## COVER SHEET FOR THERAPEUTIC EFFICACY TEST PROTOCOL

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| Title | Monitoring and evaluation of the therapeutic efficacy and safety of pyronaridine-artesunate for the treatment of uncomplicated falciparum malaria in western Cambodia, an area of artemisinin-resistant falciparum malaria |
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| Study dates | From May to December 2014 |
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**Study Synopsis**

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| Study Title | Monitoring and evaluation of the therapeutic efficacy and safety of pyronaridine-artesunate for the treatment of uncomplicated falciparum malaria in western Cambodia, an area of artemisinin-resistant falciparum malaria |
| Background | Emerging resistance to artemisinins and to its partner drugs severely threaten the treatment of falciparum malaria in Western Cambodia. To inform drug policy, it is crucial to have information on the current efficacy of pyronaridine-artesunate, considered as a new first-line treatment in Western Cambodia. Pyronaridine-artesunate is a newer artemisinin combination therapy, and was recently approved by the European Medicine Agency for single time use in adults and children >20 kg in countries with documented artemisinin resistance including Cambodia, where the drug was tested in 2005 and 2008. We here propose an open-labelled clinical trial to assess the efficacy and safety of pyronaridine-artesunate for the treatment of uncomplicated falciparum malaria or mixed infection in Pailin, Battambang and Pursat provinces in Western Cambodia. |
| Study Design | Observational study for the assessment of drug efficacy and safety over 42 days |
| Participants | Patients with acute uncomplicated *P. falciparum* malaria or mixed with another species. |
| Study sites | Referral hospital (Pailin), Promoy Health Centre (Pursat) and Tasanh Health Centre, Battambang. |
| Sample size | 145 patients |
| Inclusion Criteria | Adults and children ≥ 20 kg<br>Symptomatic of malaria infection, i.e. history of fever within 24 hours and/or presence of fever >37.5°c.<br>Microscopic confirmation of asexual stages of *P.falciparum* (mixed with non-falciparum species in Palin only)<br>Capability of taking an oral medication<br>Written informed consent given to participate in the trial |

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| | Willingness and ability to adhere to follow-up visit schedule |
| Exclusion Criteria | ○ Pregnancy or lactation (urine test for β HCG to be performed on any woman of child bearing age, that is 18 to 45 y/o)<br>○ Female aged 12-18y<br>○ *Parasitemia* > 150 000/μL).<br>○ **Signs or symptoms indicative of severe malaria:**<br>- Impaired consciousness (Blantyre Coma Score <5)<br>- Severe anaemia (Hct<15%)<br>- Bleeding disorder –evidenced by epistaxis, bleeding gums, frank haematuria, bleeding from venepuncture sites<br>- Respiratory distress<br>- Severe jaundice<br>○ Known hypersensitivity to artemisinins - defined as history of erythroderma/other severe cutaneous reaction, angioedema or to pyronaridine<br>○ History of splenectomy<br>○ Patients taking any drug which is known to be metabolised by the cytochrome enzyme CYP2D6 including flecainide, metoprol, imipramine, amitriptyline, clomipramine.<br>○ Known history or evidence of clinically significant disorders, such as:<br>○ Known active Hepatitis A, e.g. by detection of anti HAV-IgM.<br>- Known hepatitis B surface antigen (HBsAg) carrier.<br>- Known hepatitis C antibody (HCV Ab).<br>○ Liver function tests (AST/ALT levels) more than 2.5 times the upper limit of normal range. |
| Study Period | 8 months (May 2014 – December 2014) |
| Primary Objective | To assess the therapeutic efficacy of pyronaridine-artesunate for the treatment of uncomplicated falciparum malaria or mixed infection (in Pailin only) at Day 28 and 42, in an area of artemisinin resistance. |

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| Secondary Objectives | Main secondary objectives:<br>o To measure the clinical and parasitological efficacy of pyronaridine-artesunate for the treatment of uncomplicated *P.falciparum* and mixed (in Pailin only)<br>o To determine the polymorphism of molecular markers of *P falciparum* resistance (K13, pfmdr1 and copy number) |
| Primary endpoint | 28 day and 42 day PCR corrected ACPR |
| Secondary Endpoints | Main secondary endpoint:<br>o Absolute values and change from baseline related to hepatic biological values (ALT, AST, Total and conjugated bilirubin and alkaline phosphatase) at day0, day 3, day 7 and day 28 including any follow up values to confirm return to baseline values<br>Other secondary endpoints<br>• The numbers of patients with a positive malaria slide 72 hours after treatment initiation in each group<br>• Fever clearance time (i.e. the time taken for tympanic temperature to fall below 37.5˚C and remain there for at least 24 hours)<br>• Kaplan Meier analysis over 42 days for recrudescences and reinfections<br>• PCR uncorrected ACPR at D28 and D42<br>• 28 day or 42 day PCR corrected ACPR<br>• Gametocyte carriage rates and gametocyte clearance times in each treatment arm<br>• Documented AEs and SAEs and relationships to study drugs.<br>• Adverse events in both study arms<br>• Changes in haematological and biochemical parameters over time. |
| Drugs | Pyronaridine-artesunate (Pyramax®) |

## 1. Background

Artemisinin resistance in *Plasmodium falciparum* has emerged in western Cambodia. To date this has been manifest by prolonged parasite clearance rates following treatment with artemisinin derivatives (Dondorp et al, 2009). There is concern that the efficacy of the artemisinin based combination therapies may be waning in this area due to the development of resistance to the partner drug. A high failure rate following artemether-lumefantrine treatment was first documented in 2006 (Denis, 2006) , and in 2011 cure rates in a small number of patients in Pailin treated with dihydroartemisinin piperaquine (DHA-PQP) were only 75% (Leang, 2012). High 42-day failure rates are now being observed in Pursat province (unpublished CNM data).

Pyronaridine-artesunate (PYR-AS) could be an alternative option for the treatment of uncomplicated falciparum malaria in western Cambodia. On 16 February 2012, the European Medicine Agency (according to Article 58) adopted a positive scientific opinion for pyronaridine-artesunate (Pyramax) 180mg/60mg for the treatment of acute, uncomplicated malaria infection caused by Plasmodium species in adults and children weighing 20 kg or more, in areas of low transmission with evidence of artemisinin resistance (including Cambodia) as a single treatment course. It has been pre-qualified by the WHO.

Pyronaridine -rtesunate (PYAS) was first used as a fixed combination in 2005 in the context of the Phase II development; it is however not yet commercially available in Cambodia. In a RCT multi-centre trial there was a 10% recrudescence rate on D42 in the 211 patients recruited at the western Cambodian site treated with PYAS which contrasted with the overall D42 genotyping corrected efficacy rate of the ACT in the trial of 99.2% (Rueangweerayut et al 2012). The parasite clearnace time was also slower for PYAS in Pailin. It is very important for CNM to verify whether this was a chance finding or if this reflects a genuinely lower efficacy of this treatment in areas where artemisinin resistance is prevalent. The results of this study will inform the National Malaria Treatment Guidelines.

## 2. Study objectives

Primary Objective:

To assess the therapeutic efficacy of pyronaridine-artesunate for the treatment of uncomplicated falciparum malaria or mixed infection (PF+ a non-falciparum species) at Day 42, in an area of artemisinin resistance.

Secondary Objectives:

- To measure the clinical and parasitological efficacy of pyronaridine-artesunate for the treatment of uncomplicated *P.falciparum* and mixed (in Pailin)
- To determine the polymorphism of molecular markers of *P falciparum*

**3. Study endpoints**

The primary endpoint of the study is D28 PCR and D42 PCR corrected ACPR to assess therapeutic efficacy pyronaridine artesunate for the treatment of uncomplicated falciparum malaria in an area where artemisinin resistant malaria is prevalent.

Main secondary endpoints:

- Absolute values and change from baseline related to hepatic biological values (ALT, AST, Total and conjugated bilirubin, alkaline phosphatase and any other relevant parameters if available) at day 0, 3, day 7 and day 28 and where available, any additional follow up values to confirm return to baseline values.

Other secondary endpoints:

- The numbers of patients with a positive malaria slide 72 hours after treatment initiation in each group
- Fever clearance time (i.e. the time taken for tympanic temperature to fall below 37.5˚C and remain there for at least 24 hours)
- Kaplan Meier analysis over 28 and 42 days for recrudescence, reinfections and new infections
- PCR uncorrected ACPR at D28 and D42
- 28 and 42 day PCR corrected ACPR
- Gametocyte carriage rates and gametocyte clearance times in each treatment arm
- Documented AEs and SAEs and relationships to study drugs.
- Adverse events in both study arms

- Changes in haematological and biochemical parameters over time.

## 4. Study design

A prospective, single arm, open-labelled clinical study

## 5. Sample size

For an assumed efficacy of 90%, a sample size of 138 participants is needed for the study in three study sites for +/- 5% precision (this is width = 0.1 in document), i.e., 85 to 95%. Allowing for a 5% drop out, we propose a sample size of 145 patients for the three study sites in three western provinces of Pailin, Battambang and Pursat.

## 6. Study population

The study will be conducted at Pailin and Pursat in western Cambodia and Tasanh Health Centre, Samlout District, Battambang. Khmer patients will be recruited from the surrounding areas using a network of Volunteer Malaria Workers and by active case detection, pre-screening febrile patients with a malaria rapid diagnostic test before referral to the hospital to assess eligibility for study inclusion.

### 6.1 Inclusion Criteria:

- Adults and children ≥ 20 kg
- Symptomatic of malaria infection, i.e: history of fever within 24 hours and/or presence of fever >37.5°c.
- Microscopic confirmation of asexual stages of *P. falciparum* (mixed infection in Pailin) any parasite below 150,000/asexual per micro litre
- Ability to take oral medication.
- Written informed consent given to participate in the trial given by the patient or in case of children <16 years their attending guardian.

### 5.2 Exclusion Criteria:

- Pregnancy or lactation (urine test for β HCG to be performed on any woman of child bearing age that is 18 to 45 years).
- Female aged 12-18y
- *P. falciparum* asexual stage parasitaemia at any density

- Signs or symptoms indicative of severe malaria:
    - Impaired consciousness (Blantyre Coma Score <5)
    - Severe anaemia (Hct<15%)
    - Bleeding disorder –evidenced by epistaxis, bleeding gums, frank haematuria, bleeding from venepuncture sites
    - Respiratory distress
    - Severe Jaundice
- Known hypersensitivity to artemisinins - defined as history of erythroderma/other severe cutaneous reaction, angioedema or anaphylaxis or to piperaquine or pyronaridine
- History of splenectomy
- Patients taking any drug which are known to be metabolised by the cytochrome enzyme CYP2D6 including flecainide, metoprol, imipramine, amitriptyline, clomipramine.
- Known history or evidence of clinically significant liver disorders, such as:
    - Known active Hepatitis A, e.g. by detection of anti HAV-IgM.
    - Known hepatitis B surface antigen (HBsAg) carrier.
    - Known hepatitis C antibody (HCV Ab).
- Liver function tests (AST/ALT levels) more than 2.5 times the upper limit of normal range.

**6. Enrolment procedures**

All subjects enrolled in the study will be given a unique code. A case-record form will be completed with each patient documenting symptoms prior to clinic attendance, concomitant illness, drug history. Height, weight, vital signs and physical examination findings will be recorded.

At inclusion all patients will have the following samples taken (total volume for adults ≥16 years old: 5 ml; total volume for children under 16 years old: 3 ml).

- Malaria blood film (thick and thin) and haematocrit: 0.5ml

- Filter paper blood blots (3 dots on Whatman 3MM; approx 220-300 uL blood) for PCR parasite genotyping (msp1, msp2, glurp in case of recurrence during follow-up and polymorphism of drug resistance marker)
- Biochemistry analysis: (1 ml) (AST/ALT, bilirubin total/conjugated, alkaline phosphatase)

### 6.1 Laboratory procedures

#### 6.1.1 Slide microscopy

Thick and thin blood films for parasite counts should be obtained and examined at screening on day 0 to confirm adherence to the inclusion and exclusion criteria. Thick blood films will be also examined on days 2, 3, 7, 14, 21, 28, 35 and 42 or on any other day if the patient returns spontaneously and parasitological reassessment is required. Specimens will be labelled anonymously (screening number or study number, day of follow-up, date).

