Phase 2a dose escalation study of the efficacy, safety and pharmacokinetics of low single-dose primaquine for gametocytocidal activity against *P. falciparum* in sub-Saharan Africa.

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List of abbreviations

AE: adverse event
CRF: case reporting form
DNA: deoxyribonucleic acid
DP: dihydroartemisinin -piperaquine
DSMC: data and safety monitoring committee
EC: ethics committee
EDTA: Ethylenediaminetetraacetic acid
ELISA: enzyme-linked immunosorbent assay
GCP: good clinical practice
G6PD: glucose-6-phosphate dehydrogenase
MDA: mass drug administration
MRCT: Malaria Research and Training Center
PCR: polymerase chain reaction
P. falciparum: plasmodium falciparum
PQ: primaquine
QT-NASBA: quantitative nucleic acid sequence-based amplification
RT-qPCR: quantitative reverse transcriptase polymerase chain reaction
SAE: serious adverse event
WHO: World Health Organization
**Background**

The success of malaria control programs in reducing malaria transmission in many areas has led to the call for elimination. As malaria transmission reduces, traditional tools of malaria control such as indoor residual spraying and insecticide treated bed nets lose their effectiveness at further reducing transmission because transmission occurs outside the house mediated by outdoor or early evening biting vectors. In addition, countries that have reached low endemicity have large malaria free areas susceptible to re-introduction of the parasites through the movement of infected people. Thus, new tools that can target an alternative part of the parasite lifecycle would add to current malaria control strategies. Such a strategy could involve targeting the parasite in humans [1].

One such tool for targeting the parasite in humans is primaquine. Developed in the 1940s this 8-aminoquinoline has been licensed for the radical treatment of *P. vivax* and *P. ovale* infections because of its unique ability to kill the dormant liver form of these parasites. For this indication primaquine is usually prescribed over 14 days of treatment (7mg/kg total dose) administered once per day [2]. Besides the use in the radical cure of vivax or ovale malaria, primaquine has been used to prevent infection. This recommendation is adopted as policy in 20 countries worldwide [3]. Primaquine has a unique gametocytocidal action against mature (stage V) gametocytes that no other registered antimalarial has. Thus, in combination with an antimalarial that is effective on the asexual stages, primaquine can prevent onward transmission. The World Health Organization (WHO) recommends single dose primaquine (0.75 mg/kg) in the treatment of *P. falciparum* to prevent the transmission of gametocytes.

**Statement of the problem**

The safety of standard single dose primaquine

The single dose of 0.75 mg/kg primaquine for the clearance of *P. falciparum* gametocytes is based on “expert opinion” [4]. The safety of this primaquine dose is questionable. There is little evidence that the currently recommended dose is appropriate - a lower dose may be equally efficacious. The recommendation originates from historic safety data including 50,000 U.S. military personnel based in Korea [5]. The weekly administration of 45mg of primaquine for prophylaxis against *P. falciparum* malaria was shown to be well-tolerated in 15 primaquine-sensitive African American and 15 non-sensitive healthy adults [6], in one glucose-6-phosphate dehydrogenase (G6PD) deficient African American [7], and 250 Turkish military forces based in Korea [5]. One member of the Turkish force determined to be G6PD deficient did not show a clinical toxic reaction [5]. A study in the late 1950s administering 0.55-1.1 mg/kg primaquine, noted a decrease in hematocrit with daily but not weekly administration in 11 G6PD deficient African Americans [8]. No change in hematocrit with weekly administration in 64 Caucasian and 28 African American individuals, and no marked decrease in hemoglobin in 235 east African children of unknown G6PD status was seen [8]. The hemolytic reaction was noted to be more severe in G6PD deficient Caucasians than African Americans when given 45mg of primaquine although the duration of hemolysis was similar [9]. More recent studies co-administering 0.75mg/kg of primaquine to treat *P. falciparum* gametocytes in Africa
show mixed results. One study in eastern Sudan showed that the addition of primaquine to artesunate-sulfadoxine-pyrimethamine resulted in no difference in the mean packed cell volume on day 7 [10], whereas a study in Tanzania using the same drug regimen showed marked reduction in hemoglobin with primaquine which was most pronounced in G6PD deficient (G6PD A-) children (-2.5g/dl) compared to those with wild-type genotype (G6PD B) (-0.5g/dl) [11]. Furthermore, many patients (4.5%) classified as G6PD normal developed moderate anemia [11]. In G6PD deficient individuals receiving the 0.75 mg/kg dose, there is significant evidence of risk of hemolysis [12, 13, 14, 15].

