Participant Information and Consent Form

Alfred Project Number:	97/20
Full Study Title:	A two-part, Phase 1 study to assess the safety, tolerability, and pharmacokinetic profile of ascending single doses of MMV533, including a pilot food evaluation in healthy participants.
Protocol Number:	MMV-MMV533_19_01
Test Drug Code:	MMV533
International Sponsor:	Medicines for Malaria Venture (MMV)
Local Sponsor:	Southern Star Research Pty Ltd (SSR)
Principal Investigator:	Dr Jason Lickliter
Location:	Nucleus Network Pty Ltd, Melbourne, Victoria

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 (the amount of study drug in your blood and any metabolites (break down products)) of a single (Part 1)/multiple (Part 2) oral dose of a new drug called MMV533.

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.

Your information regarding participation in the study will be provided to your preferred doctor if you opt to provide their contact details to study staff.

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?

MMV533 is being developed for the curative treatment of mild malaria caused by *P. falciparum* in adults and children.

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.

Current approaches to controlling malaria 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 we need to develop and test new antimalarial drugs or combinations of drugs.

Medicines for Malaria Venture (MMV) is developing the study drug MMV533 as one such potential new treatment for the treatment of malaria.

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.

This is the first time MMV533 will be given to humans. Although unlikely, there is a risk of death in first in human studies such as this study.

In other studies, 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.

Part 1 and 2 of this study are being conducted at Nucleus Network Pty. Ltd., Melbourne, Victoria. The Clinical Research Organisation involved in monitoring the study and acting as the local

sponsor is Southern Star Research and the study 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 the Nucleus Network 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 between 3 and 3½ hours.

This study will enrol approximately 64 participants, in two parts:

Part 1 of the study will enrol approximately 56 participants in up to 7 cohorts (groups) with approximately 8 participants in each cohort. You will be enrolled in a single cohort of this study only. Each cohort will be divided into at least 2 subgroups. The first group (sentinel cohort) will include 2 participants that will be dosed on the first day, with 1 participant receiving MMV533 and 1 participant receiving placebo. The safety profile will be reviewed by a medical team (safety review committee) and if deemed safe the rest of the remaining participants in the cohort may proceed.

As this is a dose escalation study, the first cohort (group) enrolled will receive the lowest dose and once it is considered to be safe, the next group will be enrolled and will receive the next higher dose. Dose escalation will only proceed following a review of all available safety data by the Principal Investigator in consultation with the sponsor and if there is confirmation that this is safe to continue with the next higher does in the next group. The study can be stopped at any time, based on evaluation of the side effects of the study drug/experimental drug.

The study is placebo controlled, meaning that some participants will receive a tablet containing study drug and some will receive a tablet containing placebo. The tablet containing the placebo will look the same as the tablet containing the active study drug but will not contain any active ingredients in it. You will not have a choice as to whether you receive the study drug or placebo (you will be assigned randomly, like flipping a coin). Neither you nor the study staff will know if you are assigned to receive the active study drug or the placebo, although in an emergency, the study staff can find out. In each cohort (group) 6 participants will receive the study drug and 2 participants will receive placebo.

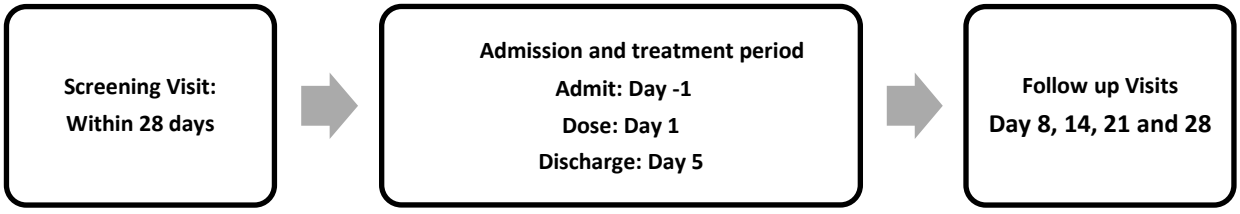
Part 2 of the study is a referred to as a ‘crossover study’, as participants will receive a sequence of different treatments. In Part 2, one cohort (group) of approximately 8 participants will receive a dose of the study drug in two separate dosing periods separated by a washout phase of 21 days. The first dose will be administered while fasting and the second dose of the study drug will be administered after a high-fat meal (described in the treatment and follow-up period below). A vegetarian meal (example: egg, avocado, almonds, toast, hashbrown, whole milk) can be made available if discussed with study staff. The range of doses of MMV533 administered in Part 1 of this study ranged from 5 to 160mg and the dose for Part 2 will be 30mg.