A fresh Giemsa stain dilution will be prepared at least once a day and possibly more often, depending on the number of slides to be processed. Giemsa-stained thick and thin blood films will be examined at a magnification of 1000× to identify the parasite species and to determine the parasite density.

Three blood slides per patient will be obtained: two thick blood smears and one thin blood smear. One slide will then be stained rapidly (10% Giemsa for 10–15 min) for initial screening, while the others will be retained. If the patient is subsequently enrolled, the second slide will be stained more carefully (e.g. 2.5–3% Giemsa for 45–60 min), and slower staining will also be used for all slides obtained at follow-up visits. The study number of the patient, the date and the day of follow-up will be recorded either on the frosted edge of the slide or on the glass with a permanent glass pen.

The thick blood smear for initial screening will be used to count the numbers of asexual parasites and white blood cells in a limited number of microscopic fields.

The second blood smear will be used to calculate the parasite density, by counting the number of asexual parasites in a set number of white blood cells (typically 200) with a hand tally counter. Once a field has been started, it must be counted to completion; the final number of white blood cells will therefore rarely be exactly 200. If more than 500 parasites have been counted before 200 white blood cells have been reached, the count will be stopped after the

reading of the last field has been completed. Parasite density, expressed as the number of asexual parasites per µl of blood, will be calculated by dividing the number of asexual parasites by the number of white blood cells counted and then multiplying by an assumed white blood cell density (typically 6000 per µl).

$$\text{Parasite density (per µl)} = \frac{\text{number of parasites counted} \times 6000}{\text{Number of leukocytes counted}}$$

The same technique will be used to establish the parasite count on each subsequent blood film. When the number of asexual parasites is less than 100 per 200 white blood cells in follow-up smears, counting will be done against at least 500 white blood cells (i.e. to completion of the field in which the 500th white blood cell is counted). A blood slide will be considered negative when examination of 1000 white blood cells reveals no asexual parasites. The presence of gametocytes on an enrolment or follow-up slide will be noted, but this information will not contribute to basic evaluation.
In addition, 100 fields of the second thick film will be examined to exclude mixed infections; in case of any doubt, the thin film will be examined for confirmation. If examination of the thin film is not conclusive, the patient will be excluded from the analysis after complete treatment and follow-up.

Two qualified microscopists will read all the slides independently, and parasite densities will be calculated by averaging the two counts. Blood smears with discordant results (differences between the two microscopists in species diagnosis, in parasite density of > 50% or in the presence of parasites) will be re-examined by a third, independent microscopist, and parasite density will be calculated by averaging the two closest counts.

### 6.1.2 Genotyping of malaria parasites

In order to differentiate a recrudescence (same parasite strain) from a newly acquired infection (different parasite strain), a genotype analysis will be conducted. This is based on the extensive genetic diversity among the malaria parasite genes *msp1*, *msp2* and *glurp*.[1] The genotypic profiles of pre- and post-parasite strains are compared.

[1] WHO. *Methods and techniques for clinical trials on antimalarial drug efficacy: genotyping to identify parasite populations.* Geneva, World Health Organization, 2008 (http://www.who.int/malaria/resistance).

In addition, samples will be analysed for the presence of the Kelch 13 propeller mutation, a recently discovered molecular marker that is associated strongly with slow parasite clearance and in vitro artemisinin resistance using the Ring Survival Assay (RSA).

The copy number of *P. falciparum* mdr1 gene will also be measured. An increasing copy number is associated with mefloquine (MQ) resistance and treatment failures with ASMQ.

In order to minimize discomfort to the patient due to repeated finger pricks, two to three drops of blood will be collected on filter paper Whatman 3MM during screening or enrolment and each time blood smears are required according to the protocol on and after day 7. Specimens will be labeled anonymously (study number, day of follow-up, date), kept in individual plastic bags with desiccant pouches and protected from light, humidity and extreme temperature until analyzed. When such room temperature conditions are not possible, for example in extremely humid environments where air-conditioning is not available, storage in a refrigerator or freezer will be considered, but great care will be taken to protect samples from frost and moisture. The PCR technique used will be performed by laboratory of Institut Pasteur in Cambodia. Paired filter papers will be used for parasite DNA extraction and genotyping. Unused filter papers will be kept in safe locations until data are eventually validated or for further research needs.

### 6.1.3 Pregnancy test

Female patients of child-bearing age, defined as those who menstruate and are aged over 18 years and married female patients aged above 12 years, will be asked to take a urine pregnancy test before enrolment in the study, because aretesunate-pyronaridine is contraindicated during pregnancy. They will also be asked to take a urine pregnancy test on day 42 or on early withdrawal from the study. Female participants of child-bearing age, defined as those who menstruate and are aged over 18 years, and who are sexually active should use barrier contraceptive devices for the duration of the study. Birth spacing pills will be provided by the investigator or study team at the time informed consent is obtained, with appropriate counselling about the risks of becoming pregnant and exposing the foetus to the study medicines.

**7. Drugs and dosages**

**Pyronaridine-artesunate** (Pyramax®, Shin Poong Pharmaceuticals). One tablet contains 60mg artesunate+ 180mg pyronaridine. Dosing will be according to body weight:

| Body Weight(kg) | Daily dose(mg) | | Number of tablets |
|---|---|---|---|
| | PYR | AS | |
| 20–<24 kg | 180 | 60 | 1 tab |
| 24–<45 kg | 360 | 120 | 2 tabs |
| 45–<65 kg | 540 | 180 | 3 tabs |
| 65 ang above | 720 | 240 | 4 tabs |

Pyronaridine-artesunate will be taken orally with water, once daily for 3 days. Each dose will be administered under supervision in the clinic or if not possible by a home visitor to the patient's home. A dose will be repeated in full if vomiting occurs within 30 minutes of administration and halved if vomiting occurs between 30 minutes and 1 hour post dosing. This event will be documented in the case record form (CRF). Dosage tables are appended (Appendix 1).

**8. Rescue treatment and treatment**

If the patient vomits twice the treatment he/she will receive parenteral therapy based on the national treatment guidelines. If a patient is unable to tolerate the trial medication he/she should discontinue the treatment and alternative anti-malaria medication should be initiated. In this case, the reason for discontinuation should be recorded in the case record form (CRF) as "Adverse experience" and be withdrawn from the study. The patient will receive parenteral therapy with artemether or quinine 7 days (IV) + tetracycline 7 days as well as relevant supportive treatments.

Any patient with signs of severe malaria, will be hospitalized and receive parenteral therapy with artemether or quinine 7 days (IV) + tetracycline 7 days as well as relevant supportive treatments. Recurrent infections with *P. falciparum* will be treated with a 3-day course of artesunate+mefloquine (A+M) according to the national treatment guideline and the patients will be followed up for 42 days.

An episode of *P. vivax* malaria during follow up will be treated with dihydroartemisinin-piperaquine (DHA-PIP) according to the national treatment guidelines and the patients will be followed up over 28 days.

## 9. Follow up (see table 1 in appendix)

- All patients will have a blood smear examined daily during the first week by microscopy until parasite clearance (2 consecutive negative slides on two consecutive days; both asexual and sexual stages). A negative blood slide will be defined as parasite count negative per 1000 WBC in two consecutive days. The sample on day 3 will be taken as close as possible to 72h after the initial blood smear.
- Blood biochemistry and basic haematology on D0, D3, D7 D14, D28 and D42. Tests for: AST/ALT, total bilirubin and alkaline phosphatase. If values increase, a confirmation test will be done within 48 hours where practical and clinically indicated. Regarding liver function tests (LFT), any elevation of ALTx3ULN on day 3 not having returned to baseline by day 7 will be followed up and repeated on day 28 and 42. A specific monitoring of LFT will be performed for any patient in which ALT values are greater than 3xULN combined with a bilirubin greater than 2xULN (Hy's law), or if ALT has risen to above x5ULN, irrespective of other accompanying abnormalities (cf Appendix 2 on "Adverse Event of Special Interest: drugs and the liver"). In such cases, LFT will need to be repeated twice a week until values return to baseline. Hy's law cases will need to be reported as a SAE (See Section 14.2). Total blood volume per time point for biochemistry and haematological assessments will be 2 mL.

*Time windows for follow-up visits:*

The time-window for the visit on Day 7 is + 1 days, for the visits on Days 14 - 35 is –1 to +1 days and for D42 is -1 to +1 days. If patients do not attend for follow-up a home-visitor from the study team will try to locate the patient and bring them to the clinic.

## 10. Treatment failures

Definition of treatment failures will follow the standard WHO definitions:

***Early treatment failure***

- danger signs or severe malaria on day 1, 2 or 3 in the presence of parasitaemia;
- parasitaemia on day 2 higher than on day 0, irrespective of axillary temperature;
- parasitaemia on day 3 with axillary temperature ≥ 37.5 ºC;

- parasitaemia on day 3 ≥ 25% of count on day 0.

***(Late treatment failure)***

***Late clinical failure***

- danger signs or severe malaria in the presence of parasitaemia on any day between day 4 and day 28 (day 42) in patients who did not previously meet any of the criteria of early treatment failure;
- presence of parasitaemia on any day between day 4 and day 42 with axillary temperature ≥ 37.5 ºC or history of fever in patients who did not previously meet any of the criteria of early treatment failure

***Late parasitological failure***

- presence of parasitaemia on any day between day 7 and day 42 with axillary temperature < 37.5 ºC in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure

***Adequate clinical and parasitological response***

- absence of parasitaemia on day 42, irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure

**11. Discontinuation/ Withdrawal of Participants from the Study**

Each participant has the right to withdraw from the study at any time. In addition, the investigator may withdraw a participant if he or she considers it necessary for any reason including:

- Development of severe malaria.
- Repeated vomiting after administration of study drugs before the last dose study dugs.
- An adverse event or Disease progression which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Significant non-compliance with treatment regimen or study requirements.
- Allergic Reaction to Study drugs after administration before the last dose study dugs.
- Liver function tests (AST/ALT levels) more than 2.5 times the upper limit of normal range.

If an individual is prematurely discontinued from study treatment for any reason, the investigator must make every effort to perform the following evaluations: physical examination and vital signs assessment, haematocrit level, parasite count and AE assessment. The reason for withdrawal will be recorded in the CRF. If the subject is withdrawn due to an adverse event, the investigator will arrange for follow-up visits until the adverse event has resolved or stabilised.

**12. Safety reporting**

Patients will be screened for common adverse events using and will be recorded in a predefined list of events, with in addition an open text field for non-listed events. Changes in liver enzymes will be recorded.

**12.1 Adverse Events (AEs)**

An Adverse Event (AE) is a sign, symptom, syndrome, disease or biological anomaly suffered by a patient or a subject participating in a clinical study and receiving a medicinal product. This term does not imply a causal relationship with the concerned treatment. Clinical signs typical of an acute malaria episode will not be considered AEs unless the healthcare personnel considers these events as exceptional due to their evolution, their seriousness, or another factor related to these events.

**12.2 Serious Adverse Events**

A serious adverse event is an AE that:

- results in death
- is life-threatening i.e. the patient was at risk of death at the time of the AE
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect
- requires acute medical or surgical care to prevent one of the outcomes listed above

**12.3 Adverse Events of Special Interest:**

An adverse event of special interest (AESI) is an adverse event for which on-going monitoring is appropriate within the context of the study. These events necessitate complementary examinations in order to characterize and understand them.

AESIs in this study can be related to:

- Hepatotoxicity
- Neurotoxicity/seizures
- Cutaneous reactions/photo toxicity

The study team, as well as the relevant referral facilities, should be trained to take particular notice of symptoms/signs suggestive of the AESIs in this study:

1) clinical and biological signs of possible hepatotoxicity such as:

- fatigue, nausea, abdominal pain, dark urine, putty or mastic coloured stools, jaundice (yellowing of the whites of the eyes or skin) and itching
- ALT value >5xULN or ALT value >3xULN AND total bilirubin value >2xULN

2) clinical signs of possible cardio-toxicity

- Palpitations
- Seizures
- Pounding/pain in the chest area
- Fainting/Syncope.

3) clinical signs of possible neurotoxicity/seizures such as:

- Seizures
- Dizziness
- Pins and needles sensations
- Visions disturbance
- Difficulties coordination
- Tinnitus

4) clinical signs of possible cutaneous reactions/photo toxicity such as:

- Urticaria
- angioedema
- Skin lesions
- Itching pruritus
- Discoloration
- Dermatitis

In all the cases of hepatotoxicity, confirmed by the PI / investigators, the sponsor. Notification will occur through the use of an ad hoc AESI form.