Our review suggests that there are small but real risks of hemolysis associated with the administration of single dose of 45 mg primaquine. This risk is most pronounced in G6PD deficient individuals. Unfortunately there is currently no field-ready, reliable, and affordable rapid point of care test for G6PD deficiency. A test with such attributes is currently being developed but will not be available for several years. Furthermore there remains a small risk of primaquine-related adverse events in G6PD-normal people.

Finding a safe lower yet efficacious primaquine dose is of critical importance for the reduction of transmission, allowing for administration to everyone in targeted or mass campaigns (MDA), including G6PD deficient individuals. Lower doses of primaquine can be highly effective at reducing gametocyte carriage and infectivity to mosquitoes [12]. There is evidence suggesting that doses as low as 0.1 mg/kg or less could be gametocytocidal [12]. Low dose primaquine is likely to have an improved safety profile. The first step is to identify the lowest efficacious dose in those with the lowest safety risk. Thus, we plan a dose escalation study to identify the lowest efficacious dose in malaria infected G6PD normal male adults that can be tested later in G6PD deficient individuals.

Objectives

Primary specific objective

1. Assess the change of infectivity of gametocytes from malaria infected patients following the administration of different doses of primaquine (PQ) combined with dihydroartemisinin-piperaquine (DP) in adults without G6PD deficiency.

Secondary specific objectives

1. Assess the safety of different doses of PQ combined with DP in malaria infected adults without G6PD deficiency
2. Determine the pharmacokinetics of PQ in malaria infected adults without G6PD deficiency
3. Explore cytochrome p450 polymorphisms in malaria infected adults without G6PD deficiency

Study design

This is a phase 2a dose escalation study. The study design is adaptive, meaning that earlier doses of drug tested will inform on whether a subsequent group is needed. The study will be conducted sequentially:
1. Adult G6PD-normal malaria patients will be enrolled and treated with DP and randomized to one of the following three doses of primaquine (PQ): 0, 0.125 and 0.5 mg/kg. The effect on gametocytes will be measured. Blood samples for membrane feeding experiments will be collected. The safety of study participants, specifically signs of hemolysis will be closely followed.  
2. Blood from study participants will be used in membrane feeding experiments.  
3. The primaquine doses will be increased or decreased to find out the lowest doses with which no oocysts can be detected in membrane feeding experiments.

Study site  
The Malaria Research and Training Centre (MRTC) in Bamako, Mali will use the field site of Ouelessebougou for recruitment. The MRTC has the unique position of being one of very few sites in Africa that can study malaria transmission endpoints. Long term collaborations with the National Institutes of Health, USA, the University of Nijmegen, The Netherlands and other American and European institutions, has built capacity in molecular gametocyte measurement and mosquito infectivity. In addition, the center is experienced in conducting Good Clinical Practice (GCP) compliant clinical trials including phase 2 malaria vaccine and drug studies. The site is in preparation for future evaluation of transmission blocking vaccines. Ouelessebougou village chosen for the study is endemic and seasonal malaria where clinical research has been ongoing since 2006 and there is a high burden of malaria in children and adults populations. In recent years the prevalence of \textit{P. falciparum} malaria in children under 5 years of age has ranged between 14\% and 26\% during the transmission season. The frequency of G6PD deficiency is in the range of 10 to 15\%.