Study sequence:

Your total participation in **Part 1** of the study will consist of approximately 8 weeks as follows:

- **Screening visit**: Will occur within 28 days of dosing. You will undergo assessments to determine if you are eligible for the study.
- **Admission, treatment and follow up 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 Days 8, 14, 21 and day 28 for follow up visits.

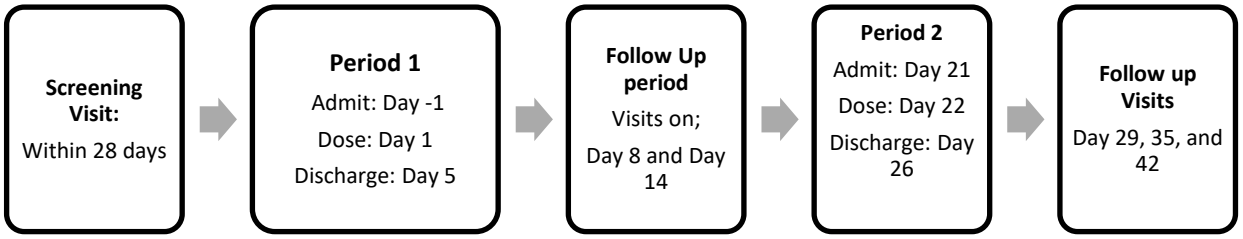
Below is a schematic outlining the study schedule:



Your total participation in **Part 2** of the study will consist of approximately 10 weeks as follows:

- **Screening visit**: Will occur within 28 days of your first dose. You will undergo assessments to determine if you are eligible for the study.
- **Admission and treatment period**: You will be required to attend the study centre for two inpatient periods of 5 days each, with a washout period of 21 days in-between study drug administration. One dose of the study drug will be with food and one will be administered without food.
- **Follow up visits:** You will be required to attend the study centre on several days following each inpatient period.

Below is a schematic outlining the study schedule:



Screening visit (between Day -28 to Day -2)

If you decide to be assessed for inclusion into the study, you will be asked to visit the Nucleus Network Pty Ltd for the screening visit. The first screening visit may take between 3 and 3½ hours.

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 history**, including all medications, over-the-counter and herbal medications that you have been, and

are currently taking. The study doctor will also ask you to complete a questionnaire related to your current mental health.

- You will be asked some personal details about yourself, including your date of birth.
- You will be asked about your alcohol history and you will undergo an alcohol breath test.
- You will be asked to provide a **urine and blood sample** to assess your general health and to test for medications of addiction as listed below:
  - to test for drugs of addiction (such as methamphetamine, cocaine, cannabinoids, opiates, phencyclidine, barbiturates, benzodiazepines, methadone, and amphetamine). This is a study requirement and the results will remain confidential. The tests may reveal that you have previously used illegal medications. That information will be stored in a re-identifiable (or coded) format. If the Nucleus Network Pty Ltd is ordered by a court of law to disclose the information regarding the use of illegal medications or illegal 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 may be excluded from further participation in this study.
  - to test for use of paracetamol
- Your **vital signs** such as blood pressure, heart rate, respiratory rate and tympanic (ear) temperature will be measured.
- You will have a full **physical examination** (PE), your height and weight will be measured to determine your body mass index (BMI).
- You will have **electrocardiograms** (ECG) (recording of your heart's electrical activity and rhythm).
- **Safety Lab Test Blood sample** (approximately 20mL / 4 teaspoons) will be collected to provide information on your general health and to screen for pregnancy, HIV (AIDS virus), and hepatitis B and C. This is because the study doctors need to know about your 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.