The patients with the following elevations may require more intensive inquiry on the part of the investigator: ALT value that exceeds 5.0 times the upper limit of normal or ALT value

that exceeds 3.0 times the upper limit of normal AND a total bilirubin value that exceeds 2 times the upper limit of normal (Hy's law).

The investigator should then consult the treating Cambodian physician to obtain an hepatitis panel (Anti-HAV IgM, Anti-HBc IgM, HBsAg, and hepatitis C RNA), hepatitis E IgM antibody, cytomegalovirus (CMV) testing polymerase chain reaction (PCR) testing, pp65 antigen, or IgM antibody; Epstein Barr virus (EBV) viral capsid antigen IgM antibody; In addition, serum creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH) would need to be measured. The treating Cambodian physician will ensure proper referral in case a diagnosis of non-malaria or study drug related pathology.

### 12.4 Pregnancy

In case of pregnancy, the anti-malarial treatment shall be the one recommended by the NMCP. The patient will not be included in the study.

Female patients will be encouraged to communicate to the PI if they will be pregnant within a period of two months after the start of the treatment.

The evolution of the pregnancy will be monitored with visits at 3, 6, 9 months and after the delivery. Information on the drugs taken during the pregnancy as well as AEs/SAEs and the health status of the newborn/s will be collected; thereafter the newborn/s will be followed at 6 and 14 weeks.

### 12.5 Reporting Procedures for Adverse Events

***Adverse Events***

The AEs, regardless of their seriousness and causal relationship to the study drug, arising between the signature of the informed consent form and the last study visit (as per the protocol), must all be recorded on the patient chart (AE recording section). When possible, the symptoms must be regrouped within a single syndrome or diagnosis. The healthcare personnel shall have to specify the date of manifestation of the event, its intensity, final evolution, the measures taken and the treatment undertaken (if any).

***Serious Adverse Events***

In case of SAEs, the healthcare personnel will Dr. Leang Rithea within 24 hours for validation of the seriousness and determination of the causality. Subsequently, the following procedure will be followed:

- A signed and dated scanned copy of the "Adverse Event form" and the form "SAE

complementary information" will be send by email within 24 hours .

• The local responsible person for pharmacovigilance of the project will be informed within 72 hours.

The follow-up of each fatal or life-threatening AE will be provided to Dr Leang Rithea, the chariman of the DSMC, the local person responsible for the pharmacovigilance of the project. The information provided will include scanned, but anonymised, copies of the source data including detailed clinical, laboratory, and other relevant data.

***Follow-up of AE***

The healthcare personnel must take all appropriate measures to protect the safety of the patients. Personnel must ensure to document follow-up of the evolution of each adverse event (clinical, biological or other) until resolution or until the stabilization of the patient's status.

All new relevant information concerning the initial SAE shall be recorded on a form "SAE follow-up information form" by the nursing staff of the health centre, and shall be validated by the PI / co-PI.

In case of a serious adverse event the patient must be followed until complete healing and normalization of all analysis results, or until chronicity of the patient's status. This can imply that the follow-up of the patient must continue beyond the period of follow-up per protocol, and that additional investigations could be requested by the sponsor.

## 13. STATISTICAL ANALYSIS:

The primary analysis will be on an 'intention to treat' basis, including all patients enrolled into the study. Primary outcome will be the Kaplan Meier analysis up to day 42 of follow-up. A per protocol analysis will be based on all enrolled patients complying with all inclusion criteria who received a full course of the study drugs. Secondary analyses include the 'adequate parasitological and clinical response' (APCR) at day 28 and day 42. Safety and tolerability measurements will be summarized for the ITT patient population.

## 14. Quality assurance/quality control procedures

All blood slides from day 0, 3, 7, 21, 28, 42 and those from any return day will be validated by a CNM expert-level technician and also.

## 15. Study drugs

### 15.1 Storage

All efforts will be made to store the study drugs in accordance with the manufacturers' recommendations in a secure area. This may be difficult at some sites where air conditioned storage rooms are not available. The ACTs should be stored between 15°C to 30°C (59°F to 86°F).

### 15.2 Accountability of the study treatment

All movements of study medication will be recorded. Both individual subject and overall drug accountability records will be kept up to date by the study staff.

## 16. Concomitant Medication

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary (e.g. antipyretics or anti-emetics) to provide adequate supportive care except for antibiotics with antimalarial activity unless unavoidable (e.g. doxycycline, azithromycin). If these are required the patients will be kept in the study and this will be noted as a protocol deviation. Antimalarials for recurrent infections will be prescribed as described above. Haematinics and anti-helmintics may be prescribed after day 7 if indicated. Any medication, other than the study medication taken during the study will be recorded in the CRF

## 17. Monitoring

Study sites have in place a system for internal monitoring. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. The monitors will check whether the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.
A data safety monitoring committee (DSMC) will be overviewing the trial. The DSMC will be headed by an independent chairman, and also include an independent statistician and one additional independent member. Their remit will be defined in the DSMC charter (appendix).

## 17. Ethics

The Investigator will ensure that this study is conducted in compliance with the current revision of the Declaration of Helsinki (Seoul 2008) and that it will follow the principles of the ICH Guidelines for Good Clinical Practice 1996. The study protocol and its associated documents will be submitted to the Ethics Committee of the MoH of Cambodia and WHO regional office, Western Pacific Region. The ethics team may visit the study at any time during the course of the study as to ensure that all research process and procedures are completely adhered to that sated in the submitted protocol.

### 17.1 Pyronaridine–artesunate

This ACT is generally well tolerated, however liver enzyme elevations have been observed after treatment in few African and Asian patients and after retreatment of some healthy Caucasian healthy volunteers. As a result it is recommended that pyronaridine-artesunate be administered not more than once until results from ongoing retreatment studies become available.

### 17.2 Risk of phlebotomy & finger stick

The primary risks of phlebotomy include local discomfort, occasional bleeding or bruising of the skin at the site of needle puncture, and rarely haematoma or infection.

### 17.3 Benefits

Malaria is a disease that needs to be treated promptly. All patients will benefit from receiving efficacious treatment at no cost. They will be followed up closely and will be given rescue treatment if clinically indicated.

### 17.4 Alternatives to Study Participation

Subjects are able to decline freely participation in this study. If so, they will receive standard care for their malaria.

### 17.5 Incentives & Compensation

Study patients or their guardian in the case of children will be compensated for time lost from work. Patients will be reimbursed the cost of local transport to attend for the follow up visits and will receive a per diem to cover the costs of meals on those days. Each site will determine the amounts in monetary terms. The study will pay for treatment for drug-related SAEs or

other research-related injuries. The study cannot pay for long term care for disability after hospital discharge resulting from complications of the illness.

### 17.6 Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. Only initials and a study number on the CRF and in the database will identify the participants. All documents will be stored securely and be accessible to trial staff and authorised personnel only.

## 18 Sample sharing and storage

Samples collected will be used for the purpose of this study as stated in the protocol and stored for future use. Consent will be obtained from subjects for sample storage and/or shipment of specific samples to collaborating institutions for investigations that cannot be performed locally. Any proposed plans to use samples other than for those investigations detailed in this protocol will be submitted to the relevant ethics committees prior to any testing.

## 19 Data ownership, use of results and publication policy

All data generated in this study will centralised and belong to CNM. A final copy of the database containing all the data will be held at CNM. The database can be shared with the other collaborators, as mutually agreed basis. Sharing the data with other parties is subject to the approval of the principal investigator.

Any data published in the peer-reviewed medical literature will protect the identity of the subjects. This trial will be registered in a web based protocol registration scheme. The results from all study sites will be published in a peer-reviewed journal. All those who have made a substantial contribution will be co-authors on publications. All the research findings will be disseminated to policy makers for an informed decision on drug policy for the treatment of malaria and other researchers.

## 20 Budget

| | WHO (US$) |
|---|---|
| **Human resources** | |
| • professional scientific staff (4 persons) | |
| *Director: 500$ x 10 month = 5000* | 5,000 |
| *PI: 900$ x 10 months = 8000* | 9,000 |
| *Co-PI: 500$ x 10 months = 5000* | 5,000 |
| *Epidemiologist: 300$ x 10 months = 3000* | 3,000 |
| technical staff (10 persons) | |
| *CNM Medical Doctors (2 persons): 600$ x 2 x 8 months = 9600* | 9,600 |
| *CNM Lab tech (2) : 600$ x 2 x 8 months = 9600* | 9,600 |
| • local support (6 persons) | |
| *MD/MA (2 persons): 450$ x 2 x 8 months = 6400* | 6,400 |
| *Lab tech (2 persons): 300$ x 2 x 8 months = 4800* | 4,800 |
| *Nurse (2 persons): 300 x 2 x 8 months = 4800* | 4,800 |
| Sub-total | **57,200** |
| **Field-based transportation** | |
| • Motor rental for following up the patients (2 motors) | 3,200 |
| *Motors: 200$ x 2 x 8 months = 3200* | |
| Sub-total | **3,200** |
| **Equipment and supplies** | |
| • equipment | |
| o *Hematocrit centrifuge* | |
| o *Stethoscopes & blood pressure* | |
| o *Hematocrit apparatus* | 1,800 |
| o *Glucose apparatus* | |
| o *Scales* | |
| o *Battery* | |
| o *Lamps* | |
| • Supplies | 1,680 |
| o *Reagent* | |
| o *Methanol* | |
| o *Urine test* | |
| o *Medicine (antipyretic, analgesic, diazepam, others)* | |
| o *Slide boxes* | |
| o *Researcher Kits* | |
| o *Slides* | |
| o *Parenteral Fluid* | |
| • operational costs (space rental, communication) | 3,800 |
| Sub-total | **7, 280** |
| **Contingency fees for clinical trials** | |

| | |
|---|---|
| ○ ethical review<br>○ registration<br>○ liability insurance | 450 |
| Sub-total | **450** |
| **Patient costs** (145 P. falciparum cases) | |
| *Work loss: 145 x 3$ x 9 times = 3262.5* | 3,263 |
| *Food cost: 145 x 3$ x 3 = 1087.5* | 1,088 |
| *Travel Cost enrolled patients: 145$ x 10$ x 7 times = 8700* | 8,700 |
| *Referral fee: 145$ x 15 = 2175* | 2,175 |
| *Hospital fee: 145 x 10$ = 1450* | 1,450 |
| *Fee for non-enrolled patients: 40 x 10.12$ = 405* | 450 |
| **Patient costs for recurrent infection**<br>*- Assumption: 10 patients will experience treatment failure: treated with A+M & follow up until 42 days: 10 patients x 129$ = 1290$* | 1,290 |
| Sub-total | **18,370** |
| **Technical assistance**<br>(training , document translation, support to research institutions, capacity building) | |
| ○ Training | 1,000 |
| ○ Translation (protocol, forms and etc.) | 800 |
| Sub-total | **1,800** |
| **Supervision** | |
| PI/CNM Director,Co-PIs, field monitoring officer | |
| *4 resource persons x 20$ x 5 days x 15 times = 5600* | 5,600 |
| *One driver: 20$ x 5 days x 15 times = 1600* | 1,600 |
| *Fuel: 157.14$ x 14 times = 2200* | 2,200 |
| Sub-total | **9,400** |
| **Quality assurance system**<br>(data validation, slides cross-check): *250$ x 8 months = 2000* | 2,000 |
| Sub-total | **2,000** |
| **Data management**<br>(data entry, data analysis, report writing): *300$ x 8 months = 2400* | 2,400 |
| Sub-total | **2,400** |
| **Laboratory support**<br>(genotyping) | |
| Liver function tests (145 patients): *145 x 45.52$ = 6600* | 6,600 |
| Sample shipment from Battambang & Pursat to IPC | 800 |
| Sub-total | **7,400** |
| **Result dissemination**<br>○ Publication in Peer review journal | |
| **Miscellaneous** | 500 |
| Sub-total | **500** |
| **Grand Total** | **110,000** |

**21 Curriculum vitae of the principal investigator**

| | |
|---|---|
| Family name (surname): Leang | First name: Rithea |
| Place of birth: Kandal | Date of birth: 17 Sept 1970 |
| Current nationality: Cambodian | |

Academic qualifications and dates:
2005-2006 Master of Health Administration, Curtin University of Technology, Perth, Western Australia

1990-1998 Diploma of General Medicine, University of Health Science, Phnom Penh, Cambodia

Posts held (type of post, institution/authority, dates chronologically starting with current appointment):

2007-present: Head, Health Research Unit, National Malaria Centre

2000-2004: Program Manager of Lymphatic Filariasis Elimination Program at National Malaria Centre

Selected relevant publications:
Efficacy of dihydroartemisinin–piperaquine for the treatment of uncomplicated Plasmodium falciparum and Plasmodium vivax in Cambodia, 2008–2010. American journal of antimicrobial chemotherapy, 2012

# Study sites

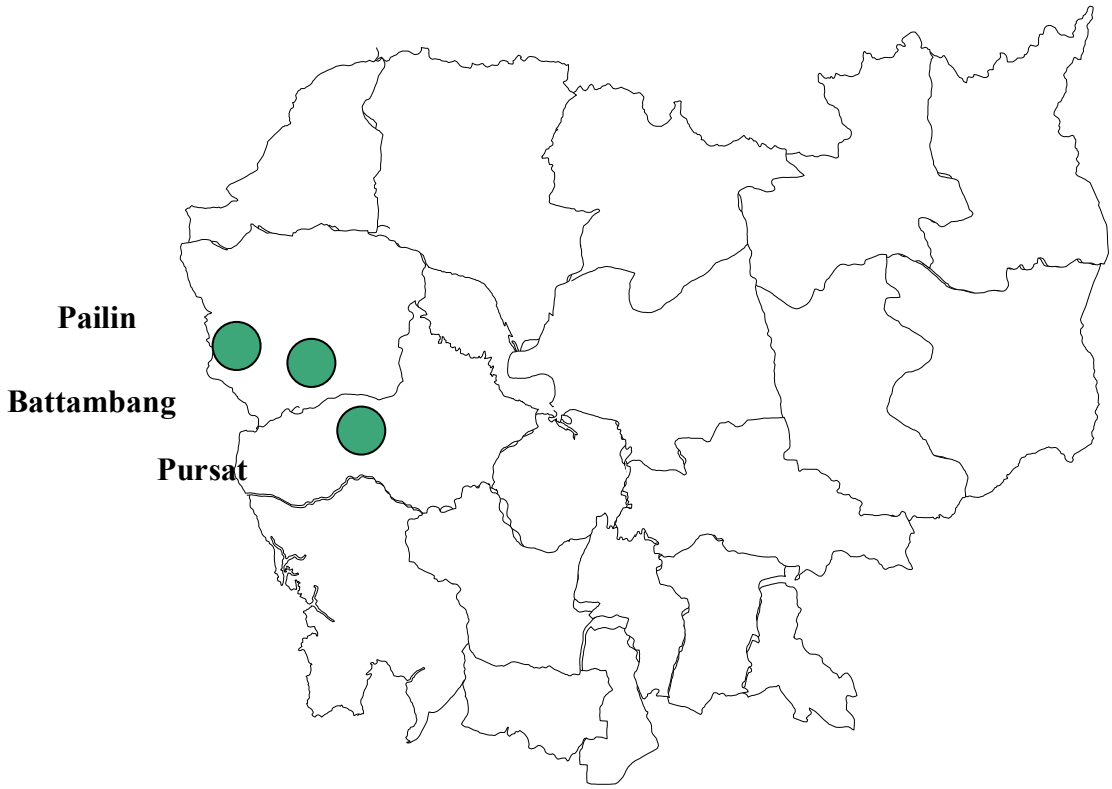


*Figure 1: Sentinel sites*

## 22 References


Brockman A, Price RN, van Vugt M, Heppner DG, Walsh D, Sookto P, Wimonwattrawatee T, Looareesuwan S, White NJ, Nosten F. *Plasmodium falciparum* antimalarial drug susceptibility on the north-western border of Thailand during five years of extensive use of artesunate-mefloquine. *Trans R Soc Trop Med Hyg,* 2000, **94**: 537-544.

Denis MB, Tsuyuoka R, Lim P, Lindegardh N, Yi P, Top SN, Socheat D, Fandeur T, Annerberg A, Christophel EM, Ringwald P Efficacy of artemether-lumefantrine for the treatment of uncomplicated falciparum malaria in northwest Cambodia. Trop Med Int Health. 2006;11:1800-7.

Dondorp AM, Nosten F, Yi P, Das D, Phyo AP, Tarning J, Lwin KM, Ariey F, Hanpithakpong W, Lee SJ, Ringwald P, Silamut K, Imwong M, Chotivanich K, Lim P, Herdman T, An SS, Yeung S, Singhasivanon P, Day NP, Lindegardh N, Socheat D, White NJ. Artemisinin resistance in *Plasmodium falciparum* malaria. N Engl J Med. 2009 Jul 30;361(5):455-67.

Karunajeewa H, Lim C, Hung TY, Ilett KF, Denis MB, Socheat D, Davis TM. Safety evaluation of fixed combination piperaquine plus dihydroartemisinin (Artekin) in Cambodian children and adults with malaria. Br J Clin Pharmacol. 2004 Jan;57(1):93-9

Leang R, Barrette A, Mey Bouth D, Menard D, Abdur R, Duong S, Ringwald P. Efficacy of dihydroartemisinin-piperaquine for the treatment of uncomplicated Plasmodium falciparum and Plasmodium vivax in Cambodia, 2008-2010. Antimicrob Agents Chemother. 2012 Dec 3. [Epub ahead of print]

Myint HY, Ashley EA, Day NP, Nosten F, White NJ. Efficacy and safety of dihydroartemisinin-piperaquine. *Trans R Soc Trop Med Hyg*. 2007, **101**:858-66.

Neena Valecha, Aung Pyae Phyo, Mayfong Mayxay, Paul N. Newton, Srivicha Krudsood, Sommay Keomany, Maniphone Khanthavong, Tiengkham Pongvongsa, Ronnatrai Ruangveerayuth, Chirapong Uthaisil, David Ubben, Stephan Duparc, Antonella Bacchieri, Marco Corsi, Bappanad H. K. Rao, Prabash C. Bhattacharya, Nagesh Dubhashi, Susanta K.

Ghosh, Vas Dev, Ashwani Kumar, Sasithon Pukittayakamee. An Open-Label, Randomised Study of Dihydroartemisinin-Piperaquine Versus Artesunate-Mefloquine for Falciparum Malaria in Asia PLoS ONE: Research Article, published 30 Jul 2010

Quique Bassat, Modest Mulenga, Halidou Tinto, Patrice Piola, Steffen Borrmann, Clara Menéndez, Michael Nambozi, Innocent Valéa, Carolyn Nabasumba, Philip Sasi, Antonella Bacchieri, Marco Corsi, David Ubben, Ambrose Talisuna, Umberto D'Alessandro
David Ubben Dihydroartemisinin-Piperaquine and Artemether-Lumefantrine for Treating Uncomplicated Malaria in African Children: A Randomised, Non-Inferiority Trial
PLoS ONE: Research Article, published 17 Nov 2009 10.1371/journal.pone.0007871

Rueangweerayut R, Phyo AP, Uthaisin C, Poravuth Y, Binh TQ, Tinto H, Pénali LK, Valecha N, Tien NT, Abdulla S, Borghini-Fuhrer I, Duparc S, Shin CS, Fleckenstein L; Pyronaridine–Artesunate Study Team. Pyronaridine-artesunate versus mefloquine plus artesunate for malaria. N Engl J Med. 2012 Apr 5;366(14):1298-309. PubMed PMID: 22475593.

Stepniewska K, Ashley E, Lee SJ, Anstey N, Barnes KI, Binh TQ, D'Alessandro U, Day NP, de Vries PJ, Dorsey G, Guthmann JP, Mayxay M, Newton PN, Olliaro P, Osorio L, Price RN, Rowland M, Smithuis F, Taylor WR, Nosten F, White NJ. In vivo parasitological measures of artemisinin susceptibility. J Infect Dis. 2010 Feb 15;201(4):570-9.

Tshefu AK, Gaye O, Kayentao K, Thompson R, Bhatt KM, Sesay SS, Bustos DG, Tjitra E, Bedu-Addo G, Borghini-Fuhrer I, Duparc S, Shin CS, Fleckenstein L; Pyronaridine-artesunate Study Team. Efficacy and safety of a fixed-dose oral combination of pyronaridine-artesunate compared with artemether-lumefantrine in children and adults with uncomplicated Plasmodium falciparum malaria: a randomised non-inferiority trial. Lancet. 2010 Apr 24;375(9724):1457-67.

## APPENDIX 1: ADVERSE EVENT OF SPECIAL INTEREST: DRUGS AND THE LIVER

**Checklist for Serious Liver Reactions:**

- stop study drug. Stop herbal remedies and concomitant medications if they are not medically necessary.
- urgently collect urine, blood, or relevant biological fluids for PK (within 24 hours of last dose, or 3 half-lives, whichever is longer), diagnostic tests
- additional history and review of medical records
- discuss details with the patients, in particular any concomitant meds, OTC meds, herbal remedies, prior exposure, previous episodes etc
- documentation of laboratory values, ECG tracings, pathology reports, PK etc
- ensure appropriate medical attention, including move to hospital Emergency Department or ICU, specialist consultation, etc
- arrange appropriate follow up for investigations
- Safety Review Team to review aggregate data from available sources for underlying trends
- Contact safety department or other internal and external experts for advice

Documentation needed in the event of a clinically significant elevation in one or more liver function tests

- Liver function test results that are codified as adverse events, and/or elevations that occur rapidly or exceed multiples of the upper limit of normal, merit further inquiry on the part of the investigator. The laboratory tests that are relevant in this regard include ALT (SGPT), AST (SGOT), GGT, and alkaline phosphatase (ALP). Examples of elevations that may require more intensive inquiry on the part of the investigator include an ALT or AST value that exceeds 5.0 times the upper limit of normal or an ALT or AST value that exceeds 3.0 times the upper limit of normal and a total bilirubin value that exceeds 2 times the upper limit of normal (Hy's law). With massive hepatic injury, the ability of the liver to excrete conjugated (or direct) bilirubin diminishes. Therefore, the presence of ALT >3xULN and concomitant bilirubin >2xULN (>35% direct), in the absence of elevated alkaline phosphatase or biliary injury, suggests significant liver injury, mandating the need for immediate drug cessation and specialist/hepatologist consultation, and follow up of liver chemistries and prothrombin time twice weekly until values normalize or substantively improve.

The laboratory will have standing orders to analyze the value of ALP isoenzymes in situations where ALP values exceed twice the upper limit of normal. Similarly, the central laboratory will have standing orders to fractionate total bilirubin into its direct and indirect components in situations where the total bilirubin value exceeds 2 times the upper limit of normal.

- The investigator should obtain a hepatitis panel (Anti-HAV IgM, Anti-HBc IgM, HBsAg, and hepatitis C RNA), hepatitis E IgM antibody (if subject outside N. America, or has travelled outside N. America in prior 3 months); cytomegalovirus (CMV) testing polymerase chain reaction (PCR) testing, pp65 antigen, or IgM antibody; Epstein Barr virus (EBV) viral capsid antigen IgM antibody; serum

creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH). If bilirubin >2 x ULN, bilirubin should be fractionated to obtain % direct bilirubin.

- When ALT >3xULN and bilirubin >2xULN (>35% direct bilirubin on fractionation), obtain: antinuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies.

If laboratory values are returned that meet the above described criteria, and if there is a possibility of past or recent exposure to infectious hepatitis, and/or a history of high-risk behaviours that would place the subject at risk for infectious hepatitis.
If laboratory values are returned that meet the above-described criteria, the investigator should attempt to document the following in the investigator comment log of the CRF prior to contacting the sponsor:

- The subject's age, gender and weight.
- The date (and visit number) on which the blood sample was obtained.
- The Randomization date as well as the dose level that the subject is currently taking, and the duration of exposure to that dose level. The exact date on which the subject took the last dose of the study medication and an objective assessment should be obtained of the subject's compliance with the study medication.
- The specific abnormal laboratory values, as well as those of each of the other LFTs noted above (regardless of value) and, when relevant, results of isoenzyme or fractionation analyses. The investigator should also document the corresponding laboratory values at screening/baseline.
- Other notable abnormalities in laboratory values (*e.g.,* complete blood count, eosinophilia, or electrolyte abnormalities, if present).
- The dates and nature of any relevant adverse events (*e.g.,* jaundice) that occurred since Randomization, with particular attention to hypotension, fever, rash, hepatitis symptoms (e.g. appearance or worsening of fatigue, nausea, anorexia, nausea, emesis, abdominal pain), or other adverse events that might have occurred in close proximity to the elevation in the laboratory value(s) of interest.
- Any associated physical findings (including results of any exams or evaluations, including heart rate, blood pressure, temperature, and abdominal exam).
- The use of concomitant medications (*e.g.,* acetaminophen, herbal products) since Randomization, as well as the dates of exposure to the concomitant medication(s). Please include any nutritional supplements, vitamins and/or herbal preparations that the subject might have taken during this time frame.
- A statement concerning whether the subject has consumed alcohol since the time of Randomization, with a description of frequency and intensity, if relevant. A blood alcohol level should be obtained if the subject's history and/or clinical presentation suggest proximal use or intoxication with alcohol.
- Any history on the subject's part of prior elevations in any of the relevant laboratory values. Provide actual dates and laboratory values.
- Any history on the subject's part of a past or recent history of exposure to known factors that can cause, or are associated with, elevations in liver function tests. Examples of these factors include alcohol abuse and/or dependence, hepatitis (infectious or chemical), infectious mononucleosis, gallbladder disease, liver disease of any kind, jaundice, myocardial infarction, heart failure and/or episodes of hypotension.
- Any family history of hepatitis (from any cause) or hepatotoxicity from medications.

Please contact the medical monitor if you have questions about the most appropriate course of action, and/or if you have questions as to whether the subject should be referred to a specialist for further evaluation.

It is anticipated that the investigator will follow any subject with clinically significant elevations of one or more liver function tests until there is clear evidence that the value(s) have stabilized and/or normalized. In addition, an explanation should be provided for any subjects that are lost to follow up.

Possible Hy's Law case following the FDA Guidance on Drug Induced Liver Injury: Premarketing Clinical Evaluation dated July 2009 A possible Hy's law case is defined as a subject with any value of ALT or AST above 3xULN together with an increase in bilirubin to a value higher than 2xULN and NOT associated to an ALP value higher than 2xULNA decision on medical and scientific grounds is required to assess whether an immediate notification of an event is warranted in other situations, such as medically important events which are not life-threatening, fatal or cause hospitalization, but could endanger the patient or could rendered necessary an intervention to prevent one of the above conditions to develop.

Remark: Examples of such events are intensive care in the emergency room or at home to treat a bronchospasm; a haematological dyscrasia; convulsions or an asymptomatic increase ALT (≥ 10 x ULN) not causing hospitalisation, or the development of drug addiction or abuse

## TABLE 1: STUDY SCHEDULE

| | D0 | D1 | D2 | D3 | D4 | D7 | D14 | D21 | D28 | D35 | D42 | REPf | blood volumes (ml) per time | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Screening* | | | | | | | | | | | | | | |
| Written informed consent | x | | | | | | | | | | | | adult | Child |
| Assign participant ID | x | | | | | | | | | | | | ≥16 yrs | <16yrs |
| Participant's history | x | | | | | | | | | | | | | |
| Symptoms checklist | x | x | x | x | x | x | x | x | x | x | x | x | | |
| Vital signs | x | x | x | x | x | x | x | x | x | x | x | x | | |
| Temperature | x | x | x | x | x | x | x | x | x | x | x | x | | |
| General Examination | x | x | x | x | x | x | x | x | x | x | x | x | | |
| ***Study Drug administration*** | | | | | | | | | | | | | | |
| PYR-Artesunate | x | x | x | | | | | | | | | | | |
| ***Laboratory Procedures*** | | | | | | | | | | | | | | |
| #Malaria blood film | x | x | x | x | x | x | x | x | x | x | x | x | 0.5 | 0.5 |
| HCT or Hb | x | x | x | x | x | x | x | x | x | x | x | x | 0.03 | 0.03 |
| Filter paper blots | x | | | | | | | | | | | x | 0.3 | 0.3 |
| FBC | x | | | x | | x | x | | x | | X | x | 1 | 1 |
| Biochemistry | x | | | x | | x | x | | x | | X | x | 1 | 1 |
| | x | | | | | x | | | | | | x | 0.5 | 0.5 |

## APPENDIX 2. CASE SCREENING FORM

| **Case screening form** | |
|---|---|
| Hospital name:<br>Locality:<br>District:<br>Province: | Study number:<br>Patient screening number:<br>Date of visit (dd-mmm-yyyy):<br>Date illness started (dd-mmm-yyyy): |
| **Demographic data** | |
| Date of birth (dd-mmm-yyyy): or estimated age: in: ☐ months or ☐ years<br>Height (cm): Weight (kg):<br>Sex: ☐ Male ☐ Female<br>If female, is the patient pregnant? ☐ Yes ☐ No ☐ Not sure<br>If pregnant, provide the date of the last menstrual period (dd-mmm-yyyy): | |
| **Pre-treatment temperature** | |
| History of fever in previous 24 h? ☐ Yes ☐ No<br>Temperature: ºC ☐ Axillary ☐ Tympanic ☐ Rectal ☐ Oral | |
| **Thick and thin blood smears for estimation of *P. falciparum* parasite counts** | |
| Species: ☐ *P. falciparum* ☐ *P. vivax* ☐ *P.f mixed+ non-P.f species*<br>Were species other than *P. falciparum* present? ☐ Yes ☐ No **(If yes, patient is not eligible).**<br>Approximate number of *P. falciparum* asexual parasites:<br>Presence of 1–100 parasites / 3–6 white blood cells? ☐ Yes ☐ No **(If no, patient is not eligible)**<br>Presence of *P. falciparum* gametocytes? ☐ Yes ☐ No | |
| Has a blood sample for PCR been collected? ☐ Yes ☐ No | |
| Haemoglobin: g/dl Haematocrit: % | |
| **Urinary analysis (pregnancy test for female patients)** | |
| Result of pregnancy test: ☐ Positive ☐ Negative **(If positive, patient is not eligible)** | |
| **Inclusion criteria** | |
| • age between xxxxxx and xxxxxx months/years<br>• mono-infection with *P. falciparum* confirmed by positive blood smear (i.e. no mixed infection)<br>• parasitaemia between xxxxxxxxx and xxxxxxxxx/µl of asexual forms<br>• measured temperature (depending on method of measurement) or history of fever within previous 24 h<br>• ability to swallow oral medication<br>• ability and willingness to comply with the study protocol for the duration of the study | |

| |
|---|
| and to comply with the study visit schedule<br>• absence of severe malnutrition (defined as per protocol) |
| Does the patient meet all the inclusion criteria? ☐ Yes ☐ No **(If no, patient is not eligible)** |
| **Case screening form (page 2)** |
| **Exclusion criteria** |
| • signs and symptoms of severe or complicated malaria requiring parenteral treatment according to WHO criteria (Appendix 1)<br>• mixed or mono-infection with another *Plasmodium* species detected by microscopy<br>• severe malnutrition<br>• febrile conditions caused by diseases other than malaria or other known underlying chronic or severe diseases<br>• regular medication which interferes with antimalarial pharmacokinetics<br>• history of hypersensitivity reactions or contraindications to the medicine tested<br>• positive pregnancy test or breastfeeding<br>• unable to or unwilling to take contraceptives. |
| Does the patient meet any of the exclusion criteria? ☐ Yes ☐ No **(If yes, the patient is not eligible)** |
| If yes, please specify the reason for exclusion: |
| **Patient informed consent and assent** |

| | |
|---|---|
| Consent form signed: ☐ Yes ☐ No<br>Assent form signed: ☐ Yes ☐ No | Patient identity number:<br>Date (dd-mmm-yyyy): |

## APPENDIX 3. CASE REPORT FORMS

| **Case report form: follow-up day 0** | |
|---|---|
| Health centre name:<br>Locality:<br>District:<br>Province: | Study number:<br>Patient identity number:<br>Date of visit (dd-mmm-yyyy): |
| **Demographic data** | |
| Date of birth (dd-mmm-yyyy): | or estimated age: in: ☐ months or ☐ years |
| Height (cm): Weight (kg): | Sex: ☐ Male ☐ Female |
| If female, is the patient pregnant? ☐ Yes ☐ No ☐ Not sure **(If yes, patient is not eligible).**<br>If pregnant, provide the date of the last menstrual period (dd-mmm-yyyy): | |
| **Pre-treatment temperature** | |
| History of fever in previous 24 h? ☐ Yes ☐ No<br>Temperature: ºC ☐ Axillary ☐ Tympanic ☐ Rectal ☐ Oral | |
| **Thick blood smears for *P. falciparum*: quantitative parasite counts and qualitative gametocyte counts** | |
| Average number of asexual *P. falciparum* parasites/µl:<br>Presence of *P. falciparum* gametocytes? ☐ Yes ☐ No<br>Were species other than *P. falciparum* present? ☐ Yes ☐ No **(If yes, patient is not eligible).**<br>If yes, which species? ☐ *P. falciparum* ☐ *P. vivax* ☐ *P.f mixed+ non-P.f species* | |
| Has blood sample for PCR been collected? ☐ Yes ☐ No | |
| **Urinary test for antimalarial drugs** | |
| Test used: | Test result: ☐ Positive ☐ Negative |
| Test used: | Test result: ☐ Positive ☐ Negative |
| **Prior medication** | |
| All prior medication, including natural remedies and homeopathic medicines, taken within the previous 14 days should be reported in this section.<br>Has the patient taken any prior antimalarial medication? ☐ Yes ☐ No. If yes, please specify below. Either the date of stopping or the 'ongoing' box should be checked. | |

| Liver Function Tests | | |
|---|---|---|
| **Items** | **Unit** | **Value** |
| 1. Total bilirubin | mg/dL | |
| 2. Albumin | g/dL | |
| 3. ALT(SGPT)* | IU/L | |
| 4. AST(SGOT)* | IU/L | |

| | | | | | |
|---|---|---|---|---|---|
| Medicine name (generic name) | Dates | Ongoing (Yes = ☒) | Total daily dose and unit (e.g. 400 mg) | Route of administration | Indication for use |
| | Start:<br>Stop: | ☐ | | | |
| | Start:<br>Stop: | ☐ | | | |
| | Start:<br>Stop: | ☐ | | | |

| Case report form: follow-up day 0 (page 2) | | | | |
|---|---|---|---|---|
| **Medication administration** | | | | |
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |
| Name(s) of other medicine(s) | | | | |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |

| Case report form: follow-up day 1 | | | | |
|---|---|---|---|---|
| Study number:<br>Patient identity number:<br>Date of visit (dd-mmm-yyyy): | | | | |
| **Clinical status** | | | | |
| Presence of danger signs or signs of severe or complicated malaria? ☐ Yes ☐ No<br>If yes, perform thick blood smear.<br>Temperature: ºC ☐ Axillary ☐ Tympanic ☐ Rectal ☐ Oral | | | | |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** | | | | |
| Average number of asexual *P. falciparum* parasites/µl:<br>Presence of *P. falciparum* gametocytes? ☐ Yes ☐ No<br>Were species other than *P. falciparum* present? ☐ Yes ☐ No<br>If yes, which species? ☐ *P. falciparum* ☐ *P. vivax* ☐ *P.f mixed+ non-P.f species* | | | | |
| **Adverse events** | | | | |
| Presence of an adverse event? ☐ Yes ☐ No<br>If yes, name the adverse event:<br>Is it a serious adverse event? ☐ Yes ☐ No. If yes, inform the sponsor. | | | | |
| **Medication administration** | | | | |
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |
| Name(s) of other medicine(s) | | | | |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |

| Case report form: follow-up day 2 | | | | |
|---|---|---|---|---|
| Study number:<br>Patient identity number:<br>Date of visit (dd-mmm-yyyy): | | | | |
| **Clinical status** | | | | |
| Presence of danger signs or signs of severe or complicated malaria? ☐ Yes ☐ No<br>Temperature: ºC ☐ Axillary ☐ Tympanic ☐ Rectal ☐ Oral | | | | |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** | | | | |
| Average number of asexual *P. falciparum* parasites/µl:<br>Presence of *P. falciparum* gametocytes? ☐ Yes ☐ No<br>Were species other than *P. falciparum* present? ☐ Yes ☐ No<br>If yes, which species? ☐ *P. falciparum* ☐ *P. vivax* ☐ *P.f mixed+ non-P.f species* | | | | |
| **Adverse events** | | | | |
| Presence of an adverse event? ☐ Yes ☐ No<br>If yes, name the adverse event:<br>Is it a serious adverse event? ☐ Yes ☐ No. If yes, inform the sponsor. | | | | |
| **Medication administration** | | | | |
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |
| Name(s) of other medicine(s) | | | | |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |

| Case report form: follow-up day 3 |
|---|
| Study number: |
| Patient identity number: |
| Date of visit (dd-mmm-yyyy): |
| **Clinical status** |
| Presence of danger signs or signs of severe or complicated malaria? ☐ Yes ☐ No |
| Temperature: ºC ☐ Axillary ☐ Tympanic ☐ Rectal ☐ Oral |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** |
| Average number of asexual *P. falciparum* parasites/μl: |
| Presence of *P. falciparum* gametocytes? ☐ Yes ☐ No |
| Were species other than *P. falciparum* present? ☐ Yes ☐ No |
| If yes, which species? ☐ *P. falciparum* ☐ *P. vivax* ☐ *P.f mixed+ non-P.f species* |
| **Adverse events** |
| Presence of an adverse event? ☐ Yes ☐ No |
| If yes, name the adverse event: |
| Is it a serious adverse event? ☐ Yes ☐ No. If yes, inform the sponsor. |

| Liver Function Tests | | |
|---|---|---|
| **Items** | **Unit** | **Value** |
| 1. Total bilirubin | mg/dL | |
| 2. Albumin | g/dL | |
| 3. ALT(SGPT)* | IU/L | |
| 4. AST(SGOT)* | IU/L | |

| Medication administration | | | | |
|---|---|---|---|---|
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |

| Case report form: follow-up day 7 |
|---|
| Study number: |
| Patient identity number: |
| Date of visit (dd-mmm-yyyy): |
| **Clinical status** |
| Presence of danger signs or signs of severe or complicated malaria? ☐ Yes ☐ No |
| History of fever within previous 24 h? ☐ Yes ☐ No |
| Temperature: ºC ☐ Axillary ☐ Tympanic ☐ Rectal ☐ Oral |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** |
| Average number of asexual *P. falciparum* parasites/µl: |
| Presence of *P. falciparum* gametocytes? ☐ Yes ☐ No |
| Were species other than *P. falciparum* present? ☐ Yes ☐ No |
| If yes, which species? ☐ *P. falciparum* ☐ *P. vivax* ☐ *P.f mixed+ non-P.f species* |
| Has a blood sample for PCR been collected? ☐ Yes ☐ No |
| **Adverse events** |
| Presence of an adverse event? ☐ Yes ☐ No |
| If yes, name the adverse event: |
| Is it a serious adverse event? ☐ Yes ☐ No. If yes, inform the sponsor. |

| Liver Function Tests | | |
|---|---|---|
| **Items** | **Unit** | **Value** |
| 1. Total bilirubin | mg/dL | |
| 2. Albumin | g/dL | |
| 3. ALT(SGPT)* | IU/L | |
| 4. AST(SGOT)* | IU/L | |

| Medication administration | | | | |
|---|---|---|---|---|
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |

| **Case report form: follow-up day 14** | | | | |
|---|---|---|---|---|
| Study number:<br>Patient identity number:<br>Date of visit (dd-mmm-yyyy): | | | | |
| **Clinical status** | | | | |
| Presence of danger signs or signs of severe or complicated malaria? ☐ Yes ☐ No<br>History of fever within previous 24 h? ☐ Yes ☐ No<br>Temperature: ºC ☐ Axillary ☐ Tympanic ☐ Rectal ☐ Oral | | | | |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** | | | | |
| Average number of asexual *P. falciparum* parasites/µl:<br>Presence of *P. falciparum* gametocytes? ☐ Yes ☐ No<br>Were species other than *P. falciparum* present? ☐ Yes ☐ No<br>If yes, which species? ☐ *P. falciparum* ☐ *P. vivax* ☐ *P.f mixed+ non-P.f species* | | | | |
| Has a blood sample for PCR been collected? ☐ Yes ☐ No | | | | |
| **Adverse events** | | | | |
| Presence of an adverse event? ☐ Yes ☐ No<br>If yes, name the adverse event:<br>Is it a serious adverse event? ☐ Yes ☐ No. If yes, inform the sponsor. | | | | |
| **Medication administration** | | | | |
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |
| Name(s) of other medicine(s) | | | | |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |

| **Case report form: follow-up day 21** | | | | |
|---|---|---|---|---|
| Study number: | | | | |
| Patient identity number: | | | | |
| Date of visit (dd-mmm-yyyy): | | | | |
| **Clinical status** | | | | |
| Presence of danger signs or signs of severe or complicated malaria? ☐ Yes ☐ No | | | | |
| History of fever within previous 24 h? ☐ Yes ☐ No | | | | |
| Temperature: ºC ☐ Axillary ☐ Tympanic ☐ Rectal ☐ Oral | | | | |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** | | | | |
| Average number of asexual *P. falciparum* parasites/µl: | | | | |
| Presence of *P. falciparum* gametocytes? ☐ Yes ☐ No | | | | |
| Were species other than *P. falciparum* present? ☐ Yes ☐ No | | | | |
| If yes, which species? ☐ *P. falciparum* ☐ *P. vivax* ☐ *P.f mixed+ non-P.f species* | | | | |
| Has a blood sample for PCR been collected? ☐ Yes ☐ No | | | | |
| **Adverse events** | | | | |
| Presence of an adverse event? ☐ Yes ☐ No | | | | |
| If yes, name the adverse event: | | | | |
| Is it a serious adverse event? ☐ Yes ☐ No. If yes, inform the sponsor. | | | | |
| **Medication administration** | | | | |
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |
| Name(s) of other medicine(s) | | | | |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |

| **Case report form: follow-up day 28** |
|---|
| Study number: |
| Patient identity number: |
| Date of visit (dd-mmm-yyyy): |

| **Clinical status** |
|---|
| Presence of danger signs or signs of severe or complicated malaria? ☐ Yes ☐ No |
| History of fever within previous 24 h? ☐ Yes ☐ No |
| Temperature: ºC ☐ Axillary ☐ Tympanic ☐ Rectal ☐ Oral |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** |
| Average number of asexual *P. falciparum* parasites/µl: |
| Presence of *P. falciparum* gametocytes? ☐ Yes ☐ No |
| Were species other than *P. falciparum* present? ☐ Yes ☐ No |
| If yes, which species? ☐ *P. falciparum* ☐ *P. vivax* ☐ *P.f mixed+ non-P.f species* |
| Has a blood sample for PCR been collected? ☐ Yes ☐ No |
| **Adverse events** |
| Presence of an adverse event? ☐ Yes ☐ No |
| If yes, name the adverse event: |
| Is it a serious adverse event? ☐ Yes ☐ No. If yes, inform the sponsor. |

| **Liver Function Tests** | | |
|---|---|---|
| **Items** | **Unit** | **Value** |
| 1. Total bilirubin | mg/dL | |
| 2. Albumin | g/dL | |
| 3. ALT(SGPT)* | IU/L | |
| 4. AST(SGOT)* | IU/L | |

| **Medication administration** | | | | |
|---|---|---|---|---|
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |

| **Case report form: day ___( any other day that is not part of regular follow-up)** | | | | |
|---|---|---|---|---|
| Study number:<br>Patient identity number:<br>Date of visit (dd-mmm-yyyy): | | | | |
| **Clinical status** | | | | |
| Presence of danger signs or signs of severe or complicated malaria? ☐ Yes ☐ No<br>History of fever within previous 24 h? ☐ Yes ☐ No<br>Temperature: ºC ☐ Axillary ☐ Tympanic ☐ Rectal ☐ Oral | | | | |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** | | | | |
| Average number of asexual *P. falciparum* parasites/µl:<br>Presence of *P. falciparum* gametocytes? ☐ Yes ☐ No<br>Were species other than *P. falciparum* present? ☐ Yes ☐ No<br>If yes, which species? ☐ *P. falciparum* ☐ *P. vivax* ☐ *P.f mixed+ non-P.f species* | | | | |
| Has a blood sample for PCR been collected? ☐ Yes ☐ No | | | | |
| **Adverse events** | | | | |
| Presence of an adverse event? ☐ Yes ☐ No<br>If yes, name the adverse event:<br>Is it a serious adverse event? ☐ Yes ☐ No. If yes, inform the sponsor. | | | | |
| **Medication administration** | | | | |
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |
| Name(s) of other medicine(s) | | | | |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |

| Case report form: follow-up day 35 | | | | |
|---|---|---|---|---|
| Study number:<br>Patient identity number:<br>Date of visit (dd-mmm-yyyy): | | | | |
| **Clinical status** | | | | |
| Presence of danger signs or signs of severe or complicated malaria? ☐ Yes ☐ No<br>History of fever within previous 24 h? ☐ Yes ☐ No<br>Temperature: ºC ☐ Axillary ☐ Tympanic ☐ Rectal ☐ Oral | | | | |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** | | | | |
| Average number of asexual *P. falciparum* parasites/μl:<br>Presence of *P. falciparum* gametocytes? ☐ Yes ☐ No<br>Were species other than *P. falciparum* present? ☐ Yes ☐ No<br>If yes, which species? ☐ *P. falciparum* ☐ *P. vivax* ☐ *P.f mixed+ non-P.f species* | | | | |
| Has a blood sample for PCR been collected? ☐ Yes ☐ No | | | | |
| **Adverse events** | | | | |
| Presence of an adverse event? ☐ Yes ☐ No<br>If yes, name the adverse event:<br>Is it a serious adverse event? ☐ Yes ☐ No. If yes, inform the sponsor. | | | | |
| **Medication administration** | | | | |
| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |
| Name(s) of other medicine(s) | | | | |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |

| **Case report form: final day of follow-up (28/42)** |
|---|
| Study number: |
| Patient identity number: |
| Date of visit (dd-mmm-yyyy): |
| **Clinical status** |
| Presence of danger signs or signs of severe or complicated malaria? ☐ Yes ☐ No |
| History of fever within previous 24 h? ☐ Yes ☐ No |
| Temperature: ºC ☐ Axillary ☐ Tympanic ☐ Rectal ☐ Oral |
| **Thick blood smears for estimation of *P. falciparum* parasite counts** |
| Average number of asexual *P. falciparum* parasites/µl: |
| Presence of *P. falciparum* gametocytes? ☐ Yes ☐ No |
| Were species other than *P. falciparum* present? ☐ Yes ☐ No |
| If yes, which species? ☐ *P. falciparum* ☐ *P. vivax* ☐ *P.f mixed+ non-P.f species* |
| Has a blood sample for PCR been collected? ☐ Yes ☐ No |
| **Adverse events** |
| Presence of an adverse event? ☐ Yes ☐ No |
| If yes, name the adverse event: |
| Is it a serious adverse event? ☐ Yes ☐ No. If yes, inform the sponsor. |
| **Medication administration** |

| Name(s) of antimalarial drug(s) | Time of dose (hh:min) | Number of tablets | Did the patient vomit? | Time of vomiting (hh:min) |
|---|---|---|---|---|
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |
| Name(s) of other medicine(s) | | | | |
| | | | ☐ Yes ☐ No | |
| | | | ☐ Yes ☐ No | |

| **Urinary analysis (pregnancy test for female patients)** |
|---|
| **Patients with a positive pregnancy test must be followed up for 6–8 weeks after delivery** |
| Result of pregnancy test: ☐ Positive ☐ Negative Date of test (dd-mmm-yyyy): |
| If the patient is pregnant, follow-up of the pregnancy is required, including: clinical examination of the infant at birth and 6-8 weeks after birth. Please provide comments below. If needed fill in |

the serious adverse event report form:

**Case report form: final day of follow-up (28/42) (page 2)**

**Overall assessment**

Outcome:

- ☐ adequate clinical and parasitological response
- ☐ early treatment failure
- ☐ late clinical failure
- ☐ late parasitological failure
- ☐ lost to follow-up
- ☐ withdrawn