Study population  
The study population will be derived from the adult male population of patients with uncomplicated \textit{P. falciparum} malaria presenting at the clinic or asymptomatic individuals who agree to be screened for malaria infection at the clinic. Adult males will be screened for G6PD deficiency with phenotypic testing (G6PD fluorescent spot test). Those with G6PD normal activity and sexual parasite on blood smear will be recruited into the dose escalation study.

Study drugs  
The study drugs to be tested will be:  
1. Dihydroartemisinin-Piperaquine  
All study participants will be treated with standard doses of DP for malaria. Although artemether-lumefantrine is the first-line drug in Mali, DP is most likely to replace current failing regimens and to be used in combination with PQ for malaria elimination programs.

2. Primaquine (PQ)  
Primaquine doses will vary by group. Trial participants will be given standard dose of DP over three days + single dose PQ on Day 0 depending on group (see below). Primaquine is absorbed rapidly and peak concentrations are reached in approximately 2 hours. It has a half-life of 6 hours and is metabolized in the liver [13] and a large volume of
distribution. The metabolically inert principle metabolite (carboxy-PQ) reaches peak concentrations within 6 hours of administration. The active metabolite has not yet been identified. The kinetics of PQ are affected by malaria (acute infection reduces oral clearance of PQ), by food (increased PQ bio-availability), or by other antimalarials (quinine induces a higher area under the curve (AUC) of the carboxy metabolite). The effect of piperaquine on the kinetics of PQ is not known but studies are ongoing to clarify a potential interaction.

**Intervention**
The intervention will be a dose escalation study in 3 groups of 10 G6PD-normal participants. They will each receive between 0 and 0.5mg/kg. A control group will receive DP without primaquine.

This will be an iterative study design depending on the results of the previous group tested. The first 90 participants will be randomly allocated to one of the treatment groups 1 to 3 (up to 30 participants/group). Due to the adaptive design, subsequent groups will not be randomized. Once the membrane feeding experiments as well as the 28 days follow-up, have been completed the findings will be reviewed by the investigators. If there is evidence that mosquitoes have become infected the next higher primaquine dose will be administered to the next group (up to 30 study participants). The DSMC will review the results and decide either to proceed or not to the next group. We will follow the dosing groups outlined below in Table1.

**Table 1: dosing groups**

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Dose of primaquine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (Negative Control)</td>
<td>0</td>
</tr>
<tr>
<td>Group 2</td>
<td>0.125 mg/kg</td>
</tr>
<tr>
<td>Group 3</td>
<td>0.5 mg/kg</td>
</tr>
<tr>
<td>Group 4</td>
<td>Dose dependent on previous findings; suggested doses are 0.0625 mg/kg, 0.25 mg/kg</td>
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<tr>
<td>Group 5</td>
<td></td>
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</tbody>
</table>

Note: Doses will be given on the first day of treatment.

1. Progressing to a higher dose will occur if either oocysts or sporozoites are found in any of the fed mosquitoes at that dose.
2. Progression to a lower dose will occur if there were no oocysts or sporozoites found in any of the fed mosquitoes at that dose.

Once a primaquine dose that can ablate infection in the human host as well as the feeding experiments has been established, the dose escalation study will be terminated.

**Outcome measure**
The primary outcome measure will be mosquito infectivity assessed through membrane feeding and measured by oocyst prevalence in mosquitoes dissected on day 7 post feed and the sporozoite carriage in mosquitoes dissected day 14 post feed. Primary endpoint
will be compared between the mean of the pretreatment infectivity and infectivity at 48 hours post dose.

Secondary outcome measures include: presence of oocysts and sporozoites in mosquito at other time points, gametocyte prevalence and density determined microscopically and by molecular methods, prevalence of sporozoite infected mosquitoes, primaquine pharmacokinetics, asexual parasite prevalence and density and safety assessment including hemoglobin measurement and signs of hemolysis.