If for any reason, the trial is found to not be suitable for you, staff from the Nucleus Network Pty Ltd will contact you and provide follow-up treatment advice where applicable.

Treatment and Follow-up Period

If you are eligible to enter the study, you will be admitted to the clinical unit the day before the planned dosing day (Day -1). On this day you will undergo a number of procedures to confirm your suitability for participation in the trial (see table below). Participants in Part 2 will also undergo procedures to ensure continued eligibility when they admit to the clinical unit for their second dosing period on Day 21.

To ensure sufficient number of participants are available for Day-1, additional volunteers called 'alternates' will be recruited and admitted to the clinical unit. If you are an alternate, you may be asked to participate in the study if someone is not included in the dosing group. You will be informed if you are an alternate on Day 1 before treatment is given.

In the clinical unit a cannula will be inserted into a vein in your arm prior to dosing. This is a small, flexible 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.

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

- **Vital signs**: tympanic (ear) temperature, heart rate and blood pressure will be measured.
- **12-Lead Electrocardiogram (ECG):** will be performed to assess your heart rhythm.
- **Physical Examination:** will be performed to assess your general health. This will include measuring your body weight.
- **Safety blood and urine samples:** approximately 15 ml (approx. 3 teaspoons) of blood and a urine sample will be collected to assess your general health and to screen for pregnancy. When you check in, the urine sample will also be collected to test for drugs of addiction. A positive test will exclude you from further participation in the trial. Additional safety samples may also be collected if required by the study doctor. You will be required to fast prior to some safety blood samples; study personnel will let you know when this is required and what length the fasting period will be.
- **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. A positive test will exclude you from further participation in the trial.
- **Study drug administration:**
  Part 1: The study drug will be administered as an oral tablet with 240ml of water under fasting conditions (10 hrs overnight).
  Part 2: You will receive the study drug **with** and **without food** in either of the two inpatient periods. When you receive the dose **with food**, you will need to fast overnight for 10 hours followed by a high fat meal.

  The high-fat meal will include 2 x pieces of toast, full cream milk, fried hash brown potatoes and animal products (egg, bacon, butter) and must be completed prior to dosing. Please talk to the study staff if you have any questions about the meal. A vegetarian meal (example: egg, avocado, almonds, toast, hashbrown, whole milk) can be made available if discussed with study staff.

  You will be required to eat the whole meal within 30 minutes and be dosed 30 minutes after you start eating.
  When you receive the drug **without food** you will need to fast overnight for 10 hours before receiving the drug.
- **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. 4mL of blood (approx. 1 teaspoon) will be collected at various time points during your inpatient stay and study visits.
  Additional PK sample may be collected if your safety blood results show out of range results.
- **Pharmacogenetic Sample**: An additional blood sample for mandatory genetic testing, 2ml of blood will be collected prior to your dose of the study drug (MMV533). This test is intended to evaluate how various genes are involved in the distribution, metabolism and elimination of the drug from your body.

- **Concomitant Medication (medications taken at same time or almost the same time) 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

Part 1: On days 8, 14, 21 and day 28, you will be required to attend the Nucleus Network Pty Ltd for follow up visits. These visits will take approximately 1-2 hours for follow-up assessments as outlined above and in the table below.

Part 2: After Period 1, you will need to attend follow up visits on Day 8 and 14. After Period 2, you will be asked to attend follow up visits on days 29, 35, and 42.

The study doctor will ask you to return to the research unit on these days and may ask you to return in between these visits days or after this period, if he/she feels it is necessary. Additional safety assessments may be carried out when you return for a visit if the study doctor 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.