Outcome occurred on follow-up day: (e.g. 1, 2, 3, 7, 14, …)

PCR:

- ☐ *P. falciparum* recrudescence
- ☐ *P. falciparum* reinfection
- ☐ other species
- ☐ mixed with *P. falciparum* recrudescence
- ☐ mixed with *P. falciparum* reinfection
- ☐ unknown

PCR corrected results:

- ☐ adequate clinical and parasitological response
- ☐ early treatment failure
- ☐ late clinical failure
- ☐ late parasitological failure
- ☐ lost to follow-up
- ☐ withdrawn

Reason for withdrawal:

| |
|---|
| Other comments: |

## APPENDIX 4. SERIOUS ADVERSE EVENT REPORT FORM

| **Serious adverse event report form** | |
|---|---|
| Health centre name:<br>Locality:<br>District:<br>Province: | Study number:<br>Patient identity number:<br>Date of visit (dd-mmm-yyyy):<br>Follow-up day: |
| **Demographic data** | |
| Date of birth (dd-mmm-yyyy): or estimated age: in: ☐ months or ☐ years<br>Height (cm): Weight (kg):<br>Sex: ☐ Male ☐ Female<br>If female, is the patient pregnant? ☐ Yes ☐ No ☐ Not sure<br>If pregnant, provide the date of the last menstrual period (dd-mmm-yyyy): | |
| **Serious adverse event** | |
| Type of event:<br>☐ Death<br>☐ Life-threatening<br>☐ Hospitalization or prolongation of hospitalization<br>☐ Permanent disability<br>☐ Congenital anomaly or birth defect<br>Date of occurrence (dd-mmm-yyyy): | |
| Describe the serious adverse event (include all relevant laboratory results): | |
| Describe how the reaction was treated: | |

| |
|---|
| |

| **Serious adverse event report form (page 2)** |
|---|
| Comments (e.g. relevant medical history, drug allergies, previous exposure to similar drugs, other laboratory data, whether reaction abated after stopping the drug, whether reaction reappeared after reintroduction): |
| **Outcome** |
| ☐ Recovered completely<br>☐ Not yet recovered<br>☐ Recovered with long-term consequences<br>If patient recovered, provide date of recovery (dd-mmm-yyyy): |
| **Medicines** (list the **medicine suspected of causing** the serious adverse event as well as all **concomitant medicines**) |

| Brand name, batch number, manufacturer name (list suspected medicine first) | Daily dose | Route | Start date | End date | Indications for use |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |

| Reporting officer | |
|---|---|
| Name: | |
| Qualification: | |
| Address: | |
| Phone: | |
| Fax: | |
| Email: | |
| Signature: | Date: |

## APPENDIX 5. GUIDELINES FOR ANALYSIS OF RESULTS

| End-point for day X (X = 28 or 42) | PCR-uncorrected results | |
|---|---|---|
| | Cumulative success or failure rate (Kaplan-Meier analysis) | Proportion (per-protocol analysis) |
| Adequate clinical and parasitological response on day X | Success | Success |
| Early treatment failure | Failure | Failure |
| Late clinical failure before day 7 | Failure | Failure |
| Late clinical failure or late parasitological failure on or after day 7 | Failure | Failure |
| Other species infection | Censored day of infection | Excluded from analysis |
| Lost to follow-up | Censored last day of follow-up according to timetable | Excluded from analysis |
| Withdrawal and protocol violation | Censored last day of follow-up according to timetable before withdrawal or protocol violation | Excluded from analysis |

| End-point for day X (X = 28 or 42) | PCR-corrected results | |
|---|---|---|
| | Cumulative success or failure rate (Kaplan-Meier analysis) | Proportion (per-protocol analysis) |
| Adequate clinical and parasitological response at day X | Success | Success |
| Early treatment failure | Failure | Failure |
| Late clinical failure before day 7 | Failure | Failure |
| Late clinical failure or late parasitological failure on or after day 7 | | |
| • falciparum recrudescence* | Failure | Failure |
| • falciparum reinfection* | Censored day of reinfection | Excluded from analysis |
| • other species mixed with falciparum recrudescence | Failure | Failure |
| • other species mixed with falciparum reinfection | Censored day of reinfection | Excluded from analysis |
| • other species infection | Censored day of infection | Excluded from analysis |
| • undetermined or missing PCR | Excluded from analysis | Excluded from analysis |
| Lost to follow-up | Censored last day of follow-up according to timetable | Excluded from analysis |
| Withdrawal and protocol violation | Censored last day of follow-up according to timetable before protocol violation or withdrawal | Excluded from analysis |

* WHO. *Methods and techniques for clinical trials on antimalarial drug efficacy: genotyping to identify parasite populations*. Geneva, World Health Organization, 2008 (http://www.who.int/malaria/resistance).

# An informed consent form for adults

This informed consent form is for adults over 18 years of age who attend _____, who has been invited to participate in a study to evaluate the efficacy of Pyramax of for the treatment of uncomplicated falciparum malaria.

| | |
|---|---|
| Name of principal investigator: | Leang Rithea |
| Name of organization: | National Centre for Parasitology, Entomology and Malaria Control |
| Name of sponsor: | Ministry of Health, Cambodia |
| Name of proposal and version: | Monitoring and evaluation of the therapeutic efficacy and safety of pyronaridine-artesunate for the treatment of uncomplicated falciparum malaria in western Cambodia, an area of artemisinin-resistant falciparum malaria, Version 1 |

This informed consent form has two parts:

I. Information sheet (to share information about the study with you)

II. Certificate of consent (for signatures if you agree to take part)

You will be given a copy of the full informed consent form.

## Part I. Information sheet

My name is_____, and I work for the Ministry of Health. We are doing a study on the treatment of malaria. Malaria is a dangerous disease; however, it can be treated with medicine. The purpose of this study is to confirm that the medicine, called **pyronaridine-artesunate** or **Pyramax** is still effective for curing malaria.

We are inviting all adults and children aged at least 7 years living in this area to take part in this study.

I am going to give you information and invite you to participate in this surveillance study. Before you decide whether to participate, you can talk to anyone you feel comfortable with. There may be some words that you do not understand. Please ask me to stop as we go through the information, and I will take time to explain. If you have questions later, you can ask me, the study doctor or the staff.

Your participation in this study is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this project, we will offer the treatment that is routinely provided in this clinic for malaria, and we will tell you more about it later. You may change your mind later and stop participating even if you agreed earlier.

You will receive_____doses of medicine over 3 days. **Pyronaridine-artesunate** is recommended by the Ministry of Health. The Ministry regularly conducts studies to make sure the medicine is still working. This medicine is known to be very effective, but you should know that it has some minor side-effects **pyronaridine-artesunate** or **Pyramax**

If we find that the medicine is not working, we will use what is called 'rescue medicine'. This medicine is called **pyronaridine-artesunate** or **Pyramax** and is given over 3 days. You should

know that this medicine has some minor side-effects such as headache, dizziness, anorexia, splenomegaly or cough.

The study will take place over 42 days. During that time, you will have to come to the health facility for 1 hour each day for 9 days according to the scheduled dates given to you. At the end of 6 weeks, the study will be finished. At each visit, you will be examined by a physician.

Today, we will take urine and blood for testing and you will receive the first dose of treatment.

On the

- 2nd visit: you will receive the 2nd dose of treatment.
- 3rd visit: you will receive the 3rd dose of treatment plus a blood test.
- 4th, 5th, 6th, 7th, 8th, 9th and 10th visits, you will have a blood test.

The urine will be tested for the presence of other medicines used to treat malaria. For the blood test, a small amount of blood will be taken from your finger. You may experience a bit of pain or fear when your finger is pricked. The pain should disappear within 1 day. The blood will be dropped onto a slide and a small piece of paper. The blood samples will be used to study the malaria in your blood. The examination of some of the blood samples will be done after the study and it will not affect the success of the treatment. Nothing else will be done with your blood.

If you do not attend the scheduled visit, we will visit you at home.

As already mentioned, this medicine an have some minor side effects. It is also possible that it may cause some problems that we are not aware of; however, we will follow you closely and keep track of these effects, if they arise, and of any other problems. We will give you a telephone number to call if you notice anything out of the ordinary or if you have concerns or questions. You can also come to this health facility at any time and ask to see Dr._____If you experience side-effects, we may use some other medicine, free of charge, which will help to reduce the symptoms or reactions, or we may stop one or more of the medicines. If this is necessary we will discuss it together. You will always be consulted before we move to the next step.

If you decide to participate in this study, any illnesses related to malaria or to the malaria treatment will be treated at no charge to you. Your participation will help us to make sure the medicine is still working, and this will benefit society and future generations. We will give you _____ to pay for your travel expenses to the clinic and a bednet.

We will not share the identity of participants in the study with anyone. The information that we collect from this study will be kept confidential. Any information collected about you will have a number on it instead of your name. Only the study team members will know what your number is, and we will lock that information up.

We will share the knowledge that we get from this study with you before it is made available to the public. Confidential information will not be shared. There will be small meetings in the community, and these will be announced. Afterwards, we will publish the results and make them available so that other interested people may learn from our study.

This proposal has been reviewed and approved by National Health Ethics Committee at Ministry of Cambodia and Ethics Committee of WHO Regional Office in Manila. This is a committee that

makes sure that study participants are protected from harm. If you wish to find about more about the institutional review board, you may contact Dr._____ with phone number:_____

**Part II. Certificate of consent**

I have been invited to participate in a study of a medicine used to treat malaria.

I have read the above information, or it has been read to me. I have had the opportunity to ask questions, and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate in this study.

Print name of participant: _____

Signature of participant: _____

Date: _____
(dd/mmm/yyyy)

**Witness' signature:** (A witness' signature and the patient's thumbprint are required only if the patient is illiterate. In this case, a literate witness must sign. If possible, this person should be selected by the participant and should have no connection with the study team.)

I have witnessed the accurate reading of the consent form to the potential participant, who has had the opportunity to ask questions. I confirm that the participant has given consent freely.

Print name of witness: _____ and thumbprint of participant:

Signature of witness: _____

Date: _____
(dd/mmm/yyyy)

**Investigator's signature:**

I have accurately read or witnessed the accurate reading of the consent form to the potential participant, who has had the opportunity to ask questions. I confirm that the participant has given consent freely.

Print name of investigator: _____

Signature of investigator: _____

Date: _____
(dd/mmm/yyyy)

A copy of this informed consent form has been provided to the participant. _____ (initials of the principal investigator or assistant).

## An informed consent form for children or minors

This informed consent form is for parents or guardians of children aged at least 7 years who attend the health facility_____ who have been invited to participate in a study to evaluate the efficacy of **Pyronaridine-artesunate** for the treatment of uncomplicated falciparum malaria.

| | |
|---|---|
| Name of principal investigator: | Leang Rithea |
| Name of organization: | National Centre for Parasitology, Entomology and Malaria Control |
| Name of sponsor: | Ministry of Health, Cambodia |
| Name of proposal and version: | Monitoring and evaluation of the therapeutic efficacy and safety of pyronaridine-artesunate for the treatment of uncomplicated falciparum malaria in western Cambodia, an area of artemisinin-resistant falciparum malaria, Version 1 |

This informed consent form has two parts:

I. Information sheet (to share information about the study with you)

II. Certificate of consent (for signatures if you agree to take part)

You will be given a copy of the full informed consent form.

### Part I: Information sheet

My name is_____, and I work for the Ministry of Health. We are doing a study on the treatment of malaria. Malaria is a dangerous disease; however, it can be treated with medicine. The purpose of this study is to confirm that the medicine, called **pyronaridine-artesunate** or **Pyramax**, is still effective for curing malaria.

We are inviting all adults and children aged at least 7 years living in this area to take part in this study.

I am going to give you information and invite you to consent to have your child participate in this study. Before you decide whether you want your child to participate, you can talk to anyone you feel comfortable with. There may be some words that you do not understand. Please ask me to stop as we go through the information, and I will take time to explain. If you have questions later, you can ask me, the study doctor or the staff.

Your decision to have your child participate in this study is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services your child receives at this clinic will continue and nothing will change. If you choose your child should not participate in this project, we will offer the treatment that is routinely provided in this clinic for malaria, and we will tell you more about it later. You may change your mind later and stop participating even if you agreed earlier.