### Table 2. Outcome measures

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gametocyte density</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Mosquito infectivity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Prevalence of oocyst infected mosquitoes</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) Prevalence of sporozoite infected mosquitoes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primaquine pharmacokinetics*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety assessment: signs of hemolysis</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*only in adult patients ≥ 18 years of age

### Sample size calculation

Sample size estimation was based on efficacy for single dose primaquine to be greater than 90% reduction in infectivity at 24 hours post treatment compared to pretreatment. Infectivity will be assessed by oocyst prevalence in mosquitoes dissected at day 7 after feeding. In the pretreated samples we expect 80% of individuals to infect at least one mosquito, and among those who infect, an average of 25-30% of mosquitoes to have oocysts. With 30 participants per group, we will have 80% power to detect a 90% difference in the number of mosquitoes with oocysts before and after treatment as significant at the 0.05 level.

### Inclusion Criteria: Dose escalation

For the dose escalation study G6PD normal participants with or without clinical/symptomatic malaria will be included.

- Male
- Age > 5 years and < 50 years
- Malaria blood thick film positive
- Presence of gametocytes on thick blood film
- Agrees to admission to study ward for 26 hours post diagnosis and available for follow up visits
- No allergies to study drugs
- Hemoglobin >= 8 g/dl
• No evidence of severe or chronic disease
• Written, informed consent

Study procedures
Participants who agree to participate and provide written, informed consent will be assessed for the presence of sexual blood stage parasite with a thick blood film and rapid diagnostic test and G6PD activity (Fluorescent Spot Test) from a finger prick sample. Those with sexual stages seen on the thick film and normal G6PD activity will be eligible for enrolment into the dose escalation study.

Consent procedure
Consenting procedures will vary based on age of the potential participant. Participants aged 18 years and above will provide informed consent. For participants aged 7-17 years, we will seek assent and parental consent. For participants aged 5 or 6 years, we will seek parental consent. The written, informed consent procedure will be conducted in French or in a local language understood by subject.

Participants will be requested to stay at the research facility for up to 26 hours so as to enable frequent sampling for infectivity and for pharmacokinetics. The participants will be given the reasons for frequent sampling and explained the risks associated with the procedure. The participants will be compensated for any travel costs and for work loss income. Participants will be informed that in addition to the testing for malaria and drug levels, they will be tested for their ability to metabolize drugs (cytochrome testing) and they will be tested for genotypic risk factors for hemolysis, such as G6PD deficiency. Participants will be followed for 28 days as described in Table 3 (below). Blood samples will be taken on 15 occasions in 6 visits (total blood volume approximately 46ml) and are shown in the sampling framework below. Risks of the trial will be clearly stated including the risk of hemolysis, which is thought to be low in G6PD normal people. All participants will have 24 hour access to a research clinician.

Eligible subjects will be allocated to one of the treatment dose groups. Those with a positive malaria slide with asexual stages only will be treated with the standard treatment (artemether + lumefantrine) as per the Ministry of Health policy.

Randomization procedure
The first 90 participants will be randomly allocated (by individual computer generated randomization) to either group 1 (primaquine free control) or to group 2 (lowest dose of primaquine, 0.125 mg/kg) or group 3 (middle dose of primaquine, 0.5 mg/kg). Due to the adaptive design, subsequent groups will not be randomized.

Blinding
The study is unblinded for patient and treating physician but is blind for the staff involved with assessing all outcomes of the study and the analysis.
The sampling frame below will be used for each study participant. For adult participants, a venous catheter may be placed for the multiple venous sampling on the first day of the study. On subsequent days single venous draws or finger pricks will be used. We will not collect pharmacokinetic samples in participants under 18 years of age.