The table below outlines the assessments that will be performed in Part 1:

Part 1 Phase	Screening/Eligibility		Treatment and Confinement				Outpatient Monitoring				EOS	Early Termination
Day	**D-28 to D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D8**	**D14**	**D21**	**D28±24h**	
Informed consent	X											
Admission to clinical unit		X										
Confinement at clinical unit			X	X	X	X						
Discharge from clinical unit							X					
Outpatient visit to clinical unit	X							X	X	X	X	X
Inclusion/exclusion criteria	X	X										
Medical/surgical history	X	X										
BDI-II	X											
Prior/concomitant medications	<	-	-	-	-	-		-	-	-	>	
Randomization			X									
Study treatment administration												
MMV533 or placebo (IMP)			X									
Safety												
Physical exam - full	X	X									X	X
Physical exam – symptom directed when clinically indicated			X				X	X	X	X		
Height (cm)	X											
Body weight (kg)	X	X										
Serology tests	X											
Drug screen, alcohol test	X	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X
Body temperature (ºCelcius)	X	X	X	X	X	X	X	X	X	X	X	X
Haematology, biochemistry, urinalysis	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X											
Pregnancy Test/ FSH	X	X									X	X
Adverse event collection	<	-	-	-	-	-		-	-	-	>	
Pharmacokinetics												
MMV533 plasma samples			X	X	X	X	X	X	X	X	X	X
MMV533 urine samples			X	X	X							
Pharmacogenetics												
DME/T DNA blood sample			X									

ABBREVIATIONS: DME = drug metabolizing enzymes; ECG = Electrocardiogram; exam = examination; FSH = follicle stimulating hormone; IMP= Investigational Medicinal Product (study drug); BDI = Beck Depression Inventory; ET – early termination

The table below outlines the assessments that will be performed in Part 2:

Part 2 Phase	Screening/ Eligibility		Period 1: Treatment and Confinement				Period 1: Out-patient Monitoring				Period 2: Treatment and Confinement					Period 2: Out-patient Monitoring		EOS	ET
Day	**D-28 to D-2**	**D-1**	**D1**	**D2**	**D3**	**D4**	**D5**	**D8**	**D 14**	**D21**	**D 22**	**D 23**	**D 24**	**D 25**	**D 26**	**D 29**	**D 35**	**D42**	
Informed consent	X																		
Admission to clinical unit		X								X									
Confinement at clinical unit			X	X	X	X					X	X	X	X					
Discharge from clinical unit							X								X				
Outpatient visit to clinical unit	X							X	X							X	X	X	X
Inclusion/exclusion criteria	X	X																	
Medical/surgical history/BDI	X																		
Prior/concomitant medications	<	-	-	-	-	-						-			-	-	-	>	
Randomization			X																
Study treatment administration																			
MMV533			X								X								
High fat breakfast when applicable			X								X								
Safety																			
Physical exam - full	X	X								X								X	X
Physical exam - symptom directed when clinically indicated				X			X	X	X				X		X	X	X		
Height (cm)	X																		
Body weight (kg)	X	X																X	X
Serology tests	X																		
Drug screen, alcohol test	X	X								X									
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X
Body temperature (ºCelcius)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematology, biochemistry, urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X																		
Pregnancy Test/ FSH	X	X								X								X	X
Adverse event collection	<	-	-	-	-	-						-			-	-		>	
Pharmacokinetics																			
MMV533 plasma samples			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacogenetics																			
DME/T DNA blood sample			X																

ABBREVIATIONS: ECG = electrocardiogram; hCG = human chorionic gonadotropin; WOCBP = woman of childbearing potential; EOS – end of study; ET – early termination; BDI = Beck Depression Inventory

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 requirements for inclusion in the study:

1. You must avoid participation in any research study involving blood sampling (more than 450 mL/unit of blood) or blood donation during the 8 weeks prior to study drug administration.
2. You must have no history of substance use disorder(s) within 5 years of screening, including alcohol consumption of more than 40g/4 units/4 standard drinks per day or any prior intravenous use of an illicit substance. A positive alcohol screen at screening, or prior to study drug dosing, will exclude you from the study.
3. You must not have smoked >1 pack of cigarettes per day for >10 years, or currently (within 14 days prior to study drug administration) smoke >5 cigarettes per day. You cannot use tobacco during confinement periods. After discharge from the clinical unit, you should not smoke more than 5 cigarettes (or equivalent) per day until after your last study visit.
4. You must not have taken any vitamin supplements within 7 days prior to study drug administration
5. You cannot take any medications (including herbal such as St John's Wort and over the counter) within 5 half-lives prior (approximately 20 days) to study drug administration except occasional intakes of
    - ibuprofen (e.g. Nurofen) at doses up to 1.8g/day
    - paracetamol at doses up to 4g/day, acetyl salicylic acid (300 to 650 mg orally every 4 to 6 hours as needed, maximum dose: 4 g in 24 hours),
    - diclofenac (e.g. Voltaren) potassium liquid-filled capsules at doses up to 25mg orally 4 times a day; diclofenac free acid capsules at doses up to 18 or 35 mg orally 3 times a day; diclofenac potassium immediate-release tablets at doses up to 50mg orally 3 times a day
    - contraceptives.

    You must not have taken any antidepressant medication in the past 12 months prior to study drug administration and you must not receive any vaccination within 28 days of screening.

    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 screening doctor can help answer any questions regarding medications and clarify how long half-lives of most medications will last.
6. You must not have a positive urine drug test at screening, or prior to study drug dosing.
7. You must not consume any citrus fruits (grapefruit, Seville oranges) or their juices during the study and within 5 days prior to study drug administration. You must not consume poppy seeds in the 24 hours prior to screening and during the first day of confinement for study drug administration (Day -1).

8. You must not consume food or beverages containing alcohol 24 hours prior to each alcohol breath test and during confinement periods. After discharge from the clinical unit, you should not drink more than 2 standard drinks per day until after your last study visit.
9. You will not be able to consume beverages containing xanthine bases (eg, Red Bull, coffee) during confinement periods. After discharge from the clinical unit, you should not consume more than 400 mg caffeine per day (equivalent to 4 cups of coffee) until after your last study visit.
10. You must abstain from strenuous exercise sessions for 4 days prior to study drug administration until Day 10 following study drug administration.
11. You should not have participated in other clinical trials within 3 months before dosing or 5 times the half-life of the IP (whichever is longer). Your screening doctor can help determine this.
12. Please refrain from any COVID-19 vaccine within 14 days of dose administration until the completion of the study and any other vaccination within 28 days of dose administration until the completion of the study.

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 always carry the Participant Wallet Card with you until the end of the study.

5. Other relevant information about the research study

This study is being conducted at the Nucleus Network Pty Ltd in Victoria for Part 1 and 2. Researchers from Nucleus Network Pty Ltd. (located in Melbourne and Geelong, Victoria) and Q-Pharm Pty Ltd (located in Brisbane, Queensland), both Nucleus Network companies, will be working together.

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 the Nucleus Network 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 and pharmacokinetics of MMV533, your alternative to be a volunteer 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, 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 participation in the trial. 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 physician or to a specialist

This research study involves the collection of information about your use of drugs and alcohol. Participation in the research study includes blood and/or urine analysis to determine the presence of amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tetrahydrocannabinol, paracetamol and tricyclic antidepressants. The test may reveal that you have previously used illegal drugs or illegal alcohol breath test levels. That information will be stored in a re-identifiable (or coded) format. In the event that the Nucleus Network Pty Ltd is required to disclose that information, it may be used against you in legal proceedings or otherwise.

Risks of Study Drug:

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 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 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.

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.

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.

Could I Have An Allergic Reaction?

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

Symptoms may include difficulty in breathing, dizziness, itching, swelling of the lips, tongue or throat, coughing, rash.

In general, most symptoms are manageable. They 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 dialling the emergency services on 000.

Please notify the study doctor immediately if you experience any of these symptoms. Some symptoms of allergic reactions are:

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

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.

Blood Draw/ Cannula Insertion Risks:

You may have pain or bruising at the site where blood is drawn or a cannula (a temporary small plastic tube) is inserted. An infection at the site of blood draws or cannula insertion is also possible. The insertion of the cannula (small plastic tube) or the drawing of blood may be associated with some pain. Possible side effects from blood drawing include faintness, inflammation of the vein, pain, bruising or bleeding at the site of puncture. These will normally disappear a few days after the procedure.

