TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	Study 200894: A double-blind, double-dummy, randomized, parallel group, placebo-controlled superiority study to evaluate the efficacy and safety of tafenoquine (SB-252263, WR238605) co-administered with dihydroartemisinin-piperaquine (DHA-PQP) for the radical cure of Plasmodium vivax malaria

Compound Number: SB-252263

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Author (s): PPD
PPD

Revision Chronology

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- A secondary study objective has been added to compare the efficacy of dihydroartemisinin- piperaquine (DHA-PQP) plus primaquine relative to DHA-PQP alone.
- A vital signs assessment has been added at Day 2 to permit evaluation of time to fever clearance (secondary objective)
- The Oxford Tropical Diseases Research Ethics Committee (OXTREC) project number (9-16), amendment number and date has been added to the footer of each page
- The secondary medical monitor has been updated to Dr PPD MD

SPONSOR SIGNATORY

PPD

20/4/2017

Justin Green, MD
Director,
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Developing World Therapy
Area Physician

Date

PPD

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): Not applicable

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 200894

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

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1. PROTOCOL SYNOPSIS FOR STUDY 200894

Rationale

Almost half of the 239 million population of Indonesia live in malaria-endemic areas. According to recent WHO estimates, the number of new cases of malaria in Indonesia is approximately two million per year [Murray, 2014]. The ratio of *P. falciparum*: *P.vivax* infections among diagnosed and reported cases is around 1:1. From a global malaria control and eradication perspective, *P. vivax* presents the greatest challenge, due to its ability to establish a dormant liver stage, the hypnozoite. Relapsing *P.vivax* malaria is caused by hypnozoite activation after initial infection. Severe anaemia, malnutrition and respiratory distress are among the symptoms caused by *P.vivax* infections and cases of severe malaria resulting in fatal outcome can occur [Price, 2009, Baird, 2013].

The current standard of care for radical cure of *P. vivax* malaria in most endemic countries is chloroquine for clearance of acute parasitemia plus primaquine (15mg or 30mg once daily for 14 days) to clear the liver stages of the parasite and prevent disease relapse. In Indonesia, chloroquine has been replaced by artemisinin-based combination therapies (ACTs) for the treatment of blood stage disease due to widespread chloroquine resistance. The Indonesian national treatment policy recommends co-administration of primaquine (PQ) with an ACT for radical cure of *P.vivax* malaria.

Tafenoquine (TQ, SB-252263 and WR 238605) is an 8-aminoquinoline anti-malarial drug being co-developed by GlaxoSmithKline and Medicines for Malaria Venture with historical support of the Walter Reed Army Institute of Research. It is a synthetic analogue of primaquine in development for the radical cure of *P. vivax* malaria, as a single dose co-administered in other studies with standard doses of chloroquine. The shorter course of tafenoquine offers the potential for improved compliance and thus effectiveness of relapse prevention, compared with the longer duration regimen for primaquine. Tafenoquine has been evaluated in >4000 subjects for the treatment and prevention of plasmodial infections during Phase I, II and III clinical studies.

This study will evaluate the efficacy and safety of a single dose of tafenoquine (300mg) co-administered with an Artemisinin Combination Therapy (ACT) in the radical treatment of *P. vivax* malaria in order to support registration of tafenoquine in Indonesia and other countries where ACTs are first line therapy. Dihydroartemisinin-piperaquine (DHA-PQP) has been selected as the ACT for this study since it is highly efficacious against the chloroquine resistant *P.vivax* of Eastern Indonesia. Subjects who are glucose-6-phosphate dehydrogenase (G6PD) deficient will be excluded due to the hemolytic risk associated with 8-aminoquinoline drugs.

We have performed a tafenoquine/ACT interaction study (GSK Study 200951). This drug-drug interaction (DDI) study assessed the pharmacokinetics and safety of tafenoquine when co-administered with DHA-PQP in healthy subjects and demonstrated no interactions requiring dose adjustment. However, given the piperaquine-induced QTc elongation observed, DHA-PQP will be dosed and ECGs monitored, in accordance with the product label.

Objectives/Endpoints

Objectives	Endpoints
Primary	
• To determine the efficacy of tafenoquine co-administered with DHA-PQP for the radical cure of *P. vivax* malaria, relative to DHA-PQP alone at 6 months.	• Subjects with relapse-free efficacy six months post-dosing.
Secondary	
• To characterize the efficacy of tafenoquine relative to primaquine when co-administered with DHA-PQP.	• Subjects with relapse-free efficacy six months post-dosing.
• To determine the efficacy of primaquine co-administered with DHA-PQP relative to DHA-PQP alone.	• Subjects with relapse-free efficacy six months post-dosing.
• To determine the efficacy of tafenoquine co-administered with DHA-PQP relative to DHA-PQP alone at four months.	• Subjects with relapse-free efficacy four months post-dosing.
• To determine the blood stage efficacy of tafenoquine in subjects with *P.vivax* malaria when co-administered with DHA-PQP.	• Time to relapse. • Time to fever clearance (in subjects with fever at baseline). • Time to parasite clearance. • Percentage of subjects with recrudescence.
• To assess the safety of tafenoquine in subjects with *P. vivax* malaria when co-administered with DHA-PQP.	• Incidence and severity of adverse events, SAEs, clinically significant abnormal laboratory tests, ECGs and vital signs. • Change from baseline in methemoglobin. • Change from baseline in QTcF. • Incidence of protocol defined SAEs (i.e. a decrease in hemoglobin of ≥30% or >3 g/dL from baseline or, a drop in hemoglobin below 7.0g/dL, in the first 15 days).
• To evaluate the pharmacokinetics of tafenoquine when co-administered with DHA-PQP in adult subjects with *P.vivax* malaria.	• Population PK parameters for tafenoquine including oral clearance (CL/F) and volume of distribution (V/F).

In addition, the study has the following objectives:

- To explore the genetics of recurrence of *P.vivax* malaria by evaluating the incidence of genetically homologous and heterologous *P.vivax* infections.
- To explore the relationship between CYP2D6 genotype and risk of *P.vivax* relapse.
- To explore the relationship between the pharmacokinetics of tafenoquine co-administered with DHA-PQP and pharmacodynamic endpoints (if applicable).

Overall Design

- Study 200894 is a double-blind, double-dummy, randomized, parallel group, placebo-controlled superiority study. The study will be conducted as a collaboration between the Eijkman Institute of Molecular Biology (Jakarta), Eijkman Oxford Clinical Research Unit (within the Eijkman Institute, Jakarta), Faculty of Medicine, University of Indonesia (Jakarta) and the Indonesian army. The protocol will require appropriate ethics committee approval.

- Approximately 150 subjects will be enrolled from the Indonesian army returning from deployment in a heavily malarious region of Indonesia (e.g. Papua) and diagnosed with *P. vivax* malaria based on microscopic examination (confirmed by a second microscopist).

- At Day 1, subjects will be screened for G6PD deficiency using a suitable Point of Care Test (e.g. Fluorescent Spot Test) in order to exclude those who are G6PD deficient. G6PD deficiency will also be assessed by a quantitative spectrophotometric assay but the results will not be available at the time of randomization.

- Subjects who have undergone screening and meet the label requirements for DHA-PQP dosing can receive open label DHA-PQP if the clinician deems that appropriate and at least 3 hours have elapsed since last food intake. Thus, DHA-PQP may be commenced whilst the results of the hematology, clinical chemistry or G6PD deficiency screening tests are pending. Once all laboratory evaluations are available and subject eligibility is confirmed, they will be randomized to blinded study treatment on a 1:1:1 basis. The first dose of blinded study treatment (tafenoquine, primaquine or placebo) will be administered with food at least 3 hours after dosing with DHA-PQP on Day 1 or Day 2.

- Parasitological assessments will be conducted throughout the treatment and follow-up periods and on recurrence (if applicable).

- Blinded study treatment will be administered daily, directly observed by site staff, for 14 days.

- Duration of study: Up to 195 days, including screening (Day 1) and randomization to treatment (Day 1 or Day 2), 14 daily visits while receiving blinded study treatment and seven follow-up visits (Days 21, 28, 60, 90, 120, 150 and 180). Subjects who do

not relapse by Day 180 will attend a follow up visit on Day 195, following 14 days of open label primaquine.

- Subjects will be closely observed throughout the study by clinical and laboratory investigations (vital signs, ECGs, routine hematology/clinical chemistry) and measurement of peripheral blood methemoglobin level at selected visits.

- Methemoglobin level will be determined by an independent assessor to avoid any potential for unblinding following 8-aminoquinoline dosing.

- Blood samples for TQ pharmacokinetic analyses will be drawn as follows: pre-dose, 6-12 hours and 24-48 hours post blinded study treatment, Day 7, Day 14, Day 28, Day 60 or at relapse (up to 60 days post dose).

- Hemoglobin decreases of ≥30% or >3g/dL from baseline or, a drop in absolute hemoglobin to <7.0g/dL in the first 15 days of the study, will be reported as a protocol-defined SAE even if asymptomatic and not requiring medical intervention. Blinded study treatment will be stopped immediately if a subject meets the protocol-defined SAE criteria for Hb drop together with clinical or laboratory evidence of hemolysis.

- Subjects diagnosed with recurrent *P.vivax* malaria during the study will receive an ACT plus PQ 0.5mg/kg daily for 14 days as rescue treatment and will be requested to continue to attend the scheduled study visits through to Day 180.

- The primary analysis population will be the Intent To Treat (ITT) population

- A subject is considered to have completed the double-blind study if they are randomized to blinded study treatment and complete the Day 180 visit.

- Subjects who have not relapsed prior to the Day 180 visit, will be given open label PQ 0.5mg/kg daily for 14 days to minimize the likelihood of *P.vivax* recurrence after the end of the study. These subjects will return for a final safety follow up visit 15 days later.

Treatment Arms and Duration

- The total duration of study for each subject is 180 – 195 days.

- All subjects will receive standard doses of open label DHA-PQP on Days 1-3.

- Subjects will be randomized to one of three parallel treatment groups in a double blind fashion:
    - TQ (300mg single dose)
    - PQ (15mg single daily dose for 14 days)
    - Placebo (daily for 14 days)

Visually matched placebos will be used to maintain the blind.

Type and Number of Subjects

- The study population will consist of male subjects, aged ≥18 years who have a positive smear for *P.vivax* and are G6PD normal.

- Approximately 200 subjects will be screened to achieve 150 randomized subjects for a total of 50 evaluable subjects per treatment group. All subjects who are randomized and receive at least one dose of blinded study treatment will be included in the intent-to-treat population. Subjects will not be replaced if they withdraw early from the study.

Analysis

The primary efficacy endpoint of subjects with relapse-free efficacy 6 months post-dosing will be analyzed using survival analysis techniques. If it is not possible to completely recruit the study from a single battalion but at least 120 subjects have been randomized, a blinded review of the relapse data will be conducted, with the intention to stop enrolment early if this review predicts that the combined relapse rate will be ≥26.7% at the end of the follow up period (based on sample size assumptions). Kaplan-Meier estimates will be made of the overall six month relapse rate, using all of the data available at that time. If this relapse criterion is met, enrolment will stop and the study will be analyzed once all the existing subjects have completed the 6 months follow up. If the blinded review predicts that the relapse rate will be < 26.7%, further subjects will be recruited from a second battalion, up to a maximum of 150 subjects in total.

2. INTRODUCTION

Tafenoquine (TQ, SB-252263 and WR 238605) is an 8-aminoquinoline anti-malarial drug being co-developed by GlaxoSmithKline and Medicines for Malaria Venture (MMV) with historical support of the Walter Reed Army Institute of Research. It is a synthetic analogue of primaquine (PQ) in development for the radical cure of *Plasmodium vivax* (*P. vivax)* malaria, as a single dose co-administered with standard doses of chloroquine. The shorter course of TQ offers the potential for improved compliance and thus effectiveness of relapse prevention, compared with the longer duration regimen for PQ.

In Indonesia, chloroquine has been replaced by artemisinin-based combination therapies (ACTs) for the treatment of blood stage disease due to the widespread emergence of chloroquine resistance. The Indonesian national treatment policy recommends co-administration of PQ with an ACT for radical cure of *P.vivax* malaria.

The study will evaluate TQ co-administered with an ACT in order to support registration of TQ as a radical cure of *P.vivax* malaria in Indonesia and other countries where ACTs are first line therapy.

2.1. Study Rationale

2.1.1. Global *P.vivax* Malaria

Malaria is a leading cause of morbidity and mortality in many developing countries with an estimated 300 to 500 million clinical cases every year. *P. vivax* malaria accounts for almost 50% of malaria cases outside of Africa and is increasingly recognized as a barrier to malaria elimination due to its ability to establish a dormant liver stage, the hypnozoite. Relapsing *P.vivax* malaria is caused by hypnozoite activation after the initial infection. The disease is associated with more severe impact than previously appreciated, including significant risk of death with delayed or inadequate treatment [Price, 2009, Baird, 2013]. *P. vivax* has been shown to be associated with substantial morbidity, particularly severe anaemia, respiratory distress and malnutrition.

2.1.2. Vivax malaria in Indonesia

In Indonesia, almost half of the 239 million population live in malaria-endemic areas [Herdiana, 2013]. The WHO recently estimated there were approximately two million new cases of malaria in Indonesia during 2013 [Murray, 2014]. However, the true incidence of malaria is unknown since laboratory-confirmation is rare and only approximately one fifth of subjects with symptomatic malaria seek treatment at government health facilities [Karyana, 2008].

Endemic vivax malaria occurs throughout the Indonesian archipelago except where excluded by more than 3000 meters (m) of altitude, urbanization or elimination areas of Java and Bali. The overall proportion of *Plasmodium falciparum:Plasmodium vivax* among diagnosed and reported cases is about 1:1. In Papua, Indonesia's most eastern province, malaria is highly prevalent and the ratio of *P.falciparum* to *P.vivax* malaria is about 2:1.

2.1.3. Clinical Management

The current standard of care for radical cure of *P. vivax* malaria in most endemic countries is chloroquine for clearance of acute parasitemia plus PQ (15mg or 30mg once daily for 14 days) to clear the liver stages of the parasite and prevent disease relapse. However, the efficacy of this regimen is threatened by the emergence and spread of chloroquine-resistant *P. vivax* in regions such as South East Asia [Lee, 2009, Sutanto, 2009, Sutanto, 2010, Price, 2014], the Indian subcontinent [Dua, 1996] and in South America [Soto, 2001]. In Indonesia, *P. vivax* resistance to chloroquine is widespread ranging from 43% in Sumatera Island to >80% in Papua [Sumawinata, 2003, Sutanto, 2010]. In 2004, the use of chloroquine was replaced by ACTs as first line therapies in Indonesia. The national malaria control program is aiming to eliminate the disease by 2030 [Kusriastuti, 2012].

There is a need to provide alternative treatments to manage *P.vivax* relapse over and above PQ which is the only treatment currently widely available. PQ is administered as a once a day oral dose for 7-14 days and it is widely accepted that this long hypnozoiticidal dosing regimen (compared to 3 day treatment for clearance of blood stage malaria parasites) leads to reduced compliance and hence reduced clinical efficacy.