Table 3. Blood Sampling frame for human participants

<table>
<thead>
<tr>
<th>Time of sampling</th>
<th>Hours</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.5</td>
<td>0</td>
</tr>
<tr>
<td>Type of sampling</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>G6PD activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0.5ml)</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Mosquito infectivity (5ml)</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Gametocyte density at blood smear (0.1ml)</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Molecular quantification of gametocytes and asexual stages (1 ml)</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Pharmacokinetics (1ml)*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Hemoglobin (0.1 ml)</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Volume of blood sampled (ml)</td>
<td>5.5</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Note: V denoted venous blood sampling and C denoted capillary sampling from a finger prick
*only in adult participants ≥18 years of age

Safety evaluation
Safety monitoring will occur in the first 24 hours. The major safety endpoint is hemolysis. For this reason, hemoglobin will be measured before treatment, at days 2, 3, 7, 14 and 28. Previous studies have shown that highest hemoglobin fall related to drug induced hemolysis can be detected 7 days after treatment. In addition at 24 hours, and subsequent days of follow up, a questionnaire assessing symptoms will be carried out. All participants will have access to contact study medical staff 24 hours a day and all medical facilities can give safe blood transfusions.

All adverse events will be recorded on individual CRF with the following information:
- the severity grade (mild, moderate, severe)
- its relationship to the study drug(s) (related/not related)
• its duration (start and end dates or if continuing at final exam)
• actions taken
• outcome
• whether it constitutes a serious adverse event (SAE).

An adverse event (AE) will be defined as the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug.

A Data and Safety Monitoring Committee (DSMC) will be established and convened before the onset of the trial to agree stopping points for each dosing group with regards to safety and efficacy. The DSMC will be informed of any serious adverse event within 48 hours of the event being notified to study personnel.

Laboratory procedures

1. Quantitative G6PD testing
All subjects will have a quantitative assessment of G6PD activity measured using a spectrophotometric validated assay. Fluorescent spot testing gives a qualitative assessment at a cut off of approximately 30% activity. We expect all participants to be G6PD replete.

2. Mosquito infectivity assay
For each assessment of infectivity 5 ml of heparinized blood will be drawn from the study participant and stored at 37°C and transported to the insectary. At the insectary, using standard procedures, 80 A. gambiae will be fed on the subjects’ blood for 15-20 minutes. Half of these mosquitoes will be dissected at 7th day after the feeding assay for prevalence of mosquitoes with oocysts and quantification of oocysts. The other half (we assume 10% mortality) will be tested by ELISA for presence of sporozoites on day 14.

3. Gametocyte and asexual stage density measurement
Blood slides stained with Giemsa will be double read over 500 fields for quantification of gametocytes and asexual stages. EDTA samples of blood (1ml) will be tested for molecular quantification of gametocytes using QT-NASBA [14] or by RT-qPCR. Asexual stage density will also be assessed using standard qPCR methodology [16], extracted parasite DNA will be compared to standards to assess total parasite density.

4. Pharmacokinetic measurement
In adult participants, 1.0 ml whole blood will be collected in appropriate collection tubes containing sodium or lithium heparin as the anticoagulant. The tube should be at room temperature (18°-25°C) prior to use. The sample may be stored at ambient temperature for up to 2 hours before processing. Transfer the blood into screw cap cryovial (Nalgene No.: 5000 0012). Freeze the whole blood samples at or below -20°C. If the samples are kept for more than 2 months they should be stored at -80°C or below. The assays will be performed by the pharmacology department of the Mahidol Oxford University Research Unit in Bangkok.
5. Genotyping for polymorphisms for G6PD deficiency and cytochrome activity
Dried blood spots collected from the first blood draw will be collected on filter paper and stored with desiccant at room temperature for later Single Nucleotide Polymorphism (SNP) analysis by PCR methodology for the known common polymorphisms for G6PD deficiency in the area. For cytochrome activity, the buffy coat of samples for the pharmacokinetic will be collected and stored at –20°C for later analysis of P450 cytochrome polymorphisms by PCR analysis using standard procedures.

6. Parasite genotyping
A portion of parasite DNA extracted for quantification of asexual parasite density will be stored and later sent to Oxford University, UK to be genotyped using genome wide sequencing.

