior member of the research team must provide the explanation of, and information concerning, the research study.

Note: All parties signing the consent section must date their own signature.

FORM FOR WITHDRAWAL OF PARTICIPATION

Alfred Project Number	125/21
Full Study Title:	A Phase 1b study to assess the safety, tolerability and antimalarial activity of MMV533 against *Plasmodium falciparum* 3D7 blood stage infection in healthy volunteers.
Protocol Number:	MMV_MMV533_20_01
Test Drug Code:	MMV533
International Sponsor:	Medicines for Malaria Venture (MMV)
Local Sponsor:	Southern Star Research Pty Ltd (SSR)
Coordinating Principal Investigator:	Dr Paul Griffin
Principal Investigator:	Dr Paul Griffin
Location:	Q-Pharm Pty Ltd, Level 5 Clive Berghofer Cancer Research Centre, (CBCRC) 300C Herston Rd, Herston QLD, 4006

Declaration by Participant

I wish to withdraw from participation in the above research study and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Q-Pharm Pty Ltd.

Participant's First Name (printed) ……Middle Initial……..Surname…….....

Signature

Date _____/_____/_____ Time _____:_____

Study Doctor to include a description of the circumstances for withdrawal, if provided by the participant.

Declaration by Study Doctor

I have given a verbal explanation of the implications of withdrawal from the research study and I believe that the participant has understood that explanation.

Study Doctor/Researcher's First Name (printed) ……Middle Initial……..Surname…….....

Signature

Date _____/_____/_____ Time _____:_____

Note: All parties signing the consent section must date their own signature.