Your child will receive_____ doses of medicine over 3 days. The medicine, (give chemical name), is recommended by the Ministry of Health. As the parasites that cause malaria can become resistant to the medicine, the Ministry regularly does studies to make sure the medicine is still working. The medicine is made by (give company name); it is produced with the trade name **Pyramax**. This medicine is known to be very effective, but you should know that it has some

minor side-effects such as fatigue, nausea, abdominal pain, dark urine, putty or mastic coloured stools, jaundice (yellowing of the whites of the eyes or skin) and itching

If we find that the medicine is not working, we will use what is called 'rescue medicine'. The medicine is called **pyronaridine-artesunate** or **Pyramax** and is given over x days. You should know that this medicine has some minor side-effects such as headache, dizziness, anorexia, splenomegaly or cough.

The study will take place over 42 days. During that time, your child will have to come to the health facility for 1 hour each day for 9 days according to the scheduled dates given to you. At the end of 6 weeks, the study will be finished. At each visit, your child will be examined by a physician. You may stay with your child during each of the visits and during the procedures.

Today, we will take urine and blood for testing and your child will receive the first dose of treatment.

On the

- 2nd visit, your child will receive the 2nd dose of treatment.
- 3rd visit, your child will receive the 3rd dose of treatment plus a blood test.
- 4th, 5th, 6th, 7th, 8th, 9th and 10th visits, your child will have a blood test.

The urine will be tested for the presence of other medicines used to treat malaria.For the blood test, a small amount of blood will be taken from your child's finger or heel. Your child may experience a bit of pain or fear when the finger or the heel is pricked. The pain should disappear within 1 day. The blood will be dropped onto a slide and a small piece of paper. The blood samples will be used to study the malaria in your child's blood. The examination of some of the blood samples will be done after the study and it will not affect the success of the treatment. Nothing else will be done with the blood.

If you do not attend the scheduled visit, we will visit you at home.

As already mentioned, this medicine and have some minor side effects. It is also possible that it may cause some problems that we are not aware of; however, we will follow your child closely and keep track of these effects, if they arise, and of any other problems. We will give you a telephone number to call if you notice anything out of the ordinary or if you have concerns or questions. You can also bring your child to this health facility at any time and ask to see Drd_____. If your child experiences side-effects, we may use some other medicine, free of charge, which will help to reduce the symptoms or reactions, or we may stop one or more of the medicines. If this is necessary we will discuss it together. You will always be consulted before we move to the next step.

If you decide that your child will participate in this study, any illnesses related to malaria or to the malaria treatment will be treated at no charge to you. Your child's participation will help us to make sure the medicine is still working, and this will benefit society and future generations. We will give you _____ to pay for your travel expenses to the clinic and a bednet.

We will not share the identity of participants in the study with anyone. The information that we collect from this study will be kept confidential. Any information collected about your child will have a number on it instead of your child's name. Only the study team members will know what the number is, and we will lock that information up.

We will share the knowledge that we get from this study with you before it is made available to the public. Confidential information will not be shared. There will be small meetings in the community, and these will be announced. Afterwards, we will publish the results and make them available so that other interested people may learn from our study.

This proposal has been reviewed and approved National Health Ethics Committee at Ministry of Cambodia and Ethics Committee of WHO Regional Office in Manila. This is a committee that makes sure that study participants are protected from harm. If you wish to find about more about the institutional review board, you may contact Dr._____and phone number:_____

**Part II: Certificate of consent**

I have been invited to have my child participate in a study of a medicine used to treat malaria.

I have read the above information, or it has been read to me. I have had the opportunity to ask questions, and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to my child's participation in this study.

Print name of participant: _____

Print name of parent or guardian: _____

Signature of parent or guardian: _____

Date: _____
(dd/mmm/yyyy)

**Witness' signature:** (A witness' signature and the thumbprint of the participant's parent or guardian are required only if the parent or guardian is illiterate. In this case, a literate witness must sign. If possible, this person should be selected by the participant's parent or guardian and should have no connection with the study team.)

I have witnessed the accurate reading of the consent form to the potential participant's parent or guardian, who has had the opportunity to ask questions. I confirm that the participant's parent or guardian has given consent freely.

Print name of witness: _____ and thumbprint of parent/guardian:

Signature of witness: _____

Date: _____
(dd/mmm/yyyy)

**Investigator's signature:**

I have accurately read or witnessed the accurate reading of the consent form to the potential participant's parent or guardian, who has had the opportunity to ask questions. I confirm that the participant's parent or guardian has given consent freely.

Print name of investigator: _____

Signature of investigator: _____

Date: _____
(dd/mmm/yyyy)

A copy of this informed consent form has been provided to participant's parent or guardian. _____ (initials of the principal investigator/assistant).

An informed assent form will _____ or will not _____ be completed.

## An informed assent form

This informed assent form is for children aged 12–18 years who attend (indicate name of the sentinel site clinic) and who have been invited to participate in a study designed to evaluate the efficacy of (name of the antimalarial drug(s) of drug combination(s)) for the treatment of uncomplicated falciparum malaria.

| | |
|---|---|
| Name of principal investigator: | Leang Rithea |
| Name of organization: | National Cenetre for Parasitology, Entomolgoy and Malaria Control |
| Name of sponsor: | Ministry of Health, Cambodia |
| Name of proposal and version: | Monitoring and evaluation of the therapeutic efficacy and safety of pyronaridine-artesunate for the treatment of uncomplicated falciparum malaria in western Cambodia, an area of artemisinin-resistant falciparum malaria, Version 1 |

This informed assent form has two parts:

I. Information sheet (to share information about the study with you)

II. Certificate of assent (for signatures if you agree to take part)

You will be given a copy of the full informed assent form.

### Part I. Information sheet

My name is_____, and I work for the Ministry of Health. We are doing a study on the treatment of malaria. Malaria is a dangerous disease; however, it can be treated with medicine. The purpose of this study is to confirm that the medicine, called (give chemical and trade names of the drug), is still effective for curing malaria.

We are inviting all adults and children at least 7 years living in this area to take part in this study.

I am going to give you information and invite you to participate in this study. You can choose whether you want to participate. We have discussed this study with your parent(s) or guardian, and they know that we are also asking you for your agreement. If you decide to participate in the study, your parent(s) or guardian also have to agree. If you do not wish to take part in the study, you do not have to, even if your parents have agreed. It is your choice. If you decide not to participate, nothing will change; this is still your clinic. Even if you say 'Yes' now, you can change your mind later and it will still be okay. You may discuss anything in this form with your parents or friends or anyone else you feel comfortable talking to. There may be some words you do not understand or things that you want me to explain more because you are interested or concerned. Please ask me to stop at any time, and I will take time to explain.

**Interviewer:** I have checked with the child, and he or she understands that participation is voluntary. _____ (initials)

You will receive x doses of medicine over x days. The medicine, Pyramax is recommended by the Ministry of Health. The Ministry regularly conducts studies to make sure the medicine is still working. The medicine is made by Sympoon it is produced with the trade name Pyramax. This medicine is known to be very effective, but you should know that it has some minor side-effects

such as fatigue, nausea, abdominal pain, dark urine, putty or mastic coloured stools, jaundice (yellowing of the whites of the eyes or skin) and itching.

The study will take place over 42 days. During that time, you will have to come to the health facility for 1 hour each day for 9 days. At the end of 6 weeks, the study will be finished.

A small amount of urine will be taken once. It will be tested for the presence of other medicines used to treat malaria. A small amount of blood will be taken from your finger, today and once at each visit during the follow-up, except tomorrow. You may experience a bit of pain or fear when your finger is pricked. The blood will be dropped onto a slide and a small piece of paper. The blood samples will be used to study the malaria in your blood. The examination of some of the blood samples will be done after the study and it will not affect the success of the treatment. Nothing else will be done with your blood.

**Interviewer:** I have checked with the child, and he or she understands the procedures. _____ (initials)

The medicine can have some unwanted effects or some effects that we are not currently aware of; however, we will follow you closely and keep track of any unwanted effects, if they arise, or any other problems. If anything unusual happens to you, we need to know, and you should feel free to call us any time with your concerns or questions. If you get sick or have concerns or questions between scheduled visits to clinic, you should let me or the staff nurse know. You do not have to wait for a scheduled visit. We have also given your parents information about what to do if you are hurt or get sick during the study.

**Interviewer:** I have checked with the child, and he or she understands the risks and discomforts. _____ (initials)

If you decide to participate in this study, any illnesses related to malaria or to the malaria treatment will be treated at no charge to you. Your participation will help us to make sure the medicine is still working, and this will benefit society and future generations.

**Interviewer:** I have checked with the child, and he or she understands the benefits. _____ (initials)

Because you live quite far from the clinic, we will give your parents or guardian enough money to pay for the trip here and back and a bednet.

We will not tell other people that you are participating in this study, and we will not share information about you with anyone who does not work in the study. Information about you that will be collected from the study will be put away, and no one but the study team will be able to see it. Any information about you will have a number on it instead of your name. Only the study team will know what your number is, and we will lock that information up.

When we have finished the research, I will sit down with you and your parent or guardian and tell you about what we learnt. Afterwards, we will be telling more people, scientists and others, about the study and what we found. We will do this by writing and sharing reports and data and by going to meetings with people who are interested in the work we do.

You can ask me questions now or later. You can ask the nurse questions. I have written a number and address where you can reach us or, if you are nearby, you can come and see us. If you want to talk to someone else whom you know, like your teacher, doctor or auntie, that is okay too.

**Part II: Certificate of assent**

I have been invited to participate in a study of the efficacy of an antimalarial medicine. I have read this information (or had the information read to me), and I understand it. I have had my questions answered and know that I can ask questions later if I have them. I agree to take part in the study. _____ (initials)

or I do not wish to take part in the study and I have not signed the assent below. _____ (initials)

**Child's signature (only if the child assents):**

Print name of child: _____

Signature of child: _____

Date: _____
(dd/mmm/yyyy)

**Witness' signature:** (A witness' signature and the child's thumbprint are required only if the child is illiterate. In this case, a literate witness must sign. If possible, this person should be selected by the participant and should have no connection with the study team.)

I have witnessed the accurate reading of the assent form to the potential participant, who has had the opportunity to ask questions. I confirm that the participant has given consent freely.

Print name of witness: _____

Signature of witness: _____

Date: _____
(dd/mmm/yyyy)

and thumbprint of the child or minor:

**Investigator's signature:**

I have accurately read or witnessed the accurate reading of the assent form to the potential participant, who has had the opportunity to ask questions. I confirm that the participant has given consent freely.

Print name of investigator: _____

Signature of investigator: _____

Date: _____
(dd/mmm/yyyy)

A copy of this informed assent form has been provided to the participant. _____ (initials of the principal investigator or assistant).

# A consent statement for a pregnancy test

I have been invited to participate in a study on the medicine used to treat malaria. I have been asked to supply a specimen of urine at the first visit and at day 42 or on the day of withdrawal from the study, all of which will be used for pregnancy testing. I understand that the results of the tests will be kept fully confidential and anonymous. I understand that I must avoid becoming pregnant during the study because the medicine I will be taking would be dangerous for my child. I have discussed the different methods of birth control with my doctor, and I have been offered _____I understand that if the test is positive, I will not be eligible to participate in this study.

**Participant's signature:**

I accept to be tested. _____ (participant's initials) or

I do not want to be tested, and I have not signed the consent form below. _____ (participant's initials)

Print name of participant: _____

Signature of participant: _____

Date: _____
(dd/mmm/yyyy)

**Witness' signature:** (A witness' signature and the thumbprint of the participant are required only if the participant is illiterate. In this case, a literate witness must sign. If possible, this person should be selected by the participant and should have no connection with the study team.)

I have witnessed the accurate reading of the consent form to the potential participant, who has had the opportunity to ask questions. I confirm that the participant has given consent freely.

Print name of witness: _____ and thumbprint of the participant:

Signature of witness: _____

Date: _____
(dd/mmm/yyyy)

**Investigator's signature:**

I have accurately read or witnessed the accurate reading of the consent form to the potential participant, who has had the opportunity to ask questions. I confirm that the participant has given consent freely.

Print name of investigator: _____

Signature of investigator: _____

Date: _____
(dd/mmm/yyyy)

A copy of this consent statement has been provided to participant. _____ (initials of the principal investigator or assistant).