Data management and analysis
All data will be stored on secure password protected databases. Data that are collected on paper forms will be double entered. Data collected through hand held devices or directly produced by laboratory equipment will be examined for quality assurance and fed directly into the database. A full analysis plan will be written before the trial starts and be reviewed by the DSMC.

Ethical issues
This research will be conducted in compliance with the protocol, Good Clinical Practice (GCP) guidelines, and all applicable regulatory requirements. A copy of the protocol, informed consent forms, and any other documents given to study participants will be submitted to the ethics committees (EC) of all the institutions involved. Written approval will be obtained for all subsequent amendments to the protocol, informed consent documents, and other study documentation referenced above. The investigator will notify the ECs and DSMC of violations of the protocol and serious adverse events.

Subject information and consent
Consenting procedures will vary based on age of the potential participant. Participants aged 18 years and above will provide informed consent. For participants aged 7-17 years, we will seek assent and parental consent. For participants aged 5 or 6 years, we will seek parental consent.

The informed consent document will be used to explain the risks and benefits of study participation to the participant and in the case of participants < 18 years, the participant’s parent or legal guardian in simple terms before the subject is enrolled in the study. The informed consent document contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the participant or the participant’s parent or legal guardian, after the receipt of detailed information on the study. Written informed consent must be obtained from each participant or participant’s parent or legal guardian prior to enrolment in the study. The informed consent form will be signed and personally dated by the participant or the participant’s parent or legal guardian and the person who conducts the informed consent discussion. A
copy of original signed informed consent form will be retained in the participant’s chart and another will be provided to him. A participant who is unable to read or write will place an imprint of his finger in the place of a signature; in addition, an independent witness will sign the consent form to attest that the information in the consent form was orally conveyed to the participant.

Confidentiality
The investigator will ensure that the subject’s anonymity is maintained. Participants will not be identified in any publicly released reports of this study. All records will be kept confidential to the extent provided by laws and regulations. The study monitors and other authorized representatives of the regulatory authorities may inspect all documents and records required to be maintained by the Investigator.

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number in order to maintain subject confidentiality.

Risks
There are minimal risks of hemolysis associated with the administration of single dose of 0.75 mg/kg of primaquine. For this dose escalation study we are selecting the lowest risk group for testing primaquine, namely, G6PD normal adult males. Each participant will be warned of the risks associated with primaquine use and will be monitored carefully for 28 days. The risks for hemolysis are low with this low dose and in this defined group. Participants will be asked to return to the clinic for reassessment should they feel unwell, feel out of breath, look pale, or notice their urine is a dark color. Other side effects of primaquine include nausea, vomiting, loss of appetite, and stomach cramps, occasionally headaches and visual disturbance and pruritus. Other allergic reactions are rare (<1/1000). In adults, the most common temporary side effects with dihydroartemisinin-piperaquine are anaemia, headache, QTc prolongation, tachycardia, asthenia and fever. Finger pricks and venipuncture are associated with pain and bruising at the site of the prick, and rarely infection.

Risks will be minimized by the study sites by ensuring adequate training of staff in all procedures and supply of consumables. The study site adheres to the standards of good clinical practice (GCP) and will be monitored.

Benefits
The benefits of the participation include free treatment of malaria and other diseases that may occur during the follow-up period. Participants who are in the groups that get the study medicine, primaquine, may be less infectious to mosquitoes and reduce the chance of having mosquitoes in their environment being infectious. Finding the lowest efficacious dose of primaquine will help in the treatment of future patients and communities with malaria.

Compensation
Participants will receive compensation for the time and travel for protocol specified visits. This compensation will be carefully evaluated and provided upon agreement of the local ethic committee. In Mali, the estimated cost of time and travel expense per visit in
Use and storage of study samples.
Samples collected will be stored at MRTC in Bamako, Mali or the University of California San Francisco, USA, or both, and may also be shipped to collaborating research centers such as Oxford University in UK to perform specific tests as described above. Samples may be kept for a maximum of the 10 years.

References