Blood Pressure Measurement Risks:

There is no risk to your health when having your blood pressure tested. You may experience some feeling on 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 such as redness or itching. If there is hair in the area where patches need to be applied, this area will be shaved in order to complete the ECG. Shaving may result in irritation.

Pregnancy Risk:

Risks related to Pregnancy

Reproductive and developmental toxicity studies to evaluate the potential impact of MMV553 during pregnancy have not been performed. Taking the study drug may involve some risks to a human unborn baby or nursing infant. Therefore, you cannot join this study if you are pregnant, if you are planning to become pregnant in the next two months, or if you are breast-feeding.

All women of childbearing potential willing to be enrolled in a clinical study with MMV533 will have pregnancy tests at screening and during the study.

Female participants of childbearing potential that have or may have male sexual partners during the course of the study must agree to the use of a double method of contraception of a highly effective method of birth control combined with a barrier contraceptive (condom) when appropriate from screening visit to until 60 days after the last dose of study drug.

Male participants who have or may have female sexual partners during the course of the study must agree to use a double method of contraception including condom plus diaphragm, or condom plus stable insertable (implant or IUD), injectable, transdermal or combination oral contraceptive by the female partner, from the time of informed consent through to 90 days after the last dose of the study drug.

Abstinent male participants must agree to start a double method if they begin a sexual relationship with a female during the trial, and through to 90 days after the last dose of the IMP. Male participants with female partners that are either surgically sterile or post-menopausal (defined as being amenorrhoeic for at least 12 months without an alternative medical cause), or male participants who have undergone sterilisation and have had testing to confirm the success of the sterilisation, may also be included and will not be required to use above described methods of contraception. Male participants must also agree not to donate sperm up to 3 months after dosing with the study drug.

Highly effective birth control methods include:

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

You will need discuss methods of effective contraception with your study doctor to be enrolled in this study.

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

If you/your partner becomes pregnant during the study or up to 60 days (female participants) or 90 days (female partners of male participants) after the last dose of study medication, 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/you partner agree to have this pregnancy followed, then you/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 the Nucleus Network Pty Ltd, and/or by telephone.

In addition, you/she will be asked to notify the study doctor about the outcome of the pregnancy. If you/she forgets, you/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 of your partner.

10. What will happen to my test samples?

By consenting to take part in this study, you also consent to the collection and testing of your urine and blood samples for this research. The total volume of blood taken for for the study will not exceed 500mL (approx. 2 cups) .For comparison, a standard blood donation is approximately 470mL (approx. 2 cups). Additional blood samples may also be collected for safety reasons.

The blood and urine samples collected for the assessment of your health status (e.g. liver and kidney function tests) 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 contain any information that can identify you personally. These samples will be destroyed following analysis.

Blood samples collected for pharmacokinetic testing will be sent to 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.

Blood samples collected for pharmacogenetics will be sent to various Sponsor-approved laboratories in the United Kingdom. These samples will be analysed to better understand how genes encoding for enzymes and transporters may influence the distribution and elimination of the drug in your body. 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.

The pharmacogenetic testing to be performed as part of the study is not a routine evaluation but research testing (as opposed to medical testing) to help the study sponsor interpreting the data. As such, the medical impact of pharmacogenetic research results will not be systematically assessed for any individual subject and results of exploratory analysis will not be returned to individual participants unless specifically requested. Extra precautions are

taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. Samples will be linked to subject ID number. Only the clinical site will be able to link individual subject ID numbers with identities. The results from this genetic research may be reported in a separate report from the Clinical Study Report or published in scientific journals.

The proposed blood tests include a screening test for HIV (also called the 'AIDS" virus) and Hepatitis. You will receive information and counselling before the test. If a test shows you have HIV or Hepatitis, you will have follow-up counselling and medical advice. If your test results are positive, the study doctors are required by law to notify government health authorities. Signing the consent form means that you agree to have this testing; it will not be done without your consent.

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.

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

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. However, if you develop a new illness (unrelated to MMV533) that requires treatment, participation in the trial will not prevent appropriate treatment.

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.

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. Before you withdraw, the study doctor will want to conduct one last study visit known as an early termination visit to check your health. The assessments completed at this visit are the same as those completed at the end of study visit. Please refer to the assessment tables above.

If you do withdraw your consent during the research study, any information collected on you up to the point of withdrawal will be used. Data collected after your withdrawal, if any, may be used:

• If you decide to withdraw from the study, any adverse event not resolved at this time will be followed until its resolution by your study doctor to ensure your medical follow-up. You may also contact your study doctor if you experience a new adverse event.

• If you withdraw from the study for a reason other than your own decision, your study doctor may contact you to request any relevant information and / or documentation regarding your medical care.

• If you withdraw your consent, all your biological sample(s) will be destroyed without disclosing your identity. If safety or PK/PD analysis is required for the study, it will be analysed before destroying your samples.

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 drug will not be available to you following completion of participation.

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.

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.

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, Members of 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, 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 the Nucleus Network 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 state 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 the Nucleus Network 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 year 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. Information from these CRFs 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 the Nucleus Network Pty Ltd' approach to privacy or access any of your information held by the Nucleus Network Pty Ltd, you can contact the privacy officer at privacyofficer@nucleusnetwork.com.au .

It is desirable that your local doctor be advised of your decision to participate in this research study. By signing the consent section, you agree to your local doctor being notified of your decision to participate in this research study.

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 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 sponsor MMV has set up a compensation process, with which the local sponsor of this research study, Southern Star Research, 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 Dr Jason Lickliter on j.lickliter@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 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 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?

Participants in **Part 1** will be reimbursed $150.00 for the screening and follow-up visits, and at a daily rate of $480.00 per day for the in-clinic stay part of this study. Please note that admission and discharge days will be reimbursed at half-day rates. The total reimbursement for participants who complete the entire Part 1 study will be approximately $3,150.00. If you are an alternate for Part 1, and do not complete the entire study, you will receive a partial reimbursement of $630.00.

Participants in **Part 2** will be reimbursed $200.00 for the screening and follow-up visits, and at a daily rate of $450.00 per day for the in-clinic stay part of this study. Please note that admission and discharge days will be reimbursed at half-day rates. The total reimbursement for participants who complete the entire Part 2 study will be approximately $5700.00. If you are an alternate for Part 2, and do not complete the entire study, you will receive a partial reimbursement of $650.00.

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 yourself from the study before the final visit, or your participation is halted early (refer to section 14), you will receive a partial reimbursement according to the number of visits you have attended.

If you are an eligible alternate, and do not get dosed, you will receive a partial reimbursement as mentioned above. 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 receive a

reimbursement 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.

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: **1800 243 733**

After hours contact (Nucleus Network Pty Ltd) 24 hours 7 days a week

On-call mobile: 0429 353 069

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 Jason Lickliter) on j.lickliter@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 HREC project number: 97/20

CONSENT

Alfred Project Number:	97/20
Full Study Title:	A two-part, Phase 1 study to assess the safety, tolerability, and pharmacokinetic profile of ascending single doses of MMV533, including a pilot food evaluation in healthy participants.
Protocol Number:	MMV-MMV533_19_01
Test Drug Code:	MMV533
International Sponsor:	Medicines for Malaria Venture (MMV)
Local Sponsor:	Southern Star Research Pty Ltd (SSR)
Principal Investigator:	Dr Jason Lickliter
Location:	Nucleus Network Pty Ltd, Melbourne, Victoria

- 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 the Nucleus Network 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:	97/20
Full Study Title:	A two-part, Phase 1 study to assess the safety, tolerability, and pharmacokinetic profile of ascending single doses of MMV533, including a pilot food evaluation in healthy participants.
Protocol Number:	MMV-MMV533_19_01
Test Drug Code:	MMV533
International Sponsor:	Medicines for Malaria Venture (MMV)
Local Sponsor:	Southern Star Research Pty Ltd (SSR)
Principal Investigator:	Dr Jason Lickliter
Location:	Nucleus Network Pty Ltd, Melbourne, Victoria

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 the Nucleus Network 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.