2.1.4. Study Background

The objective of this study is to evaluate the efficacy and safety of a single dose of TQ (300mg) co-administered with an ACT for the radical treatment of P. vivax malaria in Indonesian soldiers returning from a malarious region e.g. Papua. The study is designed to demonstrate the superiority of TQ plus dihydroartemisinin-piperaquine (DHA-PQP) compared to DHA-PQP alone as a radical cure. The DHA-PQP alone arm is required to assess the underlying relapse rate within the setting of this clinical study. A PQ plus DHA-PQP comparator arm is included to characterize the efficacy of TQ by providing an informal concurrent benchmark against a treatment that has activity against liver-stage hypnozoites.

In the Phase IIB programme, a single 300mg dose of TQ co-administered with standard doses of chloroquine was more efficacious than chloroquine alone for prevention *of P. vivax* malaria relapse with a similar safety profile [Llanos-Cuentas, 2014]. The incidence of gastrointestinal (GI)-related AEs was similar following single doses of TQ 300mg and PQ 15mg for 14 days.

In recent studies, less than 10% of subjects with *P. vivax* malaria experienced relapse/re-infection after treatment with DHA-PQP plus PQ over a 12 month follow up period in Indonesia [Pasaribu, 2013, Sutanto, 2013]. Both TQ and PQ can cause acute hemolysis if given to subjects with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Subjects who are G6PD deficient will be excluded from the study.

Preliminary data suggest there may be a relationship between CYP2D6 activity and PQ anti-relapse efficacy. In a small cohort, subjects who had low activity phenotype of CYP2D6 had reduced PQ efficacy compared to subjects who were extensive metabolizers [Bennett, 2013]. It has been hypothesized that polymorphisms in CYP2D6 may decrease formation of an active metabolite of PQ resulting in increased risk of

relapse. The relationship between CYP2D6 genotype and risk of *P.vivax* relapse following treatment with TQ or PQ will be explored in this study. The study will also examine the pharmacokinetics of TQ when co-administered with DHA-PQP in subjects with *P.vivax* malaria.

Prior to commencing this study, a TQ/ACT interaction study was performed (GSK Study 200951). This drug-drug interaction (DDI) study assessed the safety and pharmacokinetics of TQ when co-administered with DHA-PQP in three parallel groups of n=24 healthy subjects. As expected, PQP-induced prolongation of the QTc interval was observed. Whilst an absolute difference in QTcF elongation was observed between the DHA-PQP alone group and the DHA-PQP plus TQ group, confidence intervals overlapped and the difference was not considered clinically significant. No significant effect of TQ on the PK of DHA or PQP was found. There was a 12% (1 – 26%, 90% CI) increase in the $AUC_{0\text{-}inf}$ of TQ when co-administered with DHA-PQP but this is not deemed to be clinically significant, with PK parameters not reaching those previously seen with higher doses that have been tolerated and safely used in other studies. Therefore, no dose adjustments were deemed necessary for co-administration of TQ and DHA-PQP in the present study. No new safety signals were noted in Study 200951 but ECG monitoring will be performed in the present study in accordance with the DHA-PQP label (Eurartesim SmPC).

2.2. Brief Tafenoquine Background

TQ has been shown to have an acceptable safety profile in the treatment and prevention of plasmodial infections in pre-clinical models and during Phase I, II and III clinical studies in >4000 adult subjects (including >1000 females). The most common AEs included nausea, vomiting, abdominal pain, diarrhoea and vortex keratopathy (reversible corneal deposits). Gastrointestinal AEs appeared to increase with increasing dose and were more common in the fasted versus fed state. Mild, reversible corneal changes were mainly observed in repeat dose studies and were similar to those seen with other drugs including chloroquine. Methemoglobinemia has been observed with larger total doses of TQ than are being considered for the treatment of *P.vivax* malaria and is most likely secondary to TQ induced oxidative stress within red blood cells. Please refer to the TQ Investigator Brochure for more information [GlaxoSmithKline Document Number GM2007/00152/09, SB-252263 Investigator's Brochure]. All members of the 8-aminoquinoline class of drugs, including TQ and PQ, induce hemolysis in subjects with G6PD deficiency. G6PD is a housekeeping enzyme responsible for protection against oxidant stress. The effects of oxidant stress in subjects with G6PD deficiency are most apparent in red blood cells. TQ is thus being developed for treatment of patients with sufficient levels of G6PD enzyme activity.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
• To determine the efficacy of tafenoquine co-administered with DHA-PQP for the radical cure of *P. vivax* malaria, relative to DHA-PQP alone at 6 months.	• Subjects with relapse-free efficacy six months post-dosing (i.e. clearance of initial infection without subsequent microscopically confirmed recurrence during the 6 month follow up).
Secondary	
• To characterize the efficacy of tafenoquine relative to primaquine when co-administered with DHA-PQP.	• Subjects with relapse-free efficacy six months post-dosing.
• To determine the efficacy of primaquine co-administered with DHA-PQP relative to DHA-PQP alone.	• Subjects with relapse-free efficacy six months post-dosing.
• To determine the efficacy of tafenoquine co-administered with DHA-PQP relative to a DHA-PQP alone at four months.	• Subjects with relapse-free efficacy four months post-dosing.
• To determine the blood stage efficacy of tafenoquine in subjects with *P.vivax* malaria when co-administered with DHA-PQP.	• Time to relapse. • Time to fever clearance (in subjects with fever at baseline). • Time to parasite clearance. • Percentage of subjects with recrudescence (blood stage treatment failure) on or before Day 14 (i.e. a recurrence of *P. vivax* parasites which is genetically homologous to the baseline *P. vivax* infection).
• To assess the safety of tafenoquine in subjects with *P. vivax* malaria when co-administered with DHA-PQP.	• Incidence and severity of adverse events and SAEs. • Incidence of clinically significant abnormal clinical laboratory tests, ECGs and vital signs. • Key safety endpoints of interest:

Objectives	Endpoints
	○ GI tolerability – incidence of abdominal pain, heartburn, diarrhoea, constipation, nausea and vomiting. ○ Change from baseline in methemoglobin ○ Change from baseline in QTcF ○ Incidence of protocol-defined SAEs (i.e. a decrease in hemoglobin of ≥30% or >3 g/dL from baseline; or, a drop in absolute hemoglobin to < 7.0g/dL, in the first 15 days)
• To evaluate the pharmacokinetics of tafenoquine when co-administered with DHA-PQP in adult subjects with *P.vivax* malaria.	• Population PK parameters for tafenoquine including but not limited to oral clearance (CL/F) and volume of distribution (V/F).
Exploratory	
• To explore the genetics of recurrence of *P.vivax* malaria.	• Incidence of genetically homologous and genetically heterologous *P.vivax* infections (determined by PCR). • Whole genome sequencing of multiple parasite genes will be undertaken, if parasite count allows (to be reported separately).
• To examine the relationship between CYP2D6 genotype and risk of *P.vivax* relapse.	• Percentage of subjects relapsing analyzed according to CYP2D6 genotype.
• To explore the relationship between the pharmacokinetics of tafenoquine co-administered with DHA-PQP and pharmacodynamic endpoints (if appropriate).	• Population PK (e.g. tafenoquine plasma concentrations) and selected pharmacodynamic (PD) endpoints (e.g., relapse-free efficacy, change in methemoglobin).

With regards to the efficacy endpoints, it should be noted that it is not possible to determine if a subject's recurrence of malaria is a relapse or recrudescence. For the purposes of this protocol, the term "relapse" will be used to describe any recurrence of *P.vivax* malaria after clearance of the initial infection. "Recrudescence" applies to the term relating to recurrence for Days 1-14 of the study, where a genetically homologous

parasite is suggestive of recrudescence. Therefore, within this protocol, recrudescence will represent a subset of all the relapses captured. This definition of "relapse" is consistent with the definition used in the global tafenoquine studies, as agreed with the United States FDA.

4. STUDY DESIGN

4.1. Overall Design

- Study 200894 is a double-blind, double-dummy, randomized, parallel group, placebo-controlled superiority study. The study will be conducted as a collaboration between the Eijkman Institute of Molecular Biology (Jakarta), Eijkman Oxford Clinical Research Unit (within the Eijkman Institute, Jakarta), Faculty of Medicine, University of Indonesia (Jakarta) and the Indonesian army. The protocol will require appropriate ethics committee approval.

- Approximately 150 subjects will be enrolled from the Indonesian army returning from deployment in a heavily malarious region of Indonesia (e.g. Papua) and diagnosed with *P. vivax* malaria based on microscopic examination (confirmed by a second microscopist).

- Informed consent process: Research team leaders will meet commanders and the troops to explain the concept and importance of voluntary informed consent prior to inviting subjects to participate in the study. Subjects will give written informed consent prior to any screening assessments being undertaken. The written consent will be obtained by a site team member who is independent of the subject (i.e. not the subject's commander or supervisor) and the voluntary nature of the study will be emphasised (See Section 7.2).

- At Day 1, subjects will be screened for G6PD deficiency using a suitable Point of Care Test (e.g. Fluorescent Spot Test) in order to exclude those who are G6PD deficient (See Study Reference Manual, SRM). G6PD deficiency will also be assessed by a quantitative spectrophotometric assay but the results will not be available at the time of randomization. If results are discordant, the subject will be reviewed and appropriate G6PD testing will be repeated.

- Subjects who have undergone screening and meet the label requirements for DHA-PQP dosing can receive open label DHA-PQP if the clinician deems that appropriate and at least 3 hours have elapsed since last food intake. Thus, DHA-PQP may be commenced whilst the results of the hematology, clinical chemistry or G6PD deficiency screening tests are pending. Once all laboratory evaluations are available and subject eligibility is confirmed, they will be randomized to blinded study treatment on a 1:1:1 basis. The first dose of blinded study treatment will be administered with food at least 3 hours after dosing with DHA-PQP, on Day 1 or Day 2 (see Section 7.2).

- Blood smears will be done twice daily, 6-12 hours apart until two consecutive negative smears are obtained. Additional blood smears will be done throughout the treatment and follow up period and on recurrence (if applicable).

- An on-site clinic will be established at the army base, which will be available 24 hours a day and 7 days a week for the duration of the study.

- Blinded study treatment will be administered daily, directly observed by site staff, for 14 days.

- Duration of study: Up to 195 days, including screening (Day 1) and randomization to treatment (Day 1 or Day 2), 14 daily visits while receiving blinded study treatment and seven follow-up visits (Days 21, 28, 60, 90, 120, 150 and 180). Subjects who do not relapse by Day 180 will attend a follow up visit on Day 195, following 14 days of open label primaquine.

- *Plasmodium* PCR genotyping will be performed on all baseline samples and in subjects who relapse to explore the proportion of heterologous and homologous relapses using appropriate PCR markers as well as define baseline genetic variability. Parasite whole genome sequencing will also be performed in a similar fashion, if parasite counts allow; these data will be reported separately.

- Subjects will be closely observed throughout the study by clinical and laboratory investigations including vital signs, ECGs, routine hematology/clinical chemistry and peripheral blood methemoglobin (metHb) levels at selected visits. This allows subjects who have a recurrence (e.g. those that happen to be randomized to the DHA-PQP alone arm) to be rapidly identified and safely managed minimizing the risk of serious clinical consequences of recurrence.

- MetHb will be determined by an independent assessor to avoid any potential for unblinding following 8-aminoquinoline dosing (refer to SRM).

- Subjects will be asked to report to the clinic at any time of the night or day should they feel unwell or develop a fever. Any subject diagnosed with recurrent *P.vivax* malaria (defined as a positive blood smear with or without vivax symptoms) will receive an ACT plus PQ 0.5mg/kg daily for 14 days and will be requested to continue to attend the scheduled study visits through to Day 180.

- Blood samples for TQ pharmacokinetic analyses will be drawn at the following times: pre-dose, 6-12 hours and 24-48 hours post blinded study treatment, Day 7, Day 14, Day 28, Day 60 or at relapse (up to 60 days post dose).

- Hemoglobin decreases of ≥30% or >3g/dL from baseline or, a drop in absolute hemoglobin to <7.0g/dL, in the first 15 days will be reported as a protocol-defined SAE even if asymptomatic and not requiring medical intervention. Blinded study treatment will be stopped immediately if a subject meets the protocol-defined SAE criteria for Hb drop together with clinical or laboratory evidence of hemolysis (refer to Section 5.4.2 and Section 7.5.1.1).

- Exploratory CYP2D6 genotype analyses will be undertaken to test the hypothesis that null and/or intermediate metabolizers of 8-aminoquinoline drugs are more at risk of *P. vivax* relapse with PQ but not TQ [Bennett, 2013].

- The primary analysis population will be the Intent To Treat (ITT) population

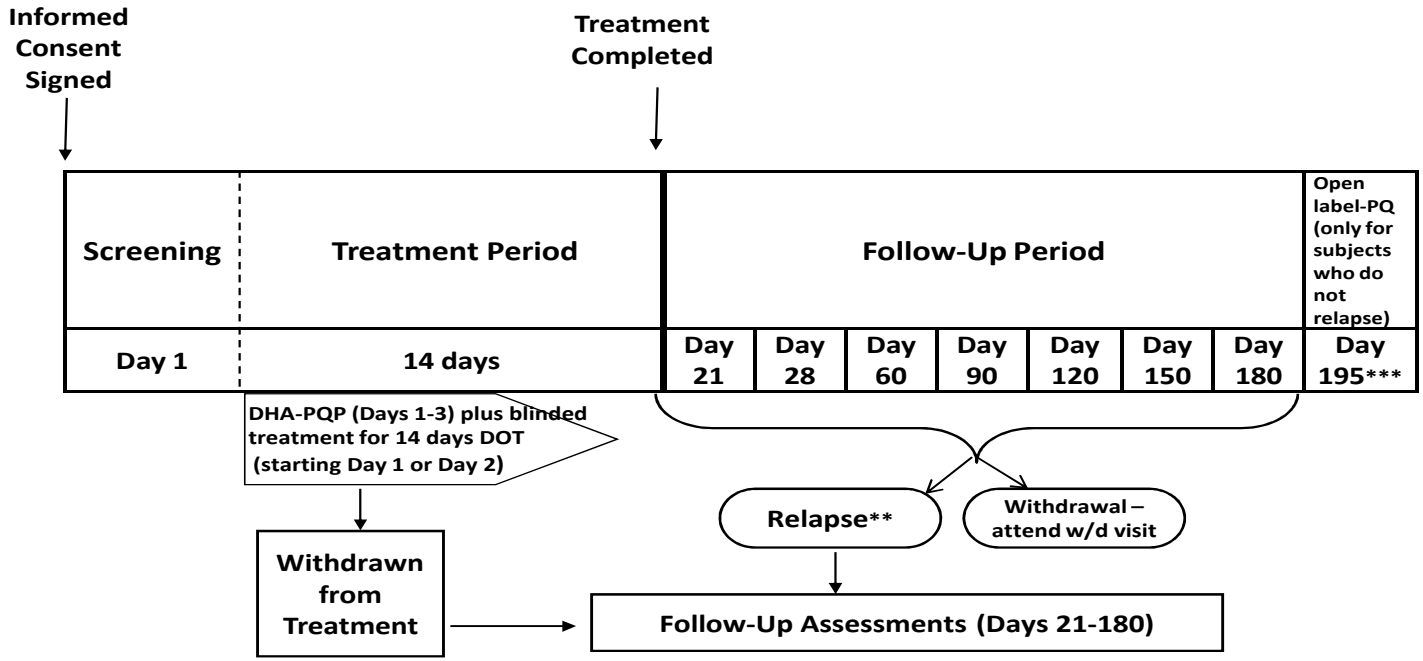
- A subject is considered to have completed the double-blind study if they are randomized to blinded study treatment and complete the Day 180 visit.

- Subjects who have not relapsed prior to the Day 180 visit will be given open label PQ 0.5mg/kg daily for 14 days to minimize the likelihood of *P. vivax* recurrence after the end of the study. These subjects will return for a final safety follow up visit 15 days later.

- If it is not possible to completely recruit the study from a single battalion but at least 120 subjects have been randomized, a blinded review of the relapse data will be conducted, with the intention to stop enrolment early if this review predicts that the combined relapse rate will be ≥26.7% at the end of the follow up period (based on sample size assumptions). Kaplan-Meier estimates will be made of the overall six month relapse rate, using all of the data available at that time. If this relapse criterion is met, enrolment will stop and the study will be analyzed once all the existing subjects have completed the 6 months follow up. If the blinded review predicts that the relapse rate will be < 26.7%, further subjects will be recruited from a second battalion, up to a maximum of 150 subjects in total (See Section 9.2.3).

- The study design schematic is provided in Figure 1.

Figure 1 200894 Study Design Schematic



Open label DHA-PQP 3 or 4 tablets per day (according to weight) on Days 1-3 plus blinded study treatment as follows:
1) Tafenoquine 300 mg single dose on Day 1 and placebo for primaquine on Day 1-14*
2) Primaquine 15mg on Days 1-14 and placebo for tafenoquine on Day 1*
3) Placebo for tafenoquine on Day 1 and placebo for primaquine on Days 1-14*
*** Blinded study treatment will start on Day 1 or Day 2 and continue for 14 days**
**** Subjects who relapse before D180 will receive immediate rescue treatment (ACT + PQ 0.5mg/kg daily for 14 days) and attend FU visits**
*****Subjects who do not relapse before D180 will receive open label PQ (0.5mg/kg daily for 14 days) and return for Day 195 visit**

4.2. Treatment Arms and Duration

Subjects will receive open label DHA-PQP plus blinded tafenoquine or blinded primaquine or placebo as shown in the table below. Visually matching placebo medication will be used to maintain the blinding.

	Open label DHA-PQP	**Blinded Tafenoquine or Placebo**	**Blinded Primaquine or Placebo**
Arm 1 **DHA-PQP alone (placebo arm)**	Open label DHA-PQP tablets * *Single daily dose on Days 1-3*	Placebo to match tafenoquine tablets 150mg (2 tablets) *Single dose on Day 1 or 2*	Placebo to match overencapsulated primaquine tablets 15mg (1 capsule) *Single daily dose for 14 days commencing Day 1 or 2*
Arm 2 **DHA-PQP plus tafenoquine 300mg single dose**	Open label DHA-PQP tablets* *Single daily dose on Days 1-3*	Tafenoquine tablets 150mg (2 tablets) *Single dose on Day 1 or 2*	Placebo to match overencapsulated primaquine tablets 15mg (1 capsule) *Single daily dose for 14 days commencing Day 1 or 2*
Arm 3 **DHA-PQP plus primaquine 15mg for 14 days**	Open label DHA-PQP tablets* *Single daily dose on Days 1-3*	Placebo to match tafenoquine tablets 150mg (2 tablets) *Single dose on Day 1 or 2*	Overencapsulated primaquine tablets 15mg (1 capsule) *Single daily dose for 14 days commencing Day 1 or 2*

* Open label DHA-PQP (piperaquine tetraphosphate (PQP) 320mg/ dihydroartemisinin (DHA) 40mg) tablets will be dosed according to weight (3 tablets per day for subjects weighing <75Kg and 4 tablets per day for subjects weighing ≥75Kg).

4.3. Type and Number of Subjects

Approximately 200 subjects will be screened to achieve 150 randomized subjects for a total of 50 evaluable subjects per treatment group. All subjects who are randomized and receive at least one dose of blinded study treatment will be included in the intent-to-treat population. Subjects will not be replaced if they withdraw early from the study.

4.4. Design Justification

Selection of soldiers as study population: The study will be conducted in male soldiers diagnosed with *P.vivax* malaria following return to a malaria non-endemic area of Indonesia after a recent deployment to a heavily malarious region (e.g. Papua). This study model has been selected as it should provide a reliable estimate of the true relapse rate (rather than overall recurrence rate) following TQ co-dosed with DHA-PQP since in this setting recurrent parasitemias are most likely to arise from re-activated hypnozoites rather than re-infection. It is recognized that members of the armed forces are considered a vulnerable population for clinical trials [ICH Guidance for Industry. Guideline E6]. Special attention will be paid to ensuring that the commanders and troops understand the concept and importance of voluntary informed consent prior to commencing the study (See Section 7.2). The study will undergo appropriate ethics committee review.

This is a soldier study population and only male subjects will be recruited. However, the safety profile of TQ has also been evaluated in over 1000 females who participated in Phase I, II and III clinical studies. The data indicate similar tolerability of TQ in males and females with the exception of G6PD heterozygous females who are at increased risk of mild to moderate hemoglobin declines. The safety of TQ in this population is being evaluated in a separate study (Study TAF116564). TQ will be contraindicated in pregnant and lactating females.

Selection of ACT: DHA-PQP has high efficacy rates (>95%) for clearing the blood stage infection of *P.vivax* in regions of Indonesia where chloroquine resistance is common [Ratcliff, 2007, Hasugian, 2007]. Both DHA-PQP and artesunate –amodiaquine are first line treatments for *P.falciparum and P.vivax* in Indonesia, although DHA-PQP is preferred due to its superior efficacy and better tolerability compared to other ACTs [Hasugian, 2007] (See Section 4.5).

Justification for DHA-PQP alone arm (relapse control arm): All subjects will receive the standard 3 day course of DHA-PQP which is expected to clear the initial blood stage infection. The inclusion of the DHA-PQP alone arm provides a relapse prevention placebo-control arm for the primary comparison of TQ versus no anti-hypnozoite treatment to confirm and quantify TQ efficacy in preventing relapse. Therefore, no subject will be left untreated for their acute malarial infection. All subjects will be under close observation and will be asked to report to the clinic at any time if they feel unwell or develop a fever. The research team aims to treat recurrent acute malaria at the earliest possible stage thereby ensuring subject safety and minimizing discomfort as a consequence of having malaria. Subjects who develop a recurrent parasitemia (symptomatic or asymptomatic) will receive immediate rescue treatment according to local treatment guidelines (see Section 6.9.1.2). On-site clinic facilities will be available 24 hours, 7 days a week to ensure the prompt management of any subject who relapses during the study. To ensure that all subjects do receive anti-hypnozoite treatment, subjects who have not relapsed by Day 180 will be dosed with PQ 0.5mg/kg daily for 14 days to minimize the likelihood of *P.vivax* recurrences after the end of the study.

The DHA-PQP alone arm is considered crucial to the study design to evaluate the true efficacy of TQ in preventing relapse. The underlying relapse rate following a course of

DHA-PQP cannot be assumed from historical data due to the natural variation in both infection rates and relapse rates among infected subjects. Therefore, it is essential to measure the relapse rate following treatment with DHA-PQP alone in the same setting and time as the study treatment arms.

Although local treatment guidelines recommend an ACT plus PQ for radical cure of *P. vivax*, in real life, PQ is used infrequently because of concerns about its potential to cause red cell hemolysis in G6PD deficient subjects and facilities for assessing G6PD status are lacking. Additionally, compliance with unsupervised PQ is low.

As an alternative, PQ could be considered as the primary control arm in a study designed to demonstrate non-inferiority. However, a superiority design study will provide more robust evidence of efficacy of TQ, given the lack of agreement over dose and duration of PQ dosing. Of note, a non-inferiority study would also require hundreds of additional subjects.

Primaquine comparator arm: PQ is selected as the benchmark comparator for this study as PQ plus DHA-PQP is a first line treatment regimen for radical cure of *P. vivax* malaria in Indonesia. Inclusion of this arm provides a context against which to interpret the observed TQ efficacy rate. A statistical comparison for non-inferiority between the TQ and PQ regimen will not be performed due to the inadequate sample size. A 1:1:1 randomization ratio will be used to ensure a sufficiently large cohort of subjects in the PQ arm to obtain a precise estimate of the efficacy of PQ.

A TQ alone arm has not been included as the drug is absorbed more slowly than ACTs or CQ and therefore a delayed fever clearance time was observed when this drug (even though used at 4 times the dose in this study) was used alone to treat *P. vivax* subjects (refer to the Investigator Brochure).

Study duration: A six month study duration is considered sufficiently long to demonstrate a statistical difference in the incidence of relapse between DHA-PQP and DHA-PQP plus TQ. It is anticipated that at least 50% of subjects in the DHA-PQP alone arm will have relapsed by 6 months compared to less than 15% in the DHA-PQP plus TQ arm. A recent Indonesian study reported a relapse rate of 78% at 6 months following artesunate alone which is a shorter acting schizonticidal drug than DHA-PQP [Sutanto, 2013]. Therefore, a lower relapse rate may be expected in the DHA-PQP arm in this study. The study is powered to demonstrate a 35% difference in the relapse rate between the DHA-PQP alone arm and the DHA-PQP plus TQ arm, assuming a 10% drop out rate.

Justification for qualitative G6PD phenotyping: G6PD deficient subjects will be excluded from the study on the basis of a suitable Point of Care test e.g. Fluorescent Spot Test (FST) rather than a quantitative spectrophotometric phenotype assay. The FST test is sufficiently sensitive to identify G6PD deficient male subjects and is a more practical test to conduct on-site at the army base. This approach has been used successfully in other anti-relapse studies [Nelwan, 2015, Sutanto, 2013]. The qualitative test will be backed up by the quantitative phenotype assay performed at the Eijkman Institute with results available shortly after enrolment. Given that the subjects are all males, intermediate G6PD values are unlikely to be encountered and the FST is highly reliable at identifying truly deficient male hemizygotes [Baird, 2015, Bancone, 2014].

Rationale for Interim Blinded Data Review: It is not possible to predict whether the target number of 150 subjects can be enrolled from one battalion. Additionally, there is uncertainty regarding the effect size of DHA-PQP plus TQ compared to DHA-PQP alone in preventing *P. vivax* relapse in this study setting, with the possibility that the study may be over-powered. Therefore, a blinded review of the relapse data will be undertaken if it is not possible to completely recruit 150 subjects from one battalion but at least 120 subjects have been enrolled, with the intention of stopping enrolment if this review predicts that there will be sufficient relapses at the end of the 6 month follow up to provide sufficient power to show a meaningful clinical difference. Kaplan-Meier estimates will be made of the overall six month relapse rate, using all of the data available at that time in order to predict the relapse rate at the end of the 6 month follow up. This blinded review will only be performed if the study site considers that 150 subjects will not be yielded from one battalion but at least 120 subjects have been enrolled to ensure an adequate safety database for the DHA-PQP plus TQ regimen (see Section 9.2.3).

4.5. Dose Justification

Justification for tafenoquine dose:

A completed Phase IIB randomized, double-blind, dose-ranging study evaluated single doses of TQ (50mg to 600mg) co-administered with standard doses of the blood stage schizonticide, chloroquine in subjects with *P.vivax* malaria. The study demonstrated a clear dose-response with regard to prevention of relapse. Doses of 300mg and 600mg were both highly efficacious and superior to placebo, but with no evidence of additional efficacy with the higher dose [Llanos-Cuentas, 2014]. There were no new safety concerns of note identified in this study; the overall incidence of adverse events was similar across TQ doses. Thus, based on the Phase IIb data and those from a safety study [GlaxoSmithKline Document Number 2013N172577_00, Study TAF110027] that estimated the hemolytic potential of TQ in subjects heterozygous for G6PD deficiency, the 300mg dose was selected for evaluation in the ongoing Phase III programme in conjunction with a chloroquine. Additional supporting data for the 300mg TQ dose is available in the Investigator Brochure which includes a full description of the data from previously conducted studies.

Justification of DHA-PQP dose regimen:

The DHA-PQP dose regimen will be in accordance with the approved European prescribing information for Eurartesim (Eurartesim SmPC). Headache, anaemia, QTc prolongation, tachycardia, asthenia and pyrexia are the most common adverse events associated with this regimen in adults. Clinical trial data showed that QTc prolongation occurred more frequently and to a larger extent following Eurartesim than with comparators. In a Phase III study, before the third dose of Eurartesim, 3/767 patients (0.4%) had a QTcF value of >500ms versus none in the comparator group (Eurartesim SmPC). Modest QTc prolongation was also detected on Day 2 following dosing with DHA-PQP plus PQ in a recent Indonesian soldier study; the effect returned to baseline by Day 7 (Nelwan, 2015). No clinically significant drug-drug interaction was observed between DHA-PQP and TQ in GSK Study 200951. However, given the piperaquine-

induced QTc elongation observed, ECGs will be monitored in line with the Eurartesim prescribing information.

Justification of primaquine dose

Subjects in the PQ treatment arm will receive a 15mg dose of PQ for 14 days (equivalent to 0.25mg/kg in a 60kg subject), in line with the local treatment guidelines [Kusriastuti, 2012]. Subjects who have a recurrence of *P.vivax* during the study will be treated with an ACT plus PQ 0.5mg/kg for 14 days (equivalent to 30mg in a 60kg subject), which is in line with local treatment guidelines for *P. vivax* relapse.

Mild gastrointestinal upset occurs in about 10% of subjects taking PQ on an empty stomach, is dose-related and is improved by dosing with food [Fryauff, 1995]. Red cell hemolysis and methemoglobinemia are the two main hematological toxicities associated with PQ (Primaquine SmPC). Routine blood examinations (including blood cell counts and hemoglobin determinations) will be performed in line with the prescribing information. Acute hemolysis can occur if PQ is given to subjects with G6PD deficiency. All subjects who are G6PD deficient at screening will be excluded from this study. An independent assessor will determine metHb levels in order to avoid any potential for unblinding due to the anticipated increases in metHb following 8-aminoquinoline dosing (refer to SRM).

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with TQ can be found in the Investigator Brochure. The following section outlines the potential key risks associated with study treatment and mitigation strategy for this protocol. For a full description of all potential risks associated with study treatment, please refer to Section 6 of the Tafenoquine Investigator Brochure and to the SmPC's for primaquine and DHA-PQP.

4.6.1. Risk Assessment

Potential Key Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Treatments		
Hemolysis in G6PD-deficient subjects	Tafenoquine and primaquine are 8-aminoquinolines, a class of drug known to exert oxidative effects on hemoglobin (Hb). In patients with G6PD deficiency (or other disorders of erythrocytic pentose phosphate pathway of glucose metabolism) hemolysis is expected due to red blood cells (RBCs) lack of capacity to protect itself against oxidative effects of such drugs. Hemolysis has been reported in G6PD deficient patients inadvertently recruited into previous TQ studies.	• All subjects who are G6PD deficient will be excluded. Subjects with Hb levels <8g/dL will also be excluded. • Hematological study treatment stopping criteria are provided. • Subjects will be closely monitored around the expected time of Hb drop to enable intervention if required. • Recommendations for clinical management of hemolysis will be provided as part of the investigator training.
Methemoglobinemia	Methemoglobinemia has been observed in previous studies associated with larger total doses of tafenoquine than are being considered for clinical investigation. Risk factors have been assessed and include a strong relationship between metHb development, tafenoquine dose, and body surface area. The 300mg dose recommended for this study should pose minimal risk of causing elevations of metHb of clinical concern. Methemoglobinemia has also been observed following administration of large doses of primaquine and in NADH methemoglobin reductase deficient individuals.	• MetHb percentage will be monitored non-invasively at selected times throughout the study.

Potential Key Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
QTcF prolongation	The product labelling for DHA-PQP (Eurartesim SmPC) notes that in clinical trials, QTc prolongation occurred more frequently and to a larger extent following DHA-PQP than with comparators. Before the 3rd dose, in one of two Phase III studies, 3/767 (0.4%) subjects were reported to have a QTc value >500msec versus none in the comparator group. Absorption of piperaquine is increased in the presence of fatty food which may increase its effect on QTc interval. Preclinical studies determined that tafenoquine has a low potential for QTc prolongation. A tafenoquine thorough QT study did not show elongation of the QTcF at clinical doses. In the 200951 DDI study, the greatest increase in QTc was observed 4 hours after the last dose of DHA-PQP in both the DHA-PQP+TQ group and the DHA-PQP alone group; this time point will be a key point of interest for ECGs in this study. The label for primaquine (US prescribing information) notes that primaquine has the potential for QT interval prolongation and advises the need for ECG monitoring in subjects with relevant underlying comorbid conditions, as well as during concomitant administration with QT interval prolonging agents.	• ECG monitoring will be conducted in this study appropriate to DHA-PQP and primaquine labels. Study treatment stopping criteria are provided for QTc prolongation. • DHA-PQP will be dosed without food.

Potential Key Risks of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Design		
Risk of relapse in DHA-PQP alone arm	Subjects in the DHA-PQP alone arm are at increased risk of relapse during the study compared to subjects randomized to DHA-PQP+primaquine or DHA-PQP+tafenoquine	• Subjects will be under close observation throughout the study and will receive standard of care treatment at first sign of recurrent malaria (symptomatic or asymptomatic). On site clinic facilities will be available 24 hours a day, 7 days a week to ensure prompt management of any subject who develops recurrent malaria. • At the end of the study, any subject who has not relapsed will be given open label PQ 0.5mg/kg daily for 14 days to minimize the likelihood of relapses after the study.
Risk of partial study unblinding	Increases in methemoglobin anticipated in the 8-aminoquinoline arms could partially unblind the study.	• The site will employ an independent metHb assessor who will not have access to other data for the study. The data will be handled securely by an independent data manager at GSK. The other site staff, CRAs and GSK study team will not have access to the metHb data prior to unblinding the database. • Selection of PQ dose (15mg rather than 30mg) will reduce the likelihood of partial unblinding due to increases in metHb.

4.6.2. Benefit Assessment

In the absence of radical cure treatment, a percentage of subjects with *P. vivax* malaria will relapse due to the liver being infected with hypnozoites (the dormant form of the parasite). *P. vivax* can cause a debilitating fever as it preferentially invades reticulocytes as well as causing bystander hemolysis, which can also lead to the development of anemia. Repeated relapses are similarly debilitating and may result in further episodes of fever, weight loss, malnutrition and high output heart failure. Other consequences are loss of work, time at school missed and hospitalization due to vomiting, dehydration and anemia (resulting in the need for transfusion).

Subjects may benefit from participating in this study since they will be closely followed for 6 months, thus ensuring that any malaria recurrences will be appropriately treated and concurrent conditions managed. Any subject who has not relapsed by the 6 month timepoint will be treated with open label PQ for 14 days, to ensure that all participants receive anti-hypnozoite medication as part of the study. In the future, patients with *P.vivax* malaria may benefit from TQ since it can be administered as a single oral dose (due to its long half life) and is therefore a more convenient treatment regimen compared with the standard 14 day regimen of PQ, with the potential to improve patient compliance. Improved compliance should lead to improved clinical outcomes for patients with *P. vivax* malaria by further reducing relapse rates.

4.6.3. Overall Benefit:Risk Conclusion

TQ is being developed with the aim of a benefit:risk profile which is at least as good as the current standard therapy PQ. It is anticipated that this study will demonstrate that a convenient single dose of TQ is effective and safe when given in conjunction with an ACT for radical cure of *P. vivax* malaria and has a comparable profile to a 14 day regimen of PQ (15mg). All subjects will be closely observed and any adverse effects associated with study treatment or relapses of malaria will be promptly managed to minimize any risk to subjects participating in the study. G6PD deficient subjects will be excluded to avoid hemolytic risks associated with hypnozoite treatment.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the TQ Investigator Brochure.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE and SEX
1. Male subjects ≥18 years at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. The subject has a positive Giemsa smear for *P. vivax* (mixed infection with *P.falciparum* is acceptable). 3. The subject has a parasite density of >20 /µL. 4. Glucose-6-phosphate dehydrogenase (G6PD) normal using a suitable qualitative assessment e.g. NADPH qualitative fluorescent spot test (Trinity Biologicals, USA). 5. The subject has a QTcF of <450 msec. *N.B.* Reading based on an average of triplicate ECGs obtained over a brief recording period by machine. 6. The subject is willing and able to comply with the study protocol.

INFORMED CONSENT
7. Capable of giving signed informed consent as described in Section 7.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Severe *P.vivax* malaria as defined by WHO criteria (see Section 12.4 Appendix 4). 2. Severe vomiting (no food or inability to take food during the previous 8 hours). 3. Screening hemoglobin (Hb) concentration <8g/dL. 4. Liver function test ALT >2 x ULN. 5. Any clinically significant concurrent illness (e.g., pneumonia, septicemia), significant pre-existing conditions (e.g., renal disease, malignancy, Type 1 diabetes), conditions that may affect absorption of study treatment (e.g., vomiting, severe diarrhea), or clinical signs and symptoms of severe cardiovascular disease (e.g., uncontrolled congestive heart failure, severe coronary artery disease). These abnormalities may be identified on the screening history and physical or laboratory examination. 6. History of hypersensitivity, allergy or adverse reactions to DHA or other artemisinins, piperaquine, tafenoquine or primaquine.

CONCOMITANT MEDICATIONS
7. Subject has previously received treatment with tafenoquine, or has received treatment with any other investigational drug within 30 days of study entry or within 5 half-lives, whichever is longer. 8. Subject has taken anti-malarials (e.g., ACTs, mefloquine, primaquine, quinacrine) or drugs with anti-malarial activity within the past 30 days (see Section 12.5 Appendix 5). 9. Subjects who will likely require the use of medications from the prohibited medications list or have taken them in the past 30 days (see Section 12.5 Appendix 5) which include the following medications and medication classes: • Drugs with hemolytic potential • Drugs known to prolong the QTc interval including: o Antiarrhythmics (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol). o Neuroleptics (e.g. phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine) and antidepressive

CONCOMITANT MEDICATIONS
agents. ○ Certain antimicrobial agents, including agents of the following classes: macrolides (e.g. erythromycin, clarithromycin), fluroquinolones (e.g. moxifloxacin, sparfloxacin), imidazole and triazole antifungal agents and also pentamidine and saquinavir. ○ Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine). ○ Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide. • The biguanides: phenformin and buformin (but excluding metformin-see Section 6.9.2). • Drugs that are substrates of the renal transporters OCT2, MATE1 and MATE2 and have a narrow therapeutic index (for example, the antiarrhythmic agents: dofetilide, procainamide and pilsicainide).

RELEVANT HABITS
10. Anticipated to be unable to consume daily study treatment under direct supervision by the research team. 11. Previous participation in the present clinical trial, i.e., subjects experiencing relapse during or after the study period may not be enrolled as a new subject. 12. History of illicit drug abuse or heavy alcohol intake, such that full participation in the study could be compromised.

CONTRAINDICATIONS
13. Any contraindication in the opinion of the Investigator to DHA-PQP or primaquine administration (refer to locally approved prescribing information for primaquine) such as: • Family history of sudden unexplained death (DHA-PQP) • Known congenital QTc prolongation (DHA-PQP) • Known history of a medical condition known to prolong the QT interval: e.g.myxoedema, cardiomyopathies, recent myocardial infarction (DHA-PQP) • History of symptomatic cardiac arrhythmias or with clinically relevant

bradycardia (DHA-PQP)

- Cardiac illnesses predisposing to arrhythmias e.g. severe hypertension, left ventricular hypertrophy, cardiomyopathies, cardiac failure with reduced ejection fraction (DHA-PQP)
- Presence of an electrolyte disturbance particularly hypokalemia, hypocalcemia, hypomagnesemia (DHA-PQP)
- Rheumatoid arthritis, lupus erythematosus and other systemic conditions that may cause granulocytopenia (primaquine)
- History of hemolytic anemia, methemoglobinemia and leucopenia (primaquine)

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events.

Any subject who receives DHA-PQP but is not subsequently randomized to blinded study treatment will be deemed a Screen Failure.

5.4. Withdrawal/Stopping Criteria

A subject may withdraw from the study or discontinue study treatment at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

Premature Study Withdrawal

A subject is considered to be withdrawn prematurely from the study if they do not complete the Day 180 assessment. Subjects may be prematurely discontinued from the study for any of the following reasons:

- Adverse event
- Protocol deviation
- Study closed/terminated

- Loss to follow-up
- Consent withdrawal
- Subject or investigator non-compliance
- At the request of the subject, investigator, or sponsor

Subjects are not obligated to state the reason for withdrawal from this study. However, the reasons for withdrawal, or failure to provide a reason, must be documented by the investigator on the Completion/Withdrawal section of the electronic Case Record Form (eCRF). If a subject is withdrawn from the study for any reason, the investigator should make every effort to perform the study evaluations as specified in the Time and Events table for the Withdrawal visit as applicable.

Premature Withdrawal of Study Treatment

If a subject prematurely discontinues from study treatment for any reason or reaches the primary endpoint of relapse, they should continue to attend study visits to Day 180. The reason for withdrawal from treatment should be recorded in the electronic case record form (eCRF). Given the long half life of tafenoquine, the maximal pharmacodynamic effects such as potential hemolysis or methemoglobinemia may occur several days after completion of dosing. These data will be recorded, as they comprise an essential evaluation that needs to be done before discharging any subject from the study. Therefore, the investigator should continue following subjects for all protocol assessments, up to and including Day 180 whenever possible. The subject should be given appropriate rescue therapy according to local treatment guidelines if they develop a malarial recurrence (see Section 6.9.1.2).

Subjects should discontinue taking study treatment if they meet **any** of the criteria below:

- Intolerable AEs:
  - Any grade 4 AE or toxicity in the absence of compelling evidence that the AE is not related to investigational product(s)
- Clinically significant laboratory results considered by the investigator to warrant withdrawal from the study treatment
- Liver chemistry stopping criteria (refer to Section 5.4.1 and Section 12.2 Appendix 2)
- Hemoglobin stopping criteria: Given the hemolytic potential of TQ and PQ in subjects with G6PD deficiency, study specific hematologic stopping criteria will be employed (refer to Section 5.4.2)
- QTc stopping criteria (refer to Section 5.4.3)

When QT or hemolytic stopping criteria are met, this must be promptly reported by the investigator to GSK as a Serious Adverse Event (see Section 7.5)

Subjects Lost to Follow Up

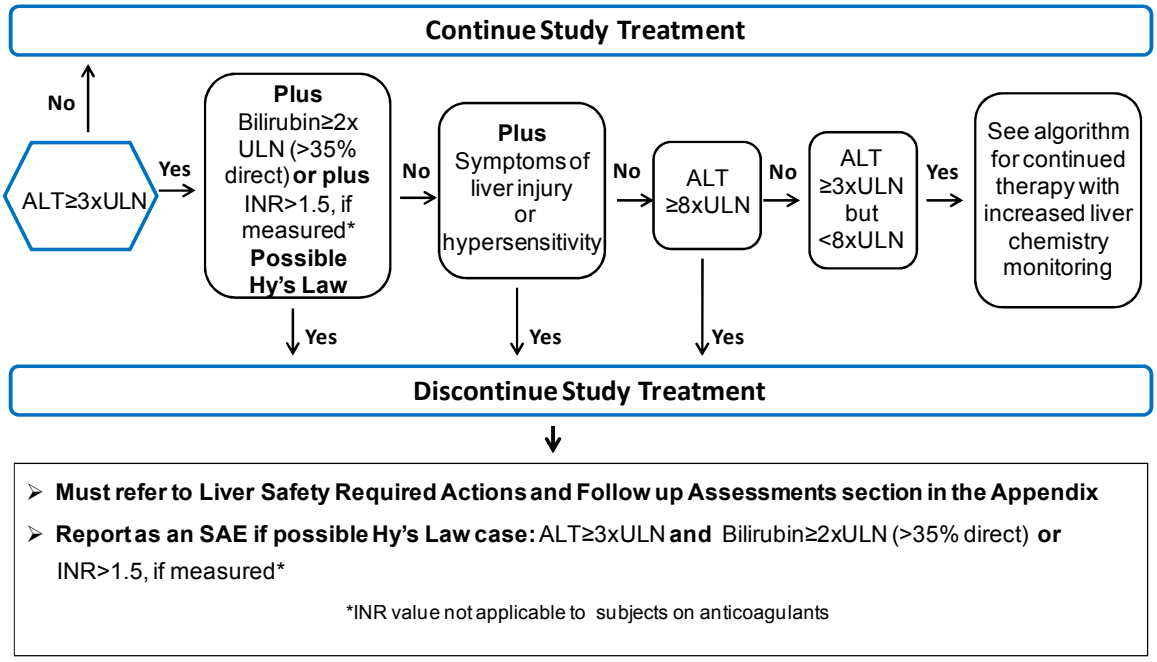
The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

5.4.1. Liver Chemistry Stopping Criteria

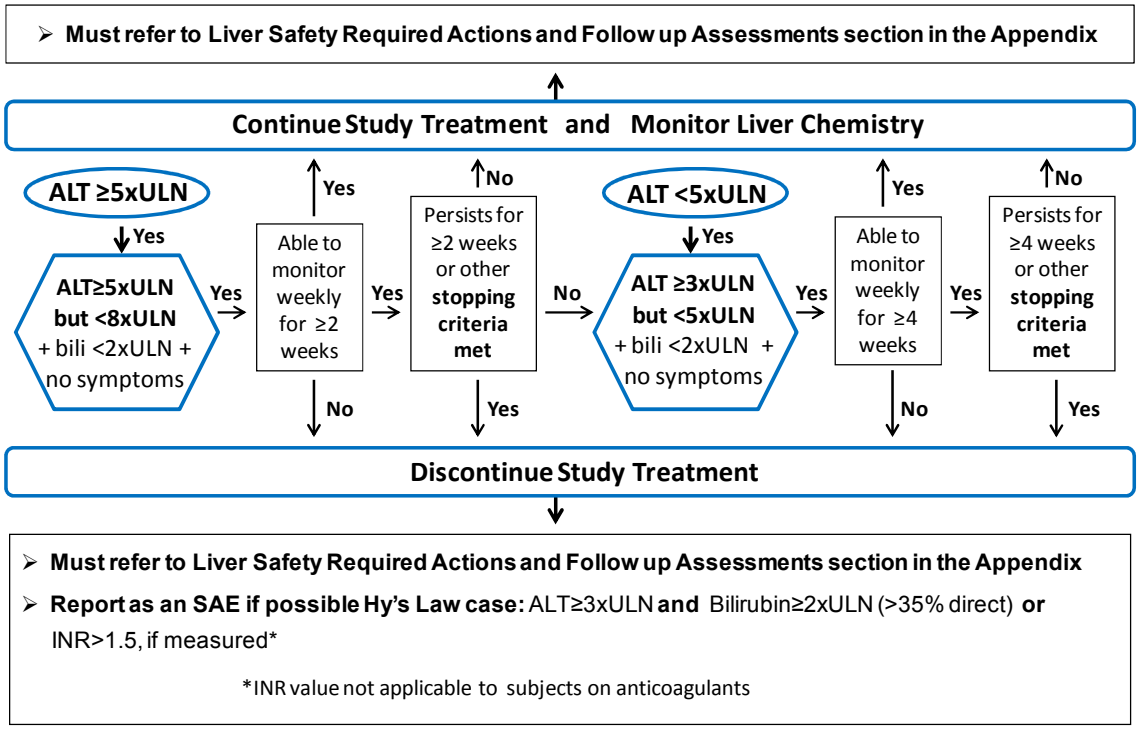
Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



As blinded tafenoquine study treatment is administered as a single dose, the above criteria for stopping medication do not apply. However, the liver safety required actions and follow up assessments must be followed if the stopping criteria are met – see Appendix 2 (Section 12.2). The liver safety follow-up assessments will be carried out by a local commercial laboratory where possible. If assessments are not available in Indonesia, samples will be stored in Indonesia until such time as a Material Transfer Agreement (MTA), if necessary, is formally approved for the transfer of the sample to the designated laboratory for analysis.

Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2 (Section 12.2).

5.4.1.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met, are not allowed by any subject participating in this study.

5.4.2. Hemoglobin Stopping Criteria

Blinded study treatment will be stopped immediately in any subject who meets the protocol-defined criteria for Hb drop (See Section 7.5.1.1) AND has EITHER clinical evidence of hemolysis OR laboratory evidence of hemolysis based on an assessment of the tests listed below. These laboratory tests will be performed immediately once a protocol-defined Hb drop is noted by the investigator.

Hematology

- Hemoglobin
- Hematocrit
- Platelets
- WBC
- RBC
- Reticulocytes

Clinical Chemistry

- Creatinine
- BUN
- Total bilirubin
- Indirect bilirubin
- AST
- ALT
- Alkaline phosphatase
- CPK
- LDH
- Visual inspection of urine and dipstick

Subjects will also be required to have a repeat G6PD quantitative phenotype test to confirm that they are not G6PD deficient. G6PD genotyping may be performed if repeat phenotyping would not define G6PD status (e.g. transfusion given or high reticulocyte count).

5.4.3. QTc Stopping Criteria

Study treatment will be stopped if any of the following criteria are met:

• QTcF >500 msec

• Uncorrected QT >600msec

These criteria should be based on the average QTcF value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QTcF interval, two more ECGs should be obtained over a brief period, and then the averaged QTcF values of the three ECGs should be used to determine whether the subject should then be discontinued from the study. ECG monitoring during the following 24-48 hours should be applied for subjects found to have a prolongation to this extent.

For subjects with underlying bundle-branch block, the criteria is QTcF ≥530msec.

5.5. Subject and Study Completion

A completed subject is one who has been randomized to blinded study treatment and has a day 180 assessment.

The end of the study is defined as the last subject's last visit.

6. STUDY TREATMENT

'Blinded study treatment' refers to tafenoquine, primaquine and the corresponding placebos.

	Study Treatment				
Product name:	Tafenoquine (SB-252263)	Matched-Placebo for Tafenoquine	Primaquine	Matched-Placebo for Primaquine	DHA-PQP 320/40 dihydroartemisinin-piperaquine
Formulation description:	Each tablet will contain 150mg tafenoquine	Each tablet will contain tafenoquine matched-placebo	Each over-encapsulated tablet will contain 15mg primaquine	Each capsule will contain primaquine matched-placebo	Each tablet will contain 320mg piperaquine tetrasphosphate (as the tetrahydrate;PQP) and 40mg dihydroartemisinin (DHA)
Unit dose strength(s) /Dosage level(s):	150 mg tafenoquine	Placebo	Equivalent to 15mg primaquine base	Placebo	Equivalent to 40mg DHA and 320 PQP base
Route of Administration:	Administer orally	Administer orally	Administer orally	Administer orally	Administer orally
Dosing instructions:	Administer 2 tablets with water as a single dose after a meal. Dose to be taken at least 3 hours after DHA-PQP	Administer 2 tablets with water as a single dose after a meal. Dose to be taken at least 3 hours after DHA-PQP	Administer 1 capsule daily with water as a single dose after a meal for 14 days. Dose to be taken at least 3 hours after DHA-PQP (Days 1, 2 and 3).	Administer 1 capsule daily with water as a single dose after a meal for 14 days. Dose to be taken at least 3 hours after DHA-PQP (Days 1, 2 and 3).	Single dose for 3 days 3 tablets per day for subjects <75Kg 4 tablets per day for subjects ≥75Kg Dose to be taken at least 3 hours after last food intake. No food to be taken for at least 3 hours after dosing

6.1. Treatment Assignment

Subjects will be assigned to one of three blinded treatment arms: DHA-PQP alone, DHA-PQP plus TQ or DHA-PQP plus PQ in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

Subjects will be randomized via an interactive web recognition system (IWRS) to blinded study treatment after beginning administration of open label DHA-PQP. Each subject scheduled to receive blinded study treatment will receive a treatment allocation number (i.e. randomization number) via the IWRS system on Day 1. The treatment allocation

ratio will be 1:1:1. Once a randomization number has been allocated to a subject, it cannot be re-assigned to any other subject.

Open label DHA-PQP will be administered daily over three consecutive days. Each dose will be taken at least 3 hours after the last food intake and no food will be taken for 3 hours after each dose. If a subject vomits within 30 minutes of taking DHA-PQP on Days 1 to 3, the whole dose should be re-administered; if the subject vomits within 30-60 minutes, half the dose should be re-administered. Repeat dosing with DHA-PQP should not be attempted more than once. If the repeat dose is vomited on Day 1, the subject should be withdrawn from the study and given appropriate rescue medication as outlined in Section 6.9.1.2.

Blinded study treatment will be administered daily over 14 days together with food (at least 3 hours after dosing with DHA-PQP on Days 1, 2 and 3). If the subject vomits within 1 hour following dosing, a repeat dose should be given. If the repeat dose is vomited on Day 1, the subject should be withdrawn from the study and given appropriate rescue medication as outlined in Section 6.9.1.2.

6.2. Planned Dose Adjustments

No planned dose adjustment is allowed.

6.3. Blinding

This will be a double-blind study and both subject and study staff will remain blinded to treatment. The following will apply:

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment via the IWRS system but this information should only be acquired in the case of an emergency.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF.
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of

the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

- The independent metHb assessor at the site and the independent data manager at GSK will have access to the metHb data which could potentially unblind them to the 8-aminoquinoline treatment arms. However, these data will be handled and stored securely and these personnel will not have access to other data for the study.

6.4. Packaging and Labeling

The following study treatment will be provided for each subject:

- Open label DHA-PQP tablets sufficient for 3 days dosing (3 or 4 tablets per day according to weight –refer to Section 6)
- One bottle containing 2 tafenoquine tablets (150mg per tablet) or 2 matched placebo tablets
- One bottle containing 16 overencapsulated primaquine tablets (15mg per overencapsulated tablet) or 16 matched placebo capsules (i.e. sufficient for 14 days dosing and 2 spare capsules)

The contents of the label will be in accordance with all applicable regulatory requirements.

6.5. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.6. Compliance with Study Treatment Administration

Subjects will receive all doses of study treatment at the site directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

6.7. Study Treatment Overdose

An overdose for this study will be considered as any dose of study treatment that is more than the planned dose for each dosing occasion.

DHA-PQP

No specific antidote for DHA-PQP has been identified. In the event that overdose or toxicity does occur, individuals should stop the mediation. Symptomatic and supportive therapy should be given as appropriate, including ECG monitoring because of the possibility of QTc interval prolongation.

Tafenoquine

No specific antidote for tafenoquine has been identified. In the event that overdose or toxicity occurs, individuals should be managed with appropriate supportive measures and clinical judgement. Immediate induction of emesis and/or gastric lavage is not recommended. Hemodialysis is unlikely to be clinically useful as tafenoquine is highly protein-bound.

Methemoglobinemia has been observed in clinical trials at therapeutic doses of tafenoquine; clinically significant levels could possibly be encountered in overdose. Signs and symptoms of methemoglobinemia include (but are not limited to) blue discoloration of the skin and lips, and shortness of breath.

Primaquine

No specific antidote for PQ has been identified. In the event that overdose or oxicity occurs, individuals should stop the medication and be managed with appropriate supportive measures and clinical judgement. Immediate induction of emesis and/or gastric lavage is not recommended.

Symptoms of PQ overdose include abdominal cramps, vomiting, burning, epigastric pain, central nervous system and cardiovascular disturbances, cyanosis, methemoglobinemia, moderate leukocytosis or leukopenia and anemia.

In the event of an overdose of any study treatment the investigator or treating physician should:

1. Contact the Medical Monitor immediately
2. Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until resolution.
3. Obtain a plasma sample for pharmacokinetic (PK) analysis if requested by the Medical Monitor (determined on a case-by-case basis)
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.8. Treatment after the End of the Study

All subjects who complete the Day 180 visit and have not had a recurrence of *P.vivax* malaria, will be treated with open label PQ (0.5mg/kg daily for 14 days) to minimize the likelihood of *P.vivax* relapses occurring after the end of the study. This medication will be sourced locally and will be taken together with food. Subjects who receive open label PQ at the end of the study will be required to return to the clinic for a safety follow up visit, 15 days later. PQ administration at the end of the study will be recorded in the eCRF.

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

6.9. Concomitant Medications and Non-Drug Therapies

6.9.1. Permitted Medications and Non-Drug Therapies

6.9.1.1. Concomitant Medications

All subjects can be given paracetamol, with caution during the study but administration time must be recorded in the eCRF. Allowable antibiotics are penicillins, cephalosporins, carbapenems and aminoglycosides (please refer to Section 12.5, Appendix 5). If the investigator considers that other antibiotics are required, the Medical Monitor should be consulted on a case by case basis.

Antiemetic choice should be based around the risk of further QTc prolongation over and above that which may be caused by DHA-PQP and in line with the approved prescribing information for DHA-PQP (refer to SRM).

All concomitant medications (prescription and non-prescription) taken during the study should be recorded in the eCRF. The minimum requirement is drug name, date of administration and reason for administration.

6.9.1.2. Rescue Medication

Subjects diagnosed with *P.vivax* relapse (i.e. a positive blood smear with or without vivax symptoms) during the 180 day follow up period will be given an ACT plus PQ 0.5mg/kg for 14 days as rescue medication. These subjects will continue to be monitored for safety and efficacy at all scheduled visits through Day 180. Details of rescue medication including reason for the rescue medication will be recorded in the eCRF. Rescue medication will be sourced locally.

6.9.2. Prohibited Medications and Non-Drug Therapies

The following drugs are prohibited for use from 30 days prior to screening:

- Anti-malarials and other medicines with known anti-malarial activity.
- Drugs with hemolytic potential.
- Drugs other than PQP known to prolong the QTc interval.
- Drugs known to interact with DHA-PQP or primaquine (refer to Eurartesim and primaquine SmPCs).
- Drugs excreted via renal transporters MATE, MATE2-K and OCT2.

  Results from an *in vitro* renal transporters study showed that tafenoquine inhibits the renal transporters MATE1, MATE2-K AND OCT2. Inhibition of these transporters may explain mild, transient, asymptomatic increases of creatinine observed in previous clinical studies and may lead to increased exposure to medications excreted via these transporters. The following drugs are therefore prohibited for use from 30

days prior to study entry and for a period of 21 days following the blinded dose of tafenoquine.

- Anti-diabetic drugs of the biguanide class:
  - Phenformin
  - Buformin
- Anti-arrhythmic drugs:
  - Dofetilide
  - Procainamide
  - Pilsicainide

Metformin, another biguanide anti-diabetic, may continue to be taken provided the subject has serum creatinine below the upper limit of normal and has no concomitant medical condition that increases the risk of lactic acidosis.

The use of herbal remedies during the course of the study should be avoided. However, if taken this should be recorded in the eCRF under concomitant medication.

See Appendix 5 in Section 12.5 for a non-exhaustive list of prohibited medicines and further guidance.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Section 7.1).

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
    1. 12-lead ECG
    2. vital signs
    3. blood draws.

  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The IRB/IEC would be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 150mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Table

Procedures	Visit Day (Treatment Period Days 1-14)															
	1	1		2[b]	3	4	5	6	7	8	9	10	11	12	13	14
	Pre DHA-PQP	DHA-PQP	Blinded med[a]													
Written Informed Consent	x															
Subject Demography	x															
Medical History	x															
Disease History	x															
Signs & Symptoms	x	x														
Therapy History	x															
Inclusion/Exclusion Criteria	x															
Efficacy Assessments																
Blood smears	x			x[c]	x[c]				x							x
Plasmodium PCR genotyping/sequencing	x															
Safety Assessments																
Concomitant Medication	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Examination	x			x	x				x							
Vital Signs [d]	x			x	x[o]				x							x
12-lead ECG [e,]	x				x				x							
Adverse Events [f]			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serious Adverse Events [g]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
G6PD (phenotyping) h	x															
G6PD/CYP2D6 (genotyping) [i]	x															
Laboratory Assessments																
Hematology/Clin.Chem/urinalysis [j]	x				x		x		x							x
Methemoglobin[l]	x			x	x	x	x	x	x	x	x	x	x	x	x	x
PK sampling	x	x[k]							x							x
Investigational Product																
Dispense Open Label DHA-PQP		x		x	x											
Dispense Blinded Study Treatment (access IWRS on day 1 only)			x	x	x	x	x	x	x	x	x	x	x	x	x	x

Time and Events Table (Continued)

Procedures		Visit Day (Follow Up Period)								
	21	28	60	90	120	150	180	195[p] (only for subjects who have not relapsed prior to Day 180)	Relapse	Withdrawal from study
Window	**-/+3d**	**-3d, +15d**	**-16 d, +15d**	**-14d, +15d**	**-14d, +15d**	**-14d, +19d**	**-/+10d**	**Day 180 + 15d to 21d**		
Efficacy Assessments										
Parasitological Assessment (blood smears)	x	x	x	x	x	x	x		x	x
Plasmodium PCR genotyping/sequencing									x	
Safety Assessments										
Concomitant Medication	x	x	x	x	x	x	x	x	x	x
Physical Examination	x	x	x	x	x	x	x		x	x
Vital Signs [d]	x	x	x	x	x	x	x		x	x
12-lead ECG [e]		x							x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x
Serious Adverse Events	x	x	x	x	x	x	x	x	x	x
Dispense rescue treatment (ACT+PQ)									x	
Laboratory Assessments										
Hematology/Clinical Chemistry	x	x	x	x	x				x[m]	x[m]
Methemoglobin[l]	x	x	x						x	x
PK Sampling		x	x						x[n]	
Open Label Primaquine										
Dispense open label PQ –only for subjects who have not relapsed prior to D180							x			

Time and Event Table Notes:

a) Blinded study treatment may be started on Day 1 or Day 2. If started on Day 2, blinded primaquine/placebo is given from Day 2-15.
b) If a subject starts blinded study treatment on Day 2, the following assessments should be completed on Day 15: Concomitant medication, AEs/SAEs, methemoglobin, dispense blinded study treatment.
c) Blood smears to be taken twice daily until two consecutive negative smears 6-12 hours apart.
d) Vital signs include height and weight (screening only), blood pressure, temperature, heart rate and respiratory rate.
e) ECGs will be done in triplicate on Day 1 (prior to DHA-PQP). Subsequent ECGs will be done as single ECGs unless prolonged QTcF is seen. ECG timings post baseline will be as follows: 1) Before the last of the three daily doses of DHA-PQP 2) 4 hours (window -1 to +2 hours) after last dose of DHA-PQP, 3) Day 7, 4) Day 28 and 5) relapse/withdrawal if within 28 days post-dose.
f) Adverse events are recorded from the time of the first dose of study treatment.
g) Serious adverse events are recorded from the time of consent in order to fulfil international regulatory requirements.
h) G6PD phenotyping to be performed by suitable qualitative test (refer to SRM) and quantitative spectrophotometric analysis.
i) Blood sample to be collected for CYP2D6 genotyping and stored for possible G6PD genotyping. Sample for G6PD genotyping may be analyzed in the event of an SAE due to hemoglobin decline where a repeat G6PD phenotype assay would not define G6PD status (e.g. transfusion given or high reticulocyte count).
j) Dipstick urinalysis to be only done at screening.
k) PK samples must be taken 6-12 hours and 24-48 hours post blinded dose of tafenoquine.
l) Methemoglobin will be measured daily up to Day 14, alternate days up to Day 28 and on Day 60.
m) Hematology/clinical chemistry to be done at relapse/withdrawal (up to Day 120 only).
n) PK will be done as close to the time of relapse as possible (up to Day 60 only).
o) Vital signs on Day 3 will be done immediately after ECGs (ie before the last of the three daily doses of DHA-PQP and 4 (-1 to +2) hours after the last dose of DHA-PQP.
p) The D195 assessment is only required for subjects who do not relapse prior to D180 and receive open label primaquine (0.5mg/kg daily for 14 days) at the end of the study. Subjects who have relapsed prior to Day 180 will complete the study at D180.

7.2 Screening and Critical Baseline Assessments

Informed Consent Procedure

Signed, written, dated informed consent must be obtained from each potentially eligible subject before any study specific procedure is undertaken. The research team leaders will meet commanders and troops to explain the concept and importance of voluntary informed consent prior to inviting subjects to participate in the study. The person obtaining written consent must be independent of the subject to ensure consent is voluntary (i.e not the subject's commander or supervisor) to avoid perceptions of coercion or undue influence on a military subject. The subject's commander or supervisor must not be in the room during the consent process. Informed consent will be obtained on an individual basis, rather than as a group, ensuring that each subject has the opportunity to ask questions about the study.

Following informed consent, the following clinical and laboratory assessments will be conducted as described below (see Time and Events Table Section 7.1)

a) Procedures to be performed prior to DHA-PQP administration

- Demographic data will be collected to include details of year of birth, gender, race and ethnicity.
- Medical history will be collected including cardiovascular history and associated risk factors.
- A physical examination will be conducted including:
    - Cardiovascular examination
    - Abdominal examination including an assessment of splenomegaly
    - Respiratory examination
- Vital signs will be assessed including height, weight, systolic and diastolic blood pressure, temperature (oral, axillary or tympanic), heart rate and respiratory rate. The same methodology should be used for measurement of temperature for all subjects.
- Investigators will assess *P. vivax* malaria symptoms at baseline. The incidence and severity (defined as absent, mild, moderate, severe, or unknown) of the following symptoms will be recorded: chills and rigours, headache, dizziness, abdominal pain, anorexia, nausea, vomiting, diarrhea, pruritis or itching, and coughing. The date of onset of symptoms will also be recorded. The investigator or designee can also assess and record any other *P. vivax* malaria symptoms.
- Blood smears for parasitological assessment will be collected and examined for asexual parasite count and gametocyte blood count (see Section 7.4 and the SRM for further details).
- Current and prior medications will be reviewed including any anti-malarial medication that has been used.

- A blood sample will be collected for *Plasmodium* genotyping analysis. An additional blood sample will be collected for future exploratory plasmodium whole genome sequencing (if parasite counts allow) (See Section 7.4 and Section 7.7).
- G6PD status will be assessed using the Fluorescent Spot Test (FST) or other suitable Point of Care Test (see SRM) to determine the subject's eligibility. An additional Point of Care Test (in development) may also be performed but the results of this test would not be used for eligibility. The quantitative spectrophotometric G6PD analysis will also be performed but results will not be available at the time of randomization. If results are discordant, the subject will be reviewed and appropriate G6PD testing will be repeated.
- Hematology and clinical chemistry assessments will be performed (refer to Section 7.5.5).
- Methemoglobin levels will be assessed using a non-invasive machine. This assessment will be performed by an independent person who will not participate in any other study procedures at the site. The data will be transmitted securely to GSK data management and will not be shared with other site staff unless result is above a preset threshold that requires a safety assessment (refer to SRM).
- A12 lead ECG will be performed with the subject in a semi-supine position having rested in this position for at least 10 minutes beforehand. Measurements that deviate substantially from previous readings will be repeated immediately. Three (3) measurements will be taken at screening, five minutes apart.

    - The mean heart rate, RR interval, QRS duration, uncorrected QT interval and QTcF (QT corrected by Friderica's formula) will be calculated from automated ECG readings and abnormal findings will be recorded in the eCRF. The mean value recorded pre-DHA-PQP will be classified as baseline.

- A blood sample will be collected for CYP2D6 genotyping and possible G6PD genotyping. The extracted nucleic acid sample for G6PD genotyping will be stored and may be analyzed in the event of an SAE due to hemoglobin decline where a repeat G6PD phenotype assay would not define G6PD status (e.g. transfusion given or high reticulocyte count).

- Subjects who have undergone screening and meet the label requirements for DHA-PQP dosing can receive open label DHA-PQP if the clinician deems that appropriate (e.g. symptomatic disease), and at least 3 hours have elapsed since last food intake. Thus, DHA-PQP may be commenced whilst the results of the hematology, clinical chemistry or G6PD deficiency screening tests are pending. Once these laboratory test results are available and the subject eligibility is confirmed, they will be randomized via the IWRS to blinded study treatment. The first dose of blinded study treatment will be administered with food at least 3 hours after DHA-PQP on Day 1 or Day 2.

7.3 Unscheduled Visits

Subjects will be encouraged to return for an unscheduled visit if they feel unwell or develop a fever at any time during the 180 day study period. The subject should be assessed for any adverse events and other procedures conducted as clinically indicated in order to diagnose/rule out malarial recurrence or explain other symptoms and signs.

7.4 Efficacy

Parasitology

- **Asexual parasite counts**

Microscope blood slides will be prepared prior to the first dose of DHA-PQP at screening on Day 1 to confirm the diagnosis of *P. vivax* malaria, and then twice a day, 6-12 hours apart for the first 3 days, or until 2 consecutive negative thick blood smears are obtained. Where the subject receives DHA/PQP < 6 hours from midnight on Day 1, a second Day 1 slide may be omitted.

Microscope blood slides will be prepared at subsequent visits on Days 7, 14, 21, 28, 60, 90, 120, 150 and 180 (refer to Section 7.1 Time and Events table). In addition, blood films should be obtained whenever parasitological re-assessment is required and at the relapse visit or withdrawal visit as applicable. For detailed instructions on the methodology for staining and counting please refer to the SRM.

Slides are considered negative after review of 100 high-power fields. A negative slide refers to the absence of asexual parasites only.

- **Gametocyte counts**

In the same way, thick film slides will be read for gametocytes on Day 1 (prior to the first dose of DHA-PQP) and then twice a day 6-12 hours apart for the first 3 days or until 2 consecutive negative thick blood smears are obtained. Slides will be prepared at subsequent visits on Days 7, 14, 21, 28, 90, 120, 150 and 180 (refer to Section 7.1 Time and Events Table).

External quality control

A proportion of slides from the study site will be examined in Indonesia by an independent laboratory, blinded to treatment assignment. The procedure for quality control will be described in the SRM.

Parasite Genotyping and Whole Genome Sequencing

A sample will be collected for subsequent DNA extraction and PCR analysis of *Plasmodium* species on all subjects at screening (Day 1; pre-dose) and if necessary, at the time of the first recurrence. PCR of the *P. vivax* genes, such as *Pv*MSP-1, *Pv*CSP and *Pv*AMA-1, as well as any other markers deemed appropriate, will be used to distinguish between genetically homologous and genetically heterologous infection.

A further sample will be taken for subsequent parasite exploratory whole genome sequencing at baseline and if occurring, at the time of first recurrence (refer to Section 7.7).

7.5 Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Blinded safety will be reviewed on a monthly basis by a GSK/MMV safety review board which includes a reviewer independent of the study sponsors.

7.5.1 Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 3 (Section 12.3). The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.5.1.1 Protocol-Defined SAE (Hb drop)

A Hb drop is defined as any ONE of the following occurring in the first 15 days of the study:

- a relative hemoglobin decrease of ≥30% from baseline, *or*
- an absolute hemoglobin decrease of >3g from baseline, *or*
- a drop in absolute hemoglobin to < 7.0g/dL.

All protocol-defined Hb drops must be reported as an SAE, even if asymptomatic and not requiring medical intervention.

If a protocol-defined SAE (Hb drop) is noted, hematology and clinical chemistry tests will be performed immediately and subjects will be required to have a repeat G6PD quantitative phenotype test to confirm they are not G6PD deficient (refer to Section 5.4.2).

7.5.1.2 Time period and Frequency for collecting AE and SAE information

- AEs will be collected from the start of study treatment until the follow-up contact (see Section 7.5.1.4), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 12.3 Appendix 3.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any

time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Section 12.3 Appendix 3.

7.5.1.3 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

7.5.1.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 3 (Section 12.3).

7.5.1.5 Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 (Section 12.3) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

7.5.1.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Occurrence of malaria is an efficacy endpoint for this study. Consequently malaria should not typically be reported as an AE/SAE and will not be subject to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of a serious adverse event). The occurrence of malaria and any associated signs and symptoms must instead be recorded on the study Malaria Signs and Symptoms (i.e., Disease-Related Event [DRE]) page in the subject's eCRF.

The following are considered to be the common signs and symptoms associated with malaria infection/relapse which should not be reported as AEs/SAEs but captured on the DRE page. However, this should be done ONLY IF confirmed with a positive slide reading for the presence of *P. vivax* malaria at the time symptoms are reported. If any of the following symptoms are reported and the slide read is negative, they should be reported as an AE or SAE as usual.

- Pyrexia
- Chills
- Rigor
- Headache

These DREs will be monitored by the GSK Safety Review Team on a routine basis. However, if the following condition applies, then the event should be reported as an SAE using the standard process:

"The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual subject."

If the above condition is met then record the event on the SAE page rather than the DRE page and report promptly (i.e., expedited reporting, see Appendix 3, Section 12.3) to GSK.

As the occurrence of malaria is an efficacy endpoint for this study, should malaria be reported as an SAE, it will not be subject to expedited reporting regardless of the "expectedness" or "relatedness" of the event.

7.5.1.7 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK or designee of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will

comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.5.2 Physical Exams

Physical examinations will be done at the timepoints indicated in the Time and Events Table (Section 7.1).

- A brief physical examination will include, at a minimum, assessments of the lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.5.3 Vital Signs

Vital signs will be measured at the timepoints indicated in the Time and Events table (Section 7.1) in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate and respiratory rate. Height and weight will be recorded at Screening only.

7.5.4 Electrocardiogram (ECG)

12 lead ECGs will be done in triplicate on Day 1 (record the average of triplicate ECGs obtained over a brief recording period in the eCRF). Subsequent ECGs will be done as single ECGs unless prolonged QTcF is seen, in which case the average of triplicate ECGs obtained over a brief recording period will be calculated and recorded in the eCRF. ECG timings will be as follows:

- Day 1 Prior to start of DHA-PQP
- Day 3 Before the last of the three daily doses of DHA-PQP
- Day 3 4 hours after the last dose of DHA-PQP (window -1 hr to +2 hrs)
- Day 7
- Day 28
- Relapse/withdrawal (if within 28 days post-dose)

12-lead ECGs will be obtained using an ECG machine that measures HR, PR, QRS, RR and uncorrected QT intervals. QTcF will be calculated from automated QT and HR readings (See SRM).

7.5.5 Clinical Safety Laboratory Assessments

Clinical chemistry and hematology samples will be analyzed by the local laboratory. All protocol required laboratory assessments, as defined in Table 1 and Table 2, must be conducted in accordance with SRM and at the timepoints indicated in the Protocol Time and Events Schedule (Section 7.1).

All laboratory data will be used for the purpose of safety analysis and reporting for this study. Any laboratory tests the attending physician or investigator deems necessary for the care and safety monitoring of the study subjects will be conducted by the local laboratory. All laboratory results that are considered clinically significant should be recorded as AEs.

Hemoglobin and/or hematocrit measurements that deviate substantially from previous readings should be immediately repeated via venous sampling. If a protocol-defined Hb drop is observed upon repeat testing (Section 7.5.1.1), all additional clinical chemistry labs should be obtained immediately.

If, after Day 3, platelet counts are $<5\times10^4$ per μL, the test should be repeated or confirmed with a manual slide reading.

Table 1 Hematology Tests

Hemoglobin	Hematocrit	Platelets	MCV
WBC	RBC	WBC Differential (neutrophils and lymphocytes as a minimum)	

Table 2 Clinical Chemistry Tests

Creatinine	BUN	Total bilirubin	Indirect bilirubin
AST	ALT	ALP	CPK

Urinalysis will be conducted at screening. Urine (approximately 20mL mid-stream urine) will be analyzed for protein, glucose, ketones, bilirubin, blood, nitrites and urobilinogen by dipstick method. Sediment microscopy will be performed if the leukocyte, nitrites, protein, or occult blood is abnormal and will include analysis for white blood cells, red blood cells, hyaline casts, granular casts and cellular casts.

Methemoglobin status will be assessed daily up to Day 14, on alternate days up to Day 28 and on Day 60 (or at relapse/withdrawal from study) (See Section 7.1). Subjects with anemia may have symptomatic methemoglobinemia at levels lower than subjects with normal hemoglobin levels (symptoms typically do NOT occur with metHb values <20% in subjects with normal hemoglobin levels).

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be reported as AEs and then tests repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.6 Pharmacokinetics

7.6.1 Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of TQ (and potentially other study treatment as deemed appropriate) will be collected at the time points indicated in Section 7.1, Time and Events Table. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points, at the discretion of GSK, to ensure thorough PK monitoring.

All pharmacokinetic blood samples will be held and stored in Indonesia until such time that an MTA, if necessary, is formally approved for the transfer of the specimen to the designated laboratory for PK analysis. If the MTA is approved, samples will be shipped to the Aptuit Laboratory, Italy for analysis and returned to Indonesia, once the analysis is completed, where they will be stored for up to 5 years.

The validated bioanalytical methodology used for measuring concentrations of TQ for pharmacokinetic analysis is not currently performed in Indonesia. Therefore, samples will be analyzed at the laboratory that is conducting the TQ analysis in the global programme in order to generate data to regulatory standards, in accordance with Indonesian requirements.

Details of the PK blood sample collection, processing and storage procedures are provided in the SRM.

7.6.2 Sample Analysis

Plasma sample analysis will be performed under the control of PTS, GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of TQ will be determined using the currently approved validated bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Plasma samples stored in Indonesia may be used for analysis of primaquine PK or immunological studies e.g. examining seromarkers of hypnozoite carriage. These analyses would be done at the Eijkman Institute and/or University of Indonesia, Jakarta, Indonesia. Any additional analyses on these stored samples will require prior agreement from GSK and the local Ethics Committee.

7.7 Genetics

Samples will be collected for genetic testing as follows:

- CYP2D6 genotyping - a sample will be collected to examine the relationship between CYP2D6 genotype and risk of *P. vivax* relapse. The analysis will be performed at the Eijkman Institute.

- G6PD genotyping - a sample will be collected for extraction of nucleic acid which will be stored for potential G6PD genotyping in the event of a hemolytic event. In this circumstance, the sample may be analyzed if repeat G6PD phenotyping would not define G6PD status (e.g. transfusion given or high reticulocyte count). The analysis will be performed at the Eijkman Institute.

- Plasmodium PCR genotyping- samples will be taken at screening and at the time of malaria recurrence (if applicable) to explore the genetics of baseline diversity and recurrence of *P.vivax* malaria. The analysis will be performed at the Eijkman Institute.

- Plasmodium whole genome sequencing- samples will be taken at screening and at the time of malaria recurrence (if applicable) for whole genome sequencing in order to better understand the biology of *P.vivax* at baseline and genetic drivers of relapse. These samples will be held and stored in Indonesia until such time that an MTA, if necessary, is formally approved for the transfer of the specimens to the Sanger, Institute, UK where they will be pooled with other samples from the global TQ studies, in order to standardize the methodology across the TQ programme. This analysis will only be done if parasite counts allow and results will be reported separately. The samples will be returned to Indonesia where they will be destroyed, once the analysis is completed.

Details of the sample collections for genetic testing (including volume of blood to be collected), processing and storage procedures are provided in the SRM.

8. DATA MANAGEMENT

- For this study, subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events (including SAEs) and concomitant medications terms will be coded using the current MedDRA (Medical Dictionary for Regulatory Activities) used at the data lock point and an internal validated medication dictionary, GSKDrug.

- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1 Hypotheses

The study is designed to test superiority of DHA-PQP plus TQ against DHA-PQP alone in the prevention of *P. vivax* malaria relapse. The null hypothesis for the primary endpoint is that the 6-month relapse-free efficacy is not different between the DHA-PQP plus TQ and DHA-PQP alone treatment groups. The alternative hypothesis is that the relapse-free efficacy of the treatments is different. The hypothesis test will be two-sided and tested at the 5% significance level.

9.2 Sample Size Considerations

9.2.1 Sample Size Assumptions

The sample size for the study is based on the comparison of the primary endpoint (i.e. relapse-free efficacy at 6 months post-dosing) between the DHA-PQP alone group versus DHA-PQP plus TQ. The comparison will be based on a Log rank test for the difference in relapse-free survival rates over 6 months using all the subjects in the intent to treat population.

It is assumed that the relapse-free efficacy will be 50% on DHA-PQP alone, 85% on DHA-PQP plus PQ, and 85% on DHA-PQP plus TQ. In order to detect a clinically meaningful difference of 35%, a sample size of 50 subjects per group will provide >90% overall power for the primary efficacy comparison, allowing for a 10% withdrawal rate. A trial of 150 subjects, with the given assumptions about DHA-PQP, DHA-PQP plus PQ, and DHA-PQP plus TQ relapse rates would expect to see 40 relapses: a combined relapse rate across all treatments of 26.7%. In addition, a DHA-PQP plus PQ arm will be used as a benchmark to help further interpret the observed relapse efficacy of DHA-PQP plus TQ.

9.2.2 Sample Size Sensitivity

An overall power of 80% will be maintained if the relapse-free efficacy of the DHA-PQP plus TQ combination is 80% rather than the expected 85% (corresponding to a combined relapse rate across all treatments of 28.3%), or if the relapse-free efficacy of DHA-PQP plus TQ is 85% but the efficacy of DHA-PQP alone is 55% (a combined relapse rate across all treatments of 25%).

9.2.3 Sample Size Re-estimation or Adjustment

If the study has not achieved its target of 150 subjects by six months, but at least 120 subjects have been enrolled, a blinded review of the relapse data will be conducted. Kaplan-Meier estimates will be made of the overall six month relapse rate, using all of the data available at that time. If the Kaplan-Meier estimate of the overall combined relapse rate at 6 months is less than 26.7%, further subjects will be recruited from a second battalion, up to a maximum of 150 subjects in total. If the Kaplan-Meier estimate is 26.7% or greater, the study will have sufficient power to show a meaningful clinical difference without requiring further subjects from a second battalion. In this scenario, recruitment will be stopped and all current subjects will be followed up for the full six months. Even if the relapse rate is shown to be higher than anticipated, the minimum number of subjects which will be recruited is 120, to ensure an adequate safety database for the DHA-PQP plus TQ treatment regimen.

9.3 Data Analysis Considerations

9.3.1 Analysis Populations

The following populations are defined for the analysis of the data to be collected as part of this study. All decisions on eligibility for inclusion in these populations will be made prior to unblinding at the end of each part.

Safety Population: all randomized subjects who received at least one dose of blinded study treatment. If subjects receive a treatment different to their randomized treatment, they will be analyzed according to the treatment actually received. This will be the primary population for all safety analyses and data presentations.

Intent to Treat (ITT) Population: all randomized subjects who received at least one dose of blinded study treatment. Subjects will be analyzed according to their randomized treatment. This population will be the primary population for all efficacy analyses.

Per Protocol (PP) Population: all subjects in the ITT population for whom there were no major protocol violations (to be defined in the study analysis plan). This population will be used for sensitivity/supporting analyses of efficacy data only.

9.4 Key Elements of Analysis Plan

The primary comparison of interest will be the treatment difference over 6 months between DHA-PQP plus TQ and DHA-PQP alone using a Logrank test. Point estimates will be derived from Kaplan Meier methods and include all subjects in the ITT population. Subjects who were lost to follow up or did not relapse by the end of the follow up will be censored at the time of withdrawal or completion of the study.

Note that data from the Day 195 visit will be not used in the assessment of relapse at 6 months. The last data to be used is the data from the Day 180 visit.

Subjects will be considered to have demonstrated relapse- free efficacy at six months if **all** of the following are true:

- Subject had a non-zero *P.vivax* asexual parasite assessment on Day 1. (Subjects who do not meet this criteria will be censored, with time to relapse censored at 0 days).
- Subject demonstrated initial clearance of *P.vivax* parasitemia. (Subjects who do not meet this criteria will be considered to have relapsed with time to relapse = 0 days).
- Subject had a non-zero *P.vivax* asexual parasite assessment on Day 1. (Subjects who do not meet this criteria will be censored, with time to relapse censored at 0 days)
- Subject demonstrated initial clearance of *P.vivax* parasitaemia. (Subjects who do not meet this criteria will be considered to have relapsed with time to relapse = 0 days)
- Subject has no positive asexual *P.vivax* parasite count at any assessment prior to the scheduled Day 180 visit following initial parasite clearance. (Subjects who do have a positive count will be considered to have relapsed with time to relapse = (date of first positive count) – (date of Day 1 visit) days).
- Subject did not take a concomitant medication with anti-malarial activity (excluding study treatment) at any point between day 1 and the scheduled Day 180 visit. (Subjects who did take a drug with anti-malarial activity but never had a positive asexual *P.vivax* parasite count after initial clearance will be censored, with time to relapse censored at (date of medication start) – (date of Day 1 visit) days).
- Subject has a scheduled Day 180 assessment, and is parasite free at this time point. (Subjects who do not have a Day 180 visit and have not already failed or been censored will be censored at (date of final parasite assessment) – (date of Day 1 visit) days).

All statistical testing will be performed using a significance level of 0.05.

9.4.1 Secondary Analyses

For evaluation of the secondary efficacy comparisons, 95% confidence intervals will be provided for the treatment differences of i) DHA-PQP plus TQ versus DHA-PQP plus PQ and ii) DHA-PQP plus PQ versus DHA-PQP alone. An exploratory p-value will also be provided for the DHA-PQP plus PQ versus DHA-PQP alone comparison.

A secondary per protocol analysis will also be performed, excluding subjects who deviate significantly from the protocol. If a subject misses a scheduled study visit from day 28 onwards, they will automatically be excluded from the per protocol population.

Statistical comparisons (i) DHA-PQP plus TQ versus DHA-PQP alone, ii) DHA-PQP plus TQ versus DHA-PQP plus PQ and iii) DHA-PQP plus PQ versus DHA-PQP alone) of secondary efficacy endpoints (relapse-free efficacy at 4 months, time to relapse,

percentage of subjects with recrudescence, parasite clearance time, fever clearance time) will also be performed using survival analysis methodology.

A further sensitivity analysis will be performed in which all subjects will be categorized as either successes or failures at 6 months, analyzed using Exact methods. Subjects taking medication with anti-malarial efficacy during the study will be classified as failures in this analysis.

All safety endpoints will be based on the safety population and presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

10 STUDY GOVERNANCE CONSIDERATIONS

10.1 Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.2 Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to site initiation, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable.
- Obtaining signed informed consent prior to participation in the study
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol.

10.3 Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors (or designee) will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK (or their designee) will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

10.4 Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK or their representative may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5 Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where

applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.

- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6 Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- The investigator must retain Investigator Site Files for 25 years from the final Clinical Study report date. The final retention date for Investigator Site Files will be provided at the same time as the Clinical Study report or equivalent results summary (local country law will apply where longer retention periods apply).
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

10.7 Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.8 Review Committees

Blinded safety data will be reviewed on a monthly basis by a GSK/MMV safety review board which includes a reviewer independent of the study sponsors.

11 REFERENCES

Baird, J. K. Evidence and implications of mortality associated with acute Plasmodium vivax malaria. *Clinical microbiology reviews*, 2013: *26*(1), 36-57.

Baird, J. K., Dewi, M., Subekti, D, *et al.* Noninferiority of glucose-6-phosphate dehydrogenase deficiency diagnosis by a point-of-care rapid test vs the laboratory fluorescent spot test demonstrated by copper inhibition in normal human red blood cells. *Translational Research,* 2015: 165 (6) 677-688.

Bancone, G., Chu, C. S., Somsakchaicharoen, R., et al. Characterization of G6PD Genotypes and Phenotypes on the Northwestern Thailand-Myanmar Border. *PloS one*, 2014: *9*(12), e116063.

Bennett, J. W., Pybus, B. S., Yadava, A., *et al.* Primaquine failure and cytochrome P-450 2D6 in Plasmodium vivax malaria. *New England Journal of Medicine*, 2013: *369*(14), 1381-1382.

Dua, V. K., Kar P.K, and Sharma V.P. Chloroquine resistant Plasmodium vivax malaria in India. *Tropical Medicine & International Health* 1.6 1996: 816-819.

Fryauff, D.J.B.L., Baird K., Basri, H.A.S.A.N., *et a*l. Randomised placebo-controlled trial of primaquine for prophylaxis of falciparum and vivax malaria. *The Lancet*, 1995: *346*(8984); 1190-1193.

Hasugian, A.R., Purba, H.L.E., Kenangalem., *et al*. Dihydroartemisinin-piperaquine versus artesunate-amodiaquine: superior efficacy and posttreatment prophylaxis against multidrug-resistant Plasmodium falciparum and Plasmodium vivax malaria. *Clin Infect Dis*, 2007: 44(8), 1067-1074.

Herdiana, H., Fuad A., Asih P.B *et al*. Progress towards malaria elimination in Sabang municipality, Aceh, Indonesia." *Malar J* 12, 2013 (42): 10-1186.

ICH Guidance for Industry. Guideline E6 Good Clinical Practice: Consolidated Guidance 1996

Karyana, M., Burdarm, L., Yeung, S., *et al*. Malaria morbidity in Papua Indonesia, an area with multidrug resistant Plasmodium vivax and Plasmodium falciparum. *Malar J 2008*, *7*(148), 10-1186.

Kusriastuti, R., and Asik S. New Treatment Policy of Malaria as a Part of Malaria Control Program in Indonesia. *Acta Med Indones - Indones J Intern Med* 2012: 44.3; 265-269.

Lee K.S, Kim T.H, Kim E.S *et al.* Short report: Chloroquine-resistant Plasmodium Vivax in the Republic of Korea.*Am. J. Trop. Med. Hyg* 2009; 80 (2):215-217.

Llanos-Cuentas A., Lacerda MV., Rueangweerayut R., *et al*. Tafenoquine plus chloroquine for the treatment and relapse prevention of Plasmodium vivax malaria (DETECTIVE): a multicentre, double-blind, randomised, phase 2b dose-selection study. *The Lancet.* 2014 Vol.383 | Number 9922 March 22.

Murray, C. J., Ortblad, K. F., Guinovart, C. *et al*, Global, regional,and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet*, 2014, *384*(9947), 1005-1070.

Nelwan, E.J., Ekawati LL., Tjahjono B. *et al*, Randomized trial of primaquine hypnozoitocidal efficacy when administered with artemisinin-combined blood schizontocides for radical cure of *Plasmodium vivax* in Indonesia. *BMC Medicine*, 2015, Dec 11:13 (1), 294.

Pasaribu A.P., Chokejindachai., W, Sirivichayakul C *et al.* A randomized comparison of dihydroartemisinin-piperaquine and artesunate-amodiaquine combined with primaquine for radical treatment of Vivax malaria in Sumatera, Indonesia. *Journal of Infectious Diseases,* 2013; 208: 1906-1913.

Price R.N., Douglas NM., Anstey NM. New developments in Plasmodium vivax malaria: severe disease and the rise of chloroquine resistance. *Curr Opin Infect Dis.* Oct 2009;22(5):430-435.

Price, R.N., von Seidlein, L., Valecha, N.,*et al*. Global extent of chloroquine-resistant *Plasmodium vivax*: a systematic review and meta-analysis. *The Lancet Infectious Diseases*, 2014: *14*(10), 982-991.

Ratcliff, A., Siswantoro, H., Kenangalem, E. et al. Two fixed-dose artemisinin combinations for drug-resistant falciparum and vivax malaria in Papua, Indonesia: an open-label randomised comparison. *The Lancet*, 2007; *369*(9563), 757-765.

SB-252263 Investigator's Brochure. GlaxoSmithKline Document Number GM2007/00152/09. Version 13 Effective Date: 7 December 2015.

Soto, J., Toledo J., Gutierrez P. Luzz, M. *et al*. Plasmodium vivax clinically resistant to chloroquine in Colombia. *Am. J. Trop. Med and Hyg.* 2001*;* 65(no.2):90-93.

Study TAF110027 GlaxoSmithKline Document Number 2013N172577_00. A Phase I Study to Investigate the Haemolytic Potential of Tafenoquine in Healthy Subjects with Glucose-6-Phosphate Dehydrogenase Deficiency and the Safety and Tolerability of Tafenoquine in Acute *Plasmodium vivax* Malaria Patients with Glucose-6-Phosphate Dehydrogenase Deficiency. Effective Date: December 2013.

Sumawinata, I. W., Leksana, B., Sutamihardja, *et al*. Very high risk of therapeutic failure with chloroquine for uncomplicated Plasmodium falciparum and P. vivax malaria in Indonesian Papua. *Am.J. of Trop Med and Hyg*, 2003: *68*(4), 416-420.

Sutanto I., Endawati D., Ling LH *et al*. Evaluation of chloroquine therapy for vivax and falciparum malaria in southern Sumatra, western Indonesia. *Malaria Journal*. 2010; 9; 52.

Sutanto I., Suprijanto S., Nurhayati PM and Baird J.K. Resistance to chloroquine by plasmodium vivax at Alor in the Lesser Sundas archipelago in Eastern Indonesia. *Am. J. Trop. Med. Hyg*. 2009; 81(2):338-342.

Sutanto I., Tjahjono B., Basri H*., et al*. Randomized, open-label trial of primaquine against vivax malaria relapse in Indonesia. *Antimicrob Agents Chemother*. Mar 2013; 57(3):1128-1135.

12 APPENDICES

12.1 Appendix 1: Abbreviations and Trademarks

Abbreviations

ACT	Artemisinin-based combination therapy
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
CRA	Clinical Research Associate
CRF	Case Report Form
CPK	Creatine Phosphokinase
CQ	Chloroquine
CV	Cardiovascular
d	Day
DHA-PQP	Dihydroartemisinin Piperaquine
DOT	Directly observed therapy
DRE	Disease-Related Event
DDI	Drug-drug Interaction
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FCT	Fever clearance time
FDA	Food and Drug Administration
FST	Fluorescent Spot Test
FU	Follow Up
HR	Heart rate
GI	Gastrointestinal
G6PD	Glucose-6-phosphate Dehydrogenase
GSK	GlaxoSmithKline
GCP	Good Clinical Practice
g	Grams
g/dL	Grams per Deciliter
Hb	Hemoglobin
Hct	Hematocrit
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
INR	International Normalized Ratio
ITT	Intention to Treat
IWRS	Interactive web recognition test
kg	Kilograms

LDH	Lactate Dehydrogenase
m	Meter
MTA	Material Transfer Agreement
MSDS	Material Safety Data Sheet
MCV	Mean Cell Volume
MMV	Medicines for Malaria Venture
MetHb	Methemoglobin
µg.h/mL	Microgram Hours per milliliter
µL	Microliters
mg	Milligrams
mL	Milliliters
MTA	Material Transfer Agreement
PCR	Polymerase chain reaction
PCT	Parasite clearance time
PD	Pharmacodynamics
PGx	Pharmacogenetics
PK	Pharmacokinetics
PQ	Primaquine
RAP	Reporting and Analysis Plan
RBC	Red Blood Count
SAE	Serious Adverse Event
SRM	Study Reference Manual
TQ	Tafenoquine
ULN	Upper Limit of Normal
WBC	White Blood Count
WHO	World Health Organization

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12.2 Appendix 2: Liver Safety Required Actions and Follow up Assessments

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase III-IV liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria - Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥ 8xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 5xULN but <8xULN persists for ≥2 weeks
ALT ≥ 3xULN but <5xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks
ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see MONITORING below)
• Do not restart/rechallenge subject with study treatment unless allowed per protocol and GSK Medical Governance approval is</td><td>• Viral hepatitis serology[4]
• Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody[5].
• Blood sample for pharmacokinetic (PK) analysis, obtained as soon as possible and within 24 hours of last dose, if liver event occurs within 60 days post-dose[6].
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).</td></tr>
</table>

granted • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)

4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Note: Hepatitis B surface antigen test is not required at the screening visit.

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

Note: If any liver event follow up assessments are not available locally in Indonesia, samples will be stored for possible export to laboratories where the analyses are available, pending MTA approval from the Ministry of Health.

12.3 Appendix 3: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.3.1 Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of

the disease/disorder being studied, unless more severe than expected for the subject's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.3.2 Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct

normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.
• Refer to Appendix 2 for the required liver chemistry follow-up instructions

12.3.3 Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias

- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

12.3.4 Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.3.5 Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

12.3.6 Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail. • Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

12.4 Appendix 4: WHO Definition of Severe Malaria

The WHO defines severe malaria as those that present with: confusion or drowsiness with extreme weakness (prostration).

In addition, the following may develop:

- Cerebral malaria, defined as unrousable coma not attributable to any other cause in a patient with malaria
- Generalized convulsions
- Severe normocytic anaemia (<5 g/dL)
- Hypoglycaemia (blood glucose < 2.2 mmol/L or < 40 mg/dL)
- Metabolic acidosis (plasma bicarbonate < 15 mmol/L) with respiratory distress
- Fluid and electrolyte disturbances
- Acute renal failure (serum creatinine >265 μmol/L)
- Acute pulmonary edema and adult respiratory distress syndrome (ARDS)
- Circulatory collapse or shock
- Abnormal bleeding
- Jaundice with organ dysfunction
- Hemoglobinuria
- Hyperparasitemia (>2%/100,000/μL in low intensity transmission areas or >5% or 250,000/μL in areas of high stable malaria transmission intensity)

NOTE: This definition of severe malaria was formulated for *P. falciparum* but other published data for *P. vivax* support this and so for the purposes of this trial this definition of severe disease will be adopted.

References:

"Management of Severe Malaria: A Practical Handbook." 2nd Edition Geneva, World Health Organisation 2000.

Price RN, Douglas NM, Anstey NM. New developments in Plasmodium vivax malaria: severe disease and the rise of chloroquine resistance. Curr Opin Infect Dis. 2009 Oct;22(5):430-5.

World Health Organization. Severe falciparum malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene, 2000:94(Suppl. 1):1–90.

12.5 Appendix 5: Prohibited Medications for Study Entry

The following drugs are not permitted to be taken during the study:

1) Acetylsalicylic acid

- Note: Paracetamol is the recommended antipyretic agent (but must be used with caution due to a potential interaction with piperaquine; see below)

2) Antimalarials:

- 4-aminoquinolines (amodiaquine, chloroquine)
- 8 aminoquinolines (primaquine, pamaquine)
- Artemisinin derivatives
- Aryl-aminoalcohol (halofantrine, lumefantrine)
- Atovaquone
- Tetracycline e.g. doxycycline
- Quinine, quinidine, quinacrine, mefloquine
- Proguanil

3) Drugs with antimalarial activity:

This list serves to provide examples of more commonly used drugs with antimalarial activity, but is not exhaustive.

- Albendazole
- Allopurinol
- Clindamycin
- Diamidines (e.g., Pentamidine)
- Fluroquinolones e.g. ciprofloxacin, nalidixic acid sparfloxacin
- Glibenclamide
- Indinavir, Saquinavir and Ritonavir
- Isoniazid
- Probenecid
- Rifampicin
- Sulfacetamide
- Sulfadiazine, Sulfadoxine or Sulfalene/pyrimethamine, Sulfamethoxazole/trimethoprim, Sulfasalazine (and other sulfonamides)

4) Drugs known to cause QTc prolongation:

The following drugs are prohibited for a period of 14 days following the start of study treatment:

- Amiodarone
- Antidepressant agents (e.g. citalopram
- Antifungal agents (e.g. imidazole and triazole)
- Non-sedating antihistamines (e.g. astemizole, mizolastine, terfenadine)
- Arsenic trioxide
- Bepridil
- Cisapride
- Diphenamil
- Disopyramide
- Dofetilide
- Domperidone
- Droperidol
- Fluoroquinolones (e.g. moxifloxacin, sparfloxacin)
- Haloperidol
- Hydroquinidine
- Ibutilide
- Isotalol
- Ketoconazole (oral or IV, but topical preparations are allowed)
- Levomethadyl
- Lidoflazine
- Macrolides (e.g. azithromycin, erythromycin, clarithromycin, roxithromycin)
- Mesoridazine

- Methadone
- Neuroleptics e.g. chlorpromazine and other phenothiazines, sertindole, sultopride
- Pentamidine
- Pimozide
- Probucol
- Procainamide hydrochloride
- Saquinavir
- Thioridazine
- Sotalol
- Sulfapyridine
- Vinca alkaloids

5) <u>Drugs excreted via the renal transporters MATE1, MATE2-K AND OCT2:</u>

The following drugs excreted via the renal transporters MATE1, MATE2-K and OCT2 are prohibited for a period of 21 days following the blinded dose of tafenoquine:

- Phenformin
- Buformin
- Dofetilide
- Procainamide
- Pilsicainide

Note: Metformin is also excreted via MATE1, MATE-2 and OCT2 but may continue to be taken provided the subject has a serum creatinine below the upper limit of normal and has no concomitant medical conditions that increase the risk of lactic acidosis.

6) <u>Others-miscellaneous:</u>

- Phenazopyridine
- Phenylhydrazine
- Chloramphenicol

7) Primaqine interactions (source eMC):

- Contraindicated with other potentially hemolytic drugs and depressants of myeloid elements of bone marrow

In addition, refer to locally approved prescribing information.

8) DHA-PQP interactions (source SmPC):

Piperaquine is an inhibitor of CYP3A4 and CYP2C19 and may increase plasma concentrations of other substrates for this enzyme. Drugs which have a narrow therapeutic index and are substrates for CYP3A4 or CYP2C19 should not be taken during this study, for example:

- Antiretroviral products
- Cyclosporine
- Omeprazole

Piperaquine is metabolised by CYP3A4 in vitro. Drugs and food which inhibit CYP3A4 may lead to a marked increase in piperaquine concentration resulting in an excerabation of the effect on QTc. Therefore, drugs and other substances which inhibit CYP3A4 are prohibited for a period of 14 days after last dose of DHA-PQP administration, for example:

- Some protease inhibitors (eg amprenavir, atazanavir, indinavir, nelfinavir, ritonavir)
- Nefazodone
- Verapamil

Additionally, CYP3A4 inducing products may lead to reduced piperaquine plasma concentrations and should not be given during the study as follows:

- Carbamazepine
- Phenytoin
- Phenobarbital
- St. John’s wort (Hypericum perforatum)

The following drugs may be administered with caution during the study:

Piperaquine has the potential to increase the rate of metabolism for CYP2E1 substrates resulting in reduced plasma concentrations. Caution is advised if administered with drugs metabolised via this pathway e.g.

- Paracetamol
- Theophylline
- Anaesthetic gases (enflurane, halothane, isoflurane)

DHA administration may result in slight decrease in CYP1A2 activity. Caution is advised if co-administered with drugs metabolised by this enzyme that have a narrow therapeutic index e.g.

- Theophylline

The following antibiotics are permitted during study:

The following antibiotics can be used after inclusion and during the study:

- Penicillins (e.g. penicillin, ampicillin, amoxicillin, amoxicillin+clavulanate, cloxacillin)
- Cephalosporins (e.g. ceftazidime, ceftriaxone)
- Aminoglycosides (e.g. gentamicin)
- Carbapenems (e.g. meropenem and imipenem)

12.6 Appendix 6: Country Specific Requirements

There are no country specific requirements

12.7 Appendix 7: Protocol Changes

Amendment 1

The primary reason for this amendment is to include a comparison of the efficacy of dihydroartemisinin-piperaquine (DHA-PQP) co-administered with primaquine as a radical cure for *P.vivax* malaria versus DHA-PQP alone, as a secondary study objective. This protocol revision was requested by the Indonesian regulatory agency (Badan POM).

Other revisions are as follows:

- A vital signs assessment has been included at Day 2 to permit evaluation of time to fever clearance (secondary study objective). This assessment was omitted in error from the final protocol (version dated 27th January 2016).
- The name and contact details of the secondary medical monitor have been revised
- The Oxford Tropical Research Ethics Committee (OXTREC) project number (9-16), amendment number and date has been added to the footer of each page, as required by the ethics committee

Footer of Each Page

ADDED TEXT

OXTREC 9-16 /Protocol 200894 Amendment Number 01/Date 20-APR-2017

Medical Monitor/Sponsor Information Page

PREVIOUS TEXT

Role	Name	Day Time Phone Number and email address	After hours Cell Number	Site Address
Secondary Medical Monitor	PPD	PPD	PPD	GlaxoSmithKline Research & Development Limited Iron Bridge Road Stockley Park West, Uxbridge, Middlesex, UB11 1BT, UK

REVISED TEXT

Role	Name	Day Time Phone number and email address	After hours Cell Number	Site Address
Secondary Medical Monitor	PPD	PPD	PPD	GlaxoSmithKline Research & Development Limited Iron Bridge Road Stockley Park West, Uxbridge, Middlesex, UB11 1BT, UK

Section 1 Protocol Synopsis Objectives/Endpoints

ADDED TEXT

Secondary Objective	Endpoints
• To determine the efficacy of primaquine co-administered with DHA-PQP relative to DHA-PQP alone.	• Subjects with relapse-free efficacy six months post-dosing

Section 3. OBJECTIVE(S) AND ENDPOINT (S)

ADDED TEXT

Secondary Objective	Endpoints
• To determine the efficacy of primaquine co-administered with DHA-PQP relative to DHA-PQP alone.	• Subjects with relapse-free efficacy six months post-dosing

Section 7.1 Time and Events Table

ADDED TEXT

One vital signs assessment added to Time and Events table for Day 2

Section 9.4.1 Secondary Analyses

PREVIOUS TEXT

The primary efficacy comparison is of DHA-PQP plus TQ versus DHA-PQP alone for relapse free-efficacy at 6 months, but a 95% confidence interval for the treatment difference of DHA-PQP plus TQ versus DHA-PQP plus PQ will also be generated, to support evaluation of this secondary treatment comparison.

A secondary per protocol analysis will also be performed, excluding subjects who deviate significantly from the protocol. If a subject misses a scheduled study visit from day 28 onwards, they will automatically be excluded from the per protocol population.

Statistical comparisons (DHA-PQP plus TQ versus DHA-PQP alone, and DHA-PQP plus TQ versus DHA-PQP plus PQ) of secondary efficacy endpoints (relapse efficacy at 4 months, time to relapse, percentage of subjects with recrudescence, parasite clearance time, fever clearance time) will also be performed using survival analysis methodology.

REVISED TEXT

For evaluation of the secondary efficacy comparisons, 95% confidence intervals will be provided for the treatment differences of i) DHA-PQP plus TQ versus DHA-PQP plus PQ and ii) DHA-PQP plus PQ versus DHA-PQP alone. An exploratory p-value will also be provided for the DHA-PQP plus PQ versus DHA-PQP alone comparison.

A secondary per protocol analysis will also be performed, excluding subjects who deviate significantly from the protocol. If a subject misses a scheduled study visit from day 28 onwards, they will automatically be excluded from the per protocol population.

Statistical comparisons (i) DHA-PQP plus TQ versus DHA-PQP alone, ii) DHA-PQP plus TQ versus DHA-PQP plus PQ and iii) DHA-PQP plus PQ versus DHA-PQP alone) of secondary efficacy endpoints (relapse-free efficacy at 4 months, time to relapse, percentage of subjects with recrudescence, parasite clearance time, fever clearance time) will also be performed using survival analysis methodology.