Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Llanos-Cuentas A, Lacerda MVG, Hien TT, et al. Tafenoquine versus primaquine to prevent relapse of *Plasmodium vivax* malaria. N Engl J Med 2019;380:229-41. DOI: 10.1056/NEJMoa1802537

Tafenoquine vs. Primaquine to prevent relapse in *Plasmodium vivax* Malaria

Alejandro Llanos-Cuentas, et al.

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.

2. Original reporting and analysis plan, final reporting and analysis plan, summary of changes.

3. Original and final reporting and analysis plan for the meta-analysis (no changes).

TITLE PAGE

Division: Worldwide Development

Title:	A Randomized, Double-Blind, Double Dummy, Comparative, Multicenter Study to Assess the Incidence of Hemolysis, Safety, and Efficacy of Tafenoquine (SB-252263, WR238605) versus Primaquine in the Treatment of Subjects with *Plasmodium vivax* Malaria.

Compound Number: SB252263

Development Phase III

Effective Date: 26-NOV-2013

Subject: *Plasmodium vivax*, glucose-6-phosphate dehydrogenase (G6PD), tafenoquine, primaquine, chloroquine, hemolysis, relapse

Authors: PPD

SPONSOR SIGNATORY:

PPD

26/11/2013

Justin Greer PPD **Date**

Director; Diseases of the Developing World Therapy
Area Physician

SPONSOR INFORMATION PAGE

Clinical Study Identifier: 116564

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Sponsor Contact Address:

GlaxoSmithKline Research & Development Limited
1250 South Collegeville Road
Collegeville, PA 19426, USA
Telephone Number: PPD

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Sponsor Medical Monitor and Serious Adverse Event (SAE) Contact Information:

PPD
GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: PPD
Mobile: PPD

Secondary Contact:

PPD
GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: PPD
Mobile: PPD

SAE Case Management Details:

SAE CRF pages and supporting documents should be sent to GSK GCSP Case Management either by email to PPD or by fax to PPD

Regulatory Agency Identifying Numbers:

IND Number: 101471

EudraCT Number: Not applicable

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical 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 Signature	Date

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline phosphotase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CL/F	Oral clearance
CPK	Creatine phosphokinase
CQ	Chloroquine
CV	Cardiovascular
DRE	Disease-Related Event
ECG	Electrocardiogram
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GCSP	Global Clinical Safety & Pharmacovigilance
g/dL	grams per deciliter
GSK	GlaxoSmithKline
Hct	Hematocrit
Hb	Hemoglobin
HPLC	High pressure liquid chromatography
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LDH	Lactate dehydrogenase
LSLV	Last subject last visit
MPV	Major Protocol Violation
MSDS	Material Safety Data Sheet
MCV	Mean Cell Volume
MetHb	Methemoglobinemia
mITT	Microbiologic Intent To Treat
µL	Microliter
mg	Milligram
msec	Millisecond
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PGx	Pharmacogenetics
PK	Pharmacokinetics
PP	Per Protocol
PQ	Primaquine
RAMOS	Registration and Medication Ordering System
RBC	Red blood cell

RAP	Reporting & Analysis Plan
SAE	Serious Adverse Event
SPM	Study Procedures Manual
SOC	System Organ Class
TQ	Tafenoquine
ULN	Upper Limit of Normal
V/F	Volume of distribution
WBC	White blood cell
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

PROTOCOL SUMMARY

Rationale

The global disease burden of malaria due to *Plasmodium vivax* is significant. There are up to 391 million persons infected annually, with an estimated 2.49 billion individuals living at risk of *P. vivax* infection. *P. vivax* has the largest geographic distribution of human malarias, extending well beyond the distribution for *P. falciparum*. Infection with *P. vivax* presents in the majority of cases as an acute but uncomplicated febrile illness; however, recent work has demonstrated that the risk of fatal outcome in patients with severe malaria was indistinguishable between those with *P. falciparum* versus *P. vivax* malaria.

P. vivax presents an added challenge to malaria eradication efforts, and that is its ability to establish a dormant liver stage, the hypnozoite. Relapsing *P. vivax* malaria is caused by hypnozoite activation after the initial infection. Left untreated, tropical *P. vivax* strains can relapse in 3 to 6 week intervals, whereas strains from temperate regions can stay dormant for 1 year or longer. The only widely available drug for the prevention of *P. vivax* relapse is primaquine (PQ), an 8-aminoquinoline derivative.

Tafenoquine (TQ, SB-252263 and WR 238605) is a novel 8-aminoquinoline anti-malarial drug being co-developed by GlaxoSmithKline and the Medicines for Malaria Venture with the assistance and historic support of the Walter Reed Army Institute of Research. It is a synthetic analog of PQ and is currently being developed for the radical cure of *P. vivax* malaria, to be co-administered as a single dose with standard doses of chloroquine (CQ).

All members of the 8-aminoquinoline class of drugs induce hemolysis in subjects with glucose-6-phosphate dehydrogenase (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. Therefore, it is important that the dose of TQ selected is not only effective but also minimizes the hemolytic potential of the drug in this population.

The primary objectives of this study is to characterize the incidence of hemolysis with TQ/CQ and compare this to the incidence of hemolysis with PQ/CQ; both in all subjects, as well as in the subset of female subjects that display a moderate deficiency in G6PD activity. The efficacy and safety of TQ/CQ will be studied in comparison to PQ/CQ, and the socioeconomic impact of infection and relapse due to *P. vivax* will be studied. In addition, a pharmacokinetic/pharmacodynamic analysis will be conducted in all subjects receiving TQ.

Objective(s)

Primary Objective(s)

- To investigate the occurrence of clinically relevant hemolysis in adult subjects with *P. vivax*. The incidence of hemolysis in the subgroup of female patients with moderate (40-70%) G6PD activity is of particular interest.

Secondary Objective(s)

- To compare the clinical and parasitological efficacy, safety and tolerability of tafenoquine to primaquine as a radical cure for adult subjects with *P. vivax* malaria when co-administered with chloroquine.
- To characterize the socioeconomic impact of *P. vivax* relapse.
- To evaluate the pharmacokinetics of tafenoquine in the treatment of adult subjects with *P. vivax* malaria.
- To characterize the pharmacokinetic/pharmacodynamic relationship in this study population.

Study Design

In this prospective, double-blind, double-dummy design, a total of 300 subjects will be randomized to treatment on Day 1, of which a minimum of 50 female subjects must be enrolled that display moderate G6PD deficiency (≥40% - <70% of the site median G6PD value). Subjects must have a blood smear that is positive for *P. vivax* at entry. Subjects must remain in the hospital for a minimum of the first 3 days of the study to monitor study medication compliance and infection status, and will continue on treatment as an outpatient for an additional 12 days. Subjects will be monitored up to day 29 for recrudescence, then continue to be monitored up to 180 days post-randomization for evidence of relapsing infection.

During the 180 day study period subjects must attend screening and randomization to treatment (Day 1), three in-hospital days (Days 1-3), four out-patient visits while on treatment with study medication (Days 5, 8, 11 and 15) and seven follow-up visits (Days 22, 29, 60, 90, 120, 150 and 180).

All subjects will receive open label CQ for the first 3 days of the study to treat the blood stage of the infection. Beginning on Day 1 or Day 2, subjects will receive TQ or the active comparator, PQ, and the corresponding placebo for treatment of the liver stage of infection. Primaquine was selected as the comparator for this study as PQ plus CQ is the current standard of care for radical cure of *P. vivax* malaria in the majority of endemic countries.

An independent data monitoring committee will be established to monitor, in an unblinded manner, safety in general and females with moderate G6PD deficiency in particular. The latter will ensure the frequency and severity of any hemoglobin declines in females remains as expected and remains clinically acceptable. This will include the use of pre-defined criteria for evaluating early stopping of recruitment of subjects with moderate G6PD deficiency.

Study Endpoints/Assessments

Primary

- Occurrence of clinically relevant hemolysis in all subjects; defined as, a decrease in hemoglobin of ≥30% or >3 g/dL from baseline; or, an overall drop in hemoglobin below 6.0 g/dL.
- Occurrence of clinically relevant hemolysis in female subjects with moderate (40-70%) G6PD deficiency; defined as, a decrease in hemoglobin of ≥30% or >3 g/dL from baseline; or, an overall drop in hemoglobin below 6.0 g/dL.

Secondary

- Relapse-free efficacy six months post-dosing
- Relapse-free efficacy four months post-dosing
- Time to relapse
- Parasite clearance time
- Fever clearance time
- Gametocyte clearance time
- Recrudescence, defined as any *P. vivax* parasitemia occurring on or before Day 29 (i.e., blood stage treatment failure).
- Incidence of genetically homologous and genetically heterologous *P. vivax* infections (determined by PCR)
- Characterization of healthcare resource use and socio-economic impact of *P. vivax* relapses and adverse events caused by treatment to prevent *P. vivax* relapses, especially hemolytic anemia.
- PK and selected PD endpoints (e.g., relapse-free efficacy, change in methemoglobin) if appropriate
- Population PK parameters for tafenoquine including but not limited to oral clearance (CL/F) and volume of distribution (V/F)
- Safety evaluation of data from clinical laboratory tests, urinalysis, spontaneous/elicited adverse event reporting, ECGs and vital signs in all subjects who received at least one dose of study medication.
- Incidence of *P. falciparum* malaria

1. INTRODUCTION

1.1. Background

The global disease burden of malaria due to *Plasmodium vivax* is significant. There are up to 391 million persons infected annually, with an estimated 2.49 billion individuals living at risk of *P. vivax* infection [Gething, 2012; Price, 2007]. *P. vivax* has the largest geographic distribution of human malarias, extending well beyond the distribution for *P. falciparum* [Gething, 2012]. The majority of cases occur in Asia, with the remainder occurring in Central and South America, Oceania and Africa. Infection with *P. vivax* presents in the majority of cases as an acute but uncomplicated febrile illness, and it was long thought that *P. vivax* infection could not cause severe disease. Recent work has demonstrated that the risk of fatal outcome in patients with severe malaria was indistinguishable between those with *P. falciparum* versus *P. vivax* malaria [Barcus, 2007]. In addition, using molecular diagnostic techniques, it has been shown that *P. vivax* monoinfection can be responsible for multiple organ dysfunction and severe, life-threatening malarial disease [Kochar, 2009].

P. vivax presents an added challenge to malaria eradication efforts, and that is its ability to establish a dormant liver stage, the hypnozoite. Relapsing *P. vivax* malaria is caused by hypnozoite activation after the initial infection. Left untreated, tropical *P. vivax* strains can relapse in 3 to 6 week intervals, whereas strains from temperate regions can stay dormant for 1 year or longer [White, 2012]. The latter explains *P. vivax* prevalence in areas where the Anopheles vector is not present at all times of the year. The only widely available drug for the prevention of *P. vivax* relapse is primaquine (PQ), an 8-aminoquinoline derivative. Primaquine was approved by the FDA for the treatment of malaria in 1952, and remains the only licensed drug that can eliminate all liver stages of *P. vivax* [Hill, 2006].

The current gold standard for treatment of *P. vivax* malaria in many areas of the world is chloroquine (CQ); typically 600 mg day 1, 600 mg day 2 and 300 mg day 3 for clearance of the acute parasitemia, immediately followed by PQ 15 mg once daily x 14 days to clear the liver stages of the parasite and prevent disease relapse [WHO, 2010]. In some regions the PQ dose is increased to 22.5 mg or 30 mg once daily x 14 days where PQ tolerant hypnozoites are present. The 14-day regimen for PQ has presented major compliance problems, resulting in a significant degree of *P. vivax* malaria relapses in treated populations. Shorter courses (e.g., 5 or 7 days) have been studied, but results have been variable. Consequently, anti-relapse therapy for *P. vivax* malaria is impractical in most epidemic regions due to duration of treatment resulting in poor compliance [WHO, 2010]. In addition, recent evidence suggests that cytochrome P450 2D6 might have a role in PQ metabolism and treatment efficacy, and as such will be investigated in this study [Bennett, 2013].

1.2. Rationale

Tafenoquine (TQ, SB-252263 and WR 238605) is a novel 8-aminoquinoline anti-malarial drug being co-developed by GlaxoSmithKline and the Medicines for Malaria Venture with the assistance and historic support of the Walter Reed Army Institute of Research. It is a synthetic analog of PQ and is currently being developed for the radical cure of acute *P. vivax* malaria, to be co-administered as a single dose with standard doses of CQ. Tafenoquine has shown to be well-tolerated in the treatment and prevention of plasmodial infections in pre-clinical models and during Phase I, II and III clinical studies in >4000 subjects. Of note, TQ possesses activity against all stages of the Plasmodium life cycle, including the dormant *P. vivax* hypnozoite.

All members of the 8-aminoquinoline class of drugs induce hemolysis in subjects with glucose-6-phosphate dehydrogenase (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. Therefore, it is important that the dose of TQ selected is not only effective but also minimizes the hemolytic potential of the drug in this population.

Historical data indicate that the degree of hemolysis observed with PQ is dose-dependent as well as dependent on the severity of G6PD deficiency [Fernando, 2011]. In many areas of the world, standard doses of PQ are routinely used to treat *P. vivax* malaria without testing for G6PD deficiency. This is done with full knowledge that the average decline in hemoglobin is approximately 25-30% in WHO class III (mild to moderate) G6PD-deficient variants, a decline that is considered clinically acceptable in *P. vivax* malaria endemic regions.

Therefore, the primary objectives of this study are to characterize the incidence of hemolysis with TQ/CQ and compare this to the incidence of hemolysis with PQ/CQ. The objectives will be studied in all subjects, and in the subset of female subjects that display a moderate deficiency in G6PD activity. In addition, the efficacy and safety of TQ/CQ will be studied in comparison to PQ/CQ, the socioeconomic impact of infection and relapse due to *P. vivax* will be studied, and a pharmacokinetic/pharmacodynamic (PK/PD) analysis will be conducted in all subjects receiving TQ.

The efficacy data produced from this study will support the results for sister study TAF112582, the pivotal phase III efficacy and safety study of the tafenoquine program. The primary safety data collected in study TAF116564 will help to understand the hemolysis risk to both G6PD-normal and G6PD-deficient subjects. The information from G6PD-deficient subjects will be particularly useful should patients inadvertently be dosed with tafenoquine who do not know or are misinformed as to their G6PD status. This study also supports the regulatory requirement of randomizing a minimum of 500 subjects in the phase III program to receive the target dose of TQ.

1.3. Benefit:Risk Assessment

1.3.1. Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with TQ can be found in the Investigator Brochure (IB) [GlaxoSmithKline Document Number GM2007/00152/06].

The current key risk associated with the development and use of tafenoquine in this study is hemolysis in moderately deficient G6PD subjects. Since TQ is to be contraindicated in cases of moderate and severe G6PD deficiency, the most severe G6PD subjects, hemizygous males and homozygous females, will not be recruited into this study. Table 1 below outlines the risk assessment and mitigation strategy for this protocol.

Table 1 Risk Assessment for Tafenoquine (SB-252263)

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation
Hemolysis in G6PD-deficient patients	Tafenoquine is an 8-aminoquinoline, 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 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.	A quantitative spectrophotometric phenotype assay will be used to determine G6PD status based on levels of enzyme activity. Levels will be compared to a normal range set by the laboratory conducting the assay in males representing the study population pool. Study exclusion are set by % activity of median of normal range. Males with <70% and females with <40% G6PD activity are excluded. Protocol-defined SAE criteria will be adopted, defined as ≥ 3.0 g/dL or 30% decline in Hb from the baseline value to aid in safety monitoring. Subjects will be closely monitored around the expected time of nadir of Hb drop to enable investigators to intervene if required.
Hemoglobin changes	Integrated clinical safety data and data from thorough QT study data indicate a dose related trend for mild decrease in Hb in non-G6PD deficient patients.	The hematological effects of TQ in G6PD normal subjects will be included as part of activities conducted to investigate risk in G6PD deficient patients. Risk mitigation is covered by the activities described for hemolysis in G6PD-deficient patients above.
Methemoglobinemia (MetHb)	Methemoglobinemia has been observed in previous studies associated with larger total	Methemoglobinemia will be monitored instream. Data will be collected to support tolerance in

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation
	doses of TQ than are being considered for clinical investigation. Risk factors have been assessed and include a strong relationship between MetHb development, TQ dose, and body surface area.	female heterozygous carriers of G6PD deficiency. An assessment will be made to determine if there is any relationship between Hb decline and Methb.
Retinal Toxicity	No ophthalmological changes have been observed with TQ in preclinical species or in any of the TQ-treated subjects in previous studies. Irreversible retinopathy has been reported with the combination partner CQ. The effects with CQ are dose related and have been observed following cumulative total doses of >1g base/kg body weight. CQ dose used in treatment of *P.vivax* is a total of 25mg/kg over 3 days. Retinopathy associated with severe malaria is reported in the literature.	In a subset of the study population, anatomical and functional ophthalmic tests will be conducted, including digital retinal photo and macular function test (Humphrey 10-2 visual field). Assessments will be taken at baseline (Day 1), Day 29 and Day 90 of the study. For any abnormality subjects will be followed for outcome.
Keratopathy	No ophthalmological changes were observed in preclinical species. Reversible vortex keratopathy was observed in previous TQ clinical trials.	Appropriate sites will conduct slit lamp procedure and be provided with standardized photos of keratopathy to capture grades of keratopathy consistently. Assessments will be taken at baseline (Day 1), Day 29 and Day 90 of the study.
QTcF	Preclinical studies determined that TQ has a low potential for QTcF prolongation. Chloroquine does have a propensity to cause	Conduct ECG monitoring in this study and all phase III studies.

Potential Risk of Clinical Significance	**Data/Rationale for Risk**	**Mitigation**
	QTcF prolongation. A previous TQ drug-drug interaction study concluded that whilst there was no trend over time for increased QTcF intervals in those treated with TQ alone those treated with CQ did experience QTcF prolongation. In those treated with a combination of CQ/TQ there did not appear to be a trend over time for increased QTcF intervals in the CQ/TQ arm beyond those observed on CQ alone. In addition, a TQ thorough QT study did not show elongation of the QTcF at clinical doses.	
Liver Transaminase Elevations	Preclinical repeat dose toxicology studies observed liver changes that were fully or partially reversible. During a TQ thorough QT study two subjects receiving 1200 mg TQ experienced transient elevations in liver transaminases. It was concluded that high doses of TQ appeared to be associated with transient increases in transaminases.	Conduct liver function testing in this study and all phase III studies.
Renal Function	Transient increases in serum creatinine have been observed in clinical studies. Most recent example includes observation of mild, transient, dose related increases in serum creatinine in human volunteers. A renal safety study was conducted and	Conduct renal function testing in this study and in all phase III studies.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation
	concluded that TQ, when given as 200 mg x 3 days loading dose followed by weekly 200 mg dosing for 6 months was not inferior to placebo when comparing mean change from baseline glomerular filtration rate.	
Use in pregnancy and lactation	Preclinical data reported no adverse effects on fertility, embryofetal development or on post-natal survival. No clinical studies have been conducted in humans during pregnancy. There may be concern about risk to a fetus who is G6PD deficient and risk to breastfed infants whose G6PD status may be unknown.	Pregnant or lactating women are excluded from this study.
Phototoxicity	Preclinical studies have been conducted to assess TQ photoirritancy factor. The conclusion of these studies was that tafenoquine was “probably” phototoxic. A review of Integrated clinical safety data (>4000 subjects) has not determined any discernible pattern of incidence of rash associated with TQ treatment.	The incidence and frequency of rash will continue to be reviewed for signs of photoirritancy in this patient population.

1.3.2. Benefit Assessment

In the absence of radical cure treatment, a percentage of patients with *P. vivax* malaria will relapse due to the liver being infected with hypnozoites (the dormant form of the parasite). *P. vivax* malaria is most prevalent primarily in Asia, Asia-Pacific and Latin American countries and frequency of relapse rates may impact product use. Relapse rates vary with strain and are difficult to measure due to confounding by re-infection. The WHO have generalized relapse rates in the following countries as: India (15-20%), Indonesia (30%) and South East Asia (50-60%). *P. vivax* can cause a debilitating fever and as it preferentially invades reticulocytes, 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, especially in children. Consequences are loss of work or school days (e.g. 5.4 days school absenteeism per episode) and hospitalization (especially children) due to vomiting, dehydration and anemia (resulting in transfusion).

Due to its long half life, tafenoquine can be administered as a single oral dose and is therefore a more convenient treatment regimen with the potential to improve patient compliance. Improved compliance could also lead to improved clinical outcomes for patients with *P. vivax* malaria by further reducing relapse rates.

1.3.3. Overall Benefit:Risk Conclusion

Tafenoquine is being developed with the aim of a benefit:risk profile which is as least as good as the current gold standard therapy PQ. Our intent is to evaluate whether improved compliance could also lead to improved clinical outcomes for patients. Tafenoquine should have no clinically significant side effects that will restrict its use as a first line agent in treatment of *P.vivax* malaria when used in combination with a G6PD test and recommended therapies to treat the blood stages of infection. With specific regard to this study, the overall benefit:risk is favorable to all subjects, given that all are receiving active treatment.

2. OBJECTIVES & ENDPOINTS

Objectives	Endpoints
Primary	
To investigate the occurrence of clinically relevant hemolysis in adult subjects with *P. vivax*. The incidence of hemolysis in the subgroup of female patients with moderate (40-70%) G6PD activity is of particular interest.	• Occurrence of clinically relevant hemolysis in all subjects; defined as, a decrease in hemoglobin of ≥30% or >3 g/dL from baseline; or, an overall drop in hemoglobin below 6.0 g/dL. • Occurrence of clinically relevant hemolysis in female subjects with moderate (40-70%) G6PD deficiency; defined as, a decrease in hemoglobin

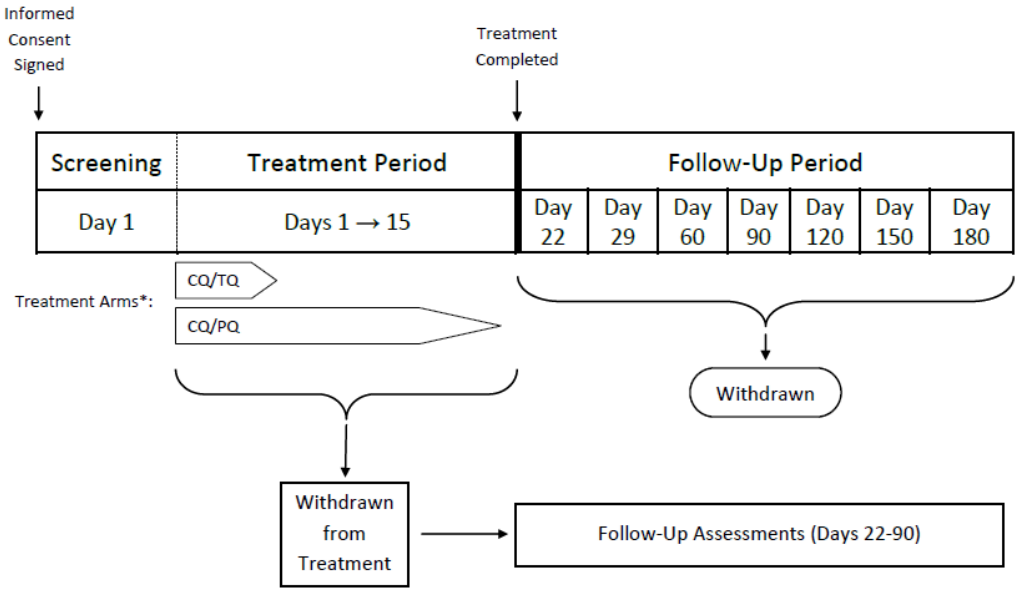
Objectives	Endpoints
	of ≥30% or >3 g/dL from baseline; or, an overall drop in hemoglobin below 6.0 g/dL.
Secondary	
To compare the clinical and parasitological efficacy, safety and tolerability of tafenoquine to primaquine as a radical cure for adult subjects with *P. vivax* malaria when co-administered with chloroquine.	• Relapse-free efficacy six months post-dosing • Relapse-free efficacy four months post-dosing • Time to relapse • Parasite clearance time • Fever clearance time • Gametocyte clearance time • Recrudescence, defined as any *P. vivax* parasitemia occurring on or before Day 29 (i.e., blood stage treatment failure). • Incidence of genetically homologous and genetically heterologous *P. vivax* infections (determined by PCR) • Safety evaluation of data from clinical laboratory tests, urinalysis, spontaneous/elicited adverse event reporting, ECGs and vital signs in all subjects who received at least one dose of study medication. • Incidence of *P. falciparum* malaria
To characterize the socioeconomic impact of *P. vivax* relapse.	• Characterization of healthcare resource use and socio-economic impact of *P. vivax* relapses and adverse events caused by treatment to prevent *P. vivax* relapses, especially hemolytic anemia.
To evaluate the pharmacokinetics of tafenoquine in the treatment of 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)
To characterize the pharmacokinetic/pharmacodynamic relationship in this study population.	• PK and selected PD endpoints (e.g., relapse-free efficacy, change in methemoglobin) if appropriate

With regard to the secondary efficacy endpoints, it should be noted that it is not possible to determine if a subject's recurrence of malaria is a relapse or a re-infection. For the purposes of this protocol, the term "relapse" will be used to describe any recurrence of malaria that occurs after Day 32 of the study. "Recrudescence" applies to the term relating to recurrence for Days 1 to 32 of the study where, although a genetically homologous parasite is highly suggestive of recrudescence and thus blood stage treatment failure, it is not absolute as re-infection is technically possible; the probability of which is related to the overall background incidence of the homologous parasite in the mosquito population.

3. INVESTIGATIONAL PLAN

Study TAF116564 is a prospective, double-blind, double-dummy, multicenter, comparative study, enrolling 300 subjects and consisting of a 3 day in-patient hospital stay and 11 further on-treatment and follow-up study visits distributed over 180 days. The study schematic diagram in Section 3.1 summarizes the study visits.

3.1. Study Design Schema



CQ/TQ = Chloroquine 600mg OD Days 1 & 2; 300mg OD Day 3 / Tafenoquine 300mg single dose Day 2
CQ/PQ = Chloroquine 600mg OD Days 1 & 2; 300mg OD Day 3 / Primaquine 15mg OD Days 2-15

3.2. Study Design

- Study TAF116564 is a prospective, double-blind, double-dummy, multicenter, comparative study.
- A total of 300 subjects will be randomized 2:1 to receive TQ/CQ or the active comparator PQ/CQ. All subjects will receive CQ on Days 1 to 3 (600mg, 600mg and 300mg each once daily), followed by TQ or PQ and matching placebo beginning on Day 1 or 2. Tafenoquine, or matching placebo, will be given as a single, 300mg dose. Subjects will receive PQ (15mg once daily) or matching placebo for 14 days.
- The duration of the study is 180 days, including screening and randomization to treatment (Day 1), three in-hospital days (Days 1-3), four out-patient visits while on treatment with study medication (Days 5, 8, 11 and 15) and seven follow-up visits (Days 22, 29, 60, 90, 120, 150 and 180).
- Subjects must have a blood smear that is positive for *P. vivax* at entry. Blood smears will be taken for parasitological assessment twice a day for the first 3 days of the study, or until two consecutive thick blood smears are negative for *P. vivax*. Additional parasitological assessments will be conducted throughout the treatment and follow-up periods.
- Subjects are required to remain in the hospital for the first three days of the study, in order to ensure clinical improvement, to monitor early study medication compliance, and so that parasitological assessments can readily be taken twice a day. Subjects may need to remain in the hospital longer than 3 days if two consecutive thick blood smears negative for *P. vivax* are not obtained within the 3 day timeframe.
- At the Day 1 visit subjects will be screened for G6PD deficiency by a quantitative assay and the result will be determined as a percentage of the predetermined median enzyme activity of the site. Female subjects must have a minimum G6PD assay value of 40% to be enrolled, and male subjects must have a minimum G6PD assay value of 70% to be enrolled. In addition, a minimum of 50 female subjects must be enrolled that display ≥40% - <70% of the site median G6PD enzyme activity.
- The status of methemoglobin, an oxidized and inactive form of hemoglobin, will be assessed at selected visits.
- An independent data monitoring committee will be established to monitor, in an unblinded manner, safety in general and females with moderate G6PD deficiency in particular. The latter will ensure the frequency and severity of any hemoglobin declines in females remains as expected and remains clinically acceptable.
- The primary analysis population will be the Microbiologic Intent To Treat (mITT) population, defined as all randomized subjects who receive at least one dose of blinded study medication and have microscopically-confirmed vivax parasitemia.

- Selected investigator centers will perform ophthalmic safety assessments at selected visits to monitor subjects for changes in the eye.
- Healthcare resource use and socio-economic impact data will be collected to characterize *P. vivax* relapse and adverse events caused by treatment to prevent *P. vivax* relapse, with particular attention to hemolytic anemia.
- Blood samples will be collected on Days 2, 3, 8, 15, 29 and 60 of the study for pharmacokinetic and pharmacodynamic analyses.

Subjects are considered to have completed the study if they meet all inclusion/exclusion criteria, are considered compliant with all study medication, complete the 3 day hospital stay, and attend the Day 180 visit.

Protocol waivers or exemptions are not allowed; therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

3.3. Discussion of Design

The design of TAF116564 has been made purposely similar to Part 2 of sister study TAF112582, the pivotal phase III efficacy and safety study of the tafenoquine program. The overall design of the studies is based on FDA guidance for the radical cure of malaria due to *P. vivax*. In this double-blind, double-dummy design, subjects will be screened and randomized to treatment on Day 1, and will remain in the hospital for the first 3 days of the study, or until two consecutive thick blood smears are negative for *P. vivax,* to monitor study medication compliance and infection status. Subjects will continue on treatment for the first 15 days of the study and will be monitored up to day 29 for recrudescence. Subjects will continue to be monitored up to 180 days post-randomization for evidence of relapsing infection. In all subjects, PCR analysis of *Plasmodium* species will be conducted to investigate the genetic constitution of *P. vivax* recurrences during the study.

All subjects will receive open label CQ for the first 3 days of the study to treat the blood stage of the infection. Beginning on Day 1 or Day 2, subjects will receive TQ or the active comparator, PQ, and the corresponding placebo for treatment of the liver stage of infection. Primaquine was selected as the comparator for this study as PQ plus CQ is the current standard of care for radical cure of *P. vivax* malaria in the majority of endemic countries.

3.3.1. Dose Rationale

Tafenoquine has demonstrated preliminary efficacy following 1-3 days of dosing, which is further supported by a prolonged half-life of 15-19 days. This shorter course of therapy should significantly improve compliance and thus effectiveness of relapse prevention.

Two separate exploratory clinical studies have demonstrated TQ's utility for the treatment and radical cure of *P. vivax* malaria: Study SB-252263/047 [GlaxoSmithKline Document Number RM2007/00309/00] was conducted in two parts, and tafenoquine was administered following chloroquine treatment of blood schizonts. Tafenoquine was found to be highly efficacious across the entire 500 mg to 3000 mg dose range. In study SB-252263/058 [GlaxoSmithKline Document Number UM2004/00017/00], a total dose of 1200 mg tafenoquine was administered over 3 days. Tafenoquine resulted in 100% relapse prevention, however, the tafenoquine monotherapy regimen exhibited slow parasite and fever clearance times relative to the CQ+PQ control. In conclusion, TQ's long half-life supported a 1 to 3 day treatment regimen when co-administered with a second blood schizonticidal drug, such as CQ.

A two-part drug-drug interaction study [GlaxoSmithKline Document Number WD2009/01503/00; Study TAF106491] has also been conducted to investigate the interaction between TQ and CQ in healthy volunteers. Part 1 was a three arm, open label pilot study to evaluate the safety and pharmacokinetics of a low dose CQ co-administered with TQ. Part 2 was a double-blind study to assess the drug-drug interaction, safety (including ECG effects), tolerability and pharmacokinetic parameters of CQ co-administered with TQ. Based on the PK results from the pivotal Part 2 portion of this study, there appears to be a short term significant effect on TQ PK (Day 2 Cmax and AUC(0-24)) when co-administered with CQ with no significant effect on the full PK profile (AUC(0-) and t1/2). TQ had no significant effect on the PK of CQ and desethylchloroquine. Taken together, these results suggest that there is no clinically significant pharmacokinetic interaction with concomitant administration of TQ and CQ.

A thorough QT study (TAF114582) was recently completed that studied two therapeutic doses (300mg and 600mg; single dose) and one supratherapeutic dose (1200mg; 400mg x 3) of tafenoquine. The therapeutic doses of tafenoquine had no marked effect on QTcF prolongation. In the 1200mg group, a mean effect of 6.6 msec in QTcF prolongation was observed, just within the 10 msec safety margin set out in E14 ICH guidelines.

Throughout the tafenoquine program, subjects have been evaluated for changes in Hb following treatment with TQ. In G6PD-normal subjects only small decreases in Hb have been observed. These changes were not considered clinically significant, and were only seen in subjects receiving doses of TQ much higher than what had been considered for clinical investigation. In studies where G6PD-deficient subjects have been included, significant Hb decreases have been observed. A study was recently completed (TAF110027) that assessed the hemolytic risk of TQ in female healthy volunteers with moderate G6PD deficiency (40%-60% of site median normal value). Results indicated a TQ dose response for hemolysis, and the highest dose of TQ tested, 300mg, resulted in Hb declines similar to daily dosing of 15mg PQ. This data factored greatly into determining a dose to take forward into phase III.

Tafenoquine was recently investigated in part 1 of TAF112582, a seamless Phase II/III study. The phase II portion (part 1) was a dose-ranging study assessing the efficacy and safety of four doses of TQ in subjects with *P. vivax* malaria. The goal was to select an efficacious and well-tolerated dose of TQ to be co-administered with CQ. The long half-life of TQ allowed it to be delivered as a single dose. The 300mg dose achieved highly

significant improvements (p<0.0001) in relapse-free efficacy compared to CQ alone. Treatment differences (TQ/CQ - CQ) ranged from 45% for the most conservative analyses to 61%. Small declines in Hb were seen; approximately 30% of subjects in the 300mg TQ dose experienced a decline in Hb of >1.5 g/dL and <2.5 g/dL. Only 2 (4%) subjects experienced a Hb drop >2.5 g/dL. All other treatment groups experienced similar Hb drops, and all were considered disease-related. At the conclusion of Phase II, the single 300mg dose of TQ was selected to carry forward to the Phase III program.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

Subjects who have a blood smear positive for a single species infection with *P. vivax* and meet all other eligibility criteria qualify for entry into the study. A total of 300 subjects will be randomized into the study, and 50 of these will be females with G6PD enzyme levels consistent with moderate G6PD deficiency. The primary study population is the mITT population, and includes all subjects who meet all eligibility criteria and receive at least one dose of blinded study medication.

4.1. Number of Subjects

Randomized: 300

Subject Screening Failures: 150

Number of Evaluable Subjects: 300

Number of Screened Subjects: 450

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study medication that may impact subject eligibility is provided in the Tafenoquine Investigator Brochure [GlaxoSmithKline Document Number GM2007/00152/06], and the locally-approved product labels for Chloroquine and Primaquine.

Deviations from inclusion 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.

Subjects eligible for enrolment in the study must meet all of the following criteria:

Safety

1. A female is eligible to enter and participate in the study if she is non-pregnant, non-lactating and if she is of:

a. Non-childbearing potential defined as: post-menopausal (12 months of spontaneous amenorrhea or <6 months of spontaneous amenorrhea with serum FSH >40 mIU/mL), or pre-menopausal and has had a hysterectomy or a bilateral oophorectomy (removal of the ovaries) or a bilateral tubal ligation, negative pregnancy test or,

b. Child-bearing potential, has a negative pregnancy test at screening, and agrees to comply with one of the following during the treatment stage of the study and for a period of 90 days after stopping study medication:

- Use of oral contraceptive, either combined or progestogen alone used in conjunction with double barrier method as defined below.
- Use of an intrauterine device with a documented failure rate of <1% per year
- Use of depo provera injection
- Double barrier method consisting of spermicide with either condom or diaphragm
- Male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female.
- Complete abstinence from intercourse for 2 weeks prior to administration of study medication, throughout the study and for a period of 90 days after stopping study medication.

2. The subject has a glucose 6-phosphate dehydrogenase (G6PD) value (measured by a quantitative spectrophotometric phenotype assay) as follows:

- **Female subjects** must have an enzyme level ≥40% of the site median value for G6PD normal males.
- **Male subjects** must have an enzyme level ≥70% of the site median value for G6PD normal males.

3. The subject has a screening hemoglobin (Hb) value as follows:

•Any subject with a G6PD value ≥70% of the site median value must have a screening Hb value ≥7 g/dL.

•Female subjects with a G6PD value is ≥40% - <70% of the site median value must have a screening Hb value ≥8 g/dL.

4. 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 or manual over-read.

Efficacy

5. The subject has a positive malarial smear for *P. vivax*.

6. The subject has a parasite density of >100 and <100,000/μL.

Other

7. Male or female subject aged 16 years or older at the time of signing the informed consent.
8. The subject agrees to G6PD genotyping.
9. The subject is willing and able to comply with the study protocol.
10. The subject or parent/legal guardian, as applicable, has given written informed, dated consent; and the subject has given written assent, if applicable, to participate in the study.

4.2.2. Exclusion Criteria

Deviations from 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.

Subjects meeting any of the following criteria must not be enrolled in the study:

Safety

1. The subject has a mixed malaria infection (identified by a malarial smear or rapid diagnostic test).
2. The subject has severe *P. vivax* malaria as defined by WHO criteria.
3. The subject has a history of allergy to chloroquine, mefloquine, tafenoquine, primaquine, or to any other 4- or 8-aminoquinoline.

Hepatic Disease

4. The subject has a liver ALT >2 x ULN.

Concurrent Disease

5. The subject has severe vomiting (no food or inability to take food during the previous 8 hours).
6. The subject has a clinically significant concurrent illness (e.g., pneumonia, septicemia), pre-existing condition (e.g., renal disease, malignancy), condition that may affect absorption of study medication (e.g., vomiting, severe diarrhea), or clinical signs and symptoms of severe cardiovascular disease (e.g., uncontrolled congestive heart failure, severe coronary artery disease).
7. The subject has a history of porphyria, psoriasis, or epilepsy.
8. The subject has a history of significant ocular disease (e.g. surgery to the globe, glaucoma, diabetic retinopathy) or has evidence of corneal or retinal abnormalities identified in the clinical screening ophthalmologic examination.

Concurrent Medication

9. The subject has taken anti-malarials (e.g., artemisinin-based combination therapies, mefloquine, primaquine, or any other 4- or 8-aminoquinoline) within 30 days prior to study entry.
10. The subject has taken or will likely require during the study the use of medications from the following classes:

    - Histamine-2 blockers and antacids
    - Drugs with hemolytic potential
    - Drugs known to prolong the QTcF interval

Other

11. The subject has received treatment with any investigational drug within 30 days of study entry, or within 5 half-lives, whichever is longer.
12. The subject has a recent history of illicit drug abuse or heavy alcohol intake, such that full participation in the study could be compromised.

NOTES ON ELIGIBILITY CRITERIA:

- See Appendix 4 (Section 11.4) for the WHO definition of severe malaria.
- Ophthalmic safety assessments will only be conducted at appropriately qualified investigator sites. Therefore, exclusion criterion 8 only applies to those pre-selected sites. A subject may be excluded from the ophthalmic assessments at one of these sites but still participate in the main portion of the study.

4.3. Withdrawal Criteria

- Adverse event
- Protocol deviation
- Study closed/terminated
- Lost to follow-up
- Consent withdrawal
- Subject or investigator non-compliance
- At the request of the subject, investigator, or sponsor
- Pregnancy

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at their discretion, discontinue the subject from participating in this study at any time. A subject is considered to be withdrawn prematurely from the study if

they do not complete the Day 180 assessment. A subject may withdraw or be prematurely withdrawn for any of the reasons presented in the list above. If a subject withdraws consent the site should offer to conduct safety assessments through Day 90.

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 must make every effort to perform the study evaluations as specified in Table 2 for the Relapse or Withdrawal visit as applicable.

4.4. Premature Withdrawal of Study Medication

If a subject prematurely discontinues from blinded study medication, the reason for withdrawal from medication should be recorded in the eCRF. As useful safety and efficacy information can still be obtained for these patients, the investigator should continue following subjects for all protocol assessments, up to and including day 180. The subject should be offered/given appropriate rescue medication as detailed in Section 5.6.1.2 if they get a recurrence of malaria due to inability to take blinded study medication.

Subjects who withdraw from open label CQ (and prior to receiving blinded study medication) will not continue in the study and should be offered alternative treatment in accordance with site (local) or national treatment guidelines for *P. vivax* malaria. These subjects should be followed up until resolution of the malaria infection.

In addition, subjects should discontinue taking study medication if they meet any of the following criteria:

- Any grade 4 AE or toxicity in the absence of compelling evidence that the AE is not related to study medication
- Clinically significant laboratory results considered by the investigator to warrant withdrawal from the study
- QT stopping criteria as defined below:
    - QTcF > 500msec
    - Uncorrected QT > 600msec

      These criteria should be based on the average QTcF value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTcF values of the three ECGs to determine whether the patient should be discontinued from the study.
    - For subjects with underlying Bundle Branch Block, the criterion is ≥ 530 msec.

- Liver chemistry stopping criteria as specified in Section 6.4.1
- Given the hemolytic potential of TQ and PQ in subjects with G6PD deficiency, study specific hemoglobin stopping criteria will be employed. Refer to Section 6.4.2 for details.

When QT or hematologic stopping criteria are met, this must be promptly reported by the investigator to GSK (see Section 6.4.11).

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

Throughout the protocol, study treatments will be defined and described as follows:

- "Study medication" refers to all drugs and placebos used in the study
- "Blinded study medication" refers to tafenoquine, primaquine and the corresponding placebos

The contents of the study medication labels will be in accordance with all applicable regulatory requirements. All study medication is being supplied by GlaxoSmithKline.

5.1.1. Tafenoquine

Tafenoquine will be supplied as a dark pink, 17.1mm × 9.0mm, capsule-shaped, film-coated tablet that is plain on both sides. Each tablet will contain 150mg tafenoquine.

5.1.2. Tafenoquine Placebo

Placebo tafenoquine tablets will be supplied as a dark pink, 17.1mm × 9.0mm, capsule-shaped, film-coated tablet that is plain on both sides, with common excipients of appropriate quality.

5.1.3. Chloroquine

Commercially available generic chloroquine tablets containing 500 mg chloroquine phosphate (equivalent to 300 mg chloroquine free base) will be utilized in this study.

5.1.4. Primaquine

Commercially available primaquine containing primaquine phosphate USP 26.3 mg (equivalent to primaquine base 15 mg) will be utilized in this study. Primaquine, a pink film-coated tablet imprinted W on one side and P97 on the other is made by SANOFI AVENTIS U.S. The primaquine tablets for this study have been over-encapsulated in a Swedish orange size B supro capsule.

5.1.5. Primaquine Placebo

Placebo to match primaquine will be supplied as Swedish orange size B supro capsules with common excipients of appropriate quality.

5.1.6. Handling and Storage of Investigational Product

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product at a temperature up to 30°C (87°F). Access to and administration of the investigational product will be limited to the investigator and authorized site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

A temperature log must be maintained at all study sites where study medication is stored.

Following full drug accountability, all used study medication should be destroyed at site according to local guidelines.

5.1.7. Duration of Treatment of Active Study Medication

The total duration of treatment is 15 days.

Chloroquine will be dosed orally once daily for three days starting on Day 1 of the study.

Tafenoquine will be dosed orally as a single dose on Day 1 or Day 2 of the study.

Primaquine will be given as a 14-dose course administered orally once daily for 14 days starting from Day 1 or Day 2 of the study.

5.1.8. Dose and Administration

Study medication should be administered with food. If the subject vomits within 1 hour following dosing, a repeat dose should be given. If a subject sequentially vomits two doses of study medication he/she will be considered intolerant to study medication. These subjects will be withdrawn from study medication and be given appropriate rescue medication as outlined in Section 5.6.1.2. Subjects and all site staff will be blinded to the study treatment.

Subjects will be randomized into one of two treatment arms and receive the following number of CQ tablets, TQ/placebo tablets and PQ/placebo capsules:

Treatment Arm	**Day 1**	**Day 2**	**Day 3**	**Days 4 – 15**
tafenoquine	2×CQ 300mg	2×CQ 300mg + 2×TQ 150mg + 1×PQ placebo	1×CQ 300mg + 1×PQ placebo	1×PQ placebo
primaquine	2×CQ 300mg	2×CQ 300mg + 2×TQ placebo + 1×PQ 15mg	1×CQ 300mg + 1×PQ 15mg	1×PQ 15mg
Total number of capsules/tablets per treatment arm	**2 tablets**	**4 tablets + 1 capsule**	**1 tablet + 1 capsule**	**1 capsule × 12 days**

NOTE: subjects may begin blinded study medication (TQ or PQ and corresponding placebo) on Day 1 or Day 2 of the study.

5.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule generated prior to the start of the study by the study statistician, using the validated internal software RANDALL.

Each subject scheduled to receive study medication will receive a treatment allocation number when randomized. The randomization number will indicate which therapy the subject will receive, the treatment allocation ratio will be 2:1 (TQ/CQ: PQ/CQ). Once a randomization number has been allocated to a subject, it cannot be re-assigned to any other subject.

5.3. Blinding

This is a double-blind study and both subject and study staff will remain blinded to treatment.

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. It is preferred (but not required) that the investigator first contacts the GSK Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment. If GSK study personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible, 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 appropriate data collection tool.

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 clinical investigators in accordance with local regulations and/or GSK policy.

5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

5.5. Treatment Compliance

Compliance with study medication will be assessed in all subjects by directly observing the taking of medication for days 1-3 of the study. Compliance with respect to PQ medication/placebo in the subgroup of female subjects with moderate G6PD deficiency will be assessed for days 4-15 also by directly observing the taking of study medication. In all other subjects, outpatient compliance will be assessed by pill count and will be evaluated using details of dose administration recorded in the eCRF.

As part of the assessment of PQ compliance, levels of PQ and 7-carboxy PQ will be measured on Days 2, 3, 8 and 15 using TQ pharmacokinetic samples (see Section 6 and Section 6.6.1). Refer to the SPM for detailed methodology on measuring PQ and 7-carboxy PQ in these samples.

5.6. Concomitant Medications and Non-Drug Therapies

5.6.1. Permitted Medications and Non-Drug Therapies

5.6.1.1. Concomitant Medication

All subjects can be given paracetamol during the study but administration time must be recorded in the eCRF. Allowable antibiotics are penicillins, cephalosporins, carbapenems and aminoglycosides.

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

5.6.1.2. Rescue Medication

Subjects requiring rescue medication will be given appropriate medication in accordance with site (local) or national treatment guidelines for *P. vivax* malaria or; e.g., *P. falciparum* malaria, whichever is applicable. Subjects offered rescue medication should be followed up for safety assessment until resolution of the malaria infection.

Details of rescue medication including reason for the rescue medication offered (e.g. withdrawal from study, treatment failure) should be recorded in the eCRF.

5.6.2. Prohibited Medications and Non-Drug Therapies

The following drugs are prohibited for use from 30 days prior to entry in the study through Day 180:

- Anti-malarials and other medicines with known anti-malarial activity.
- Drugs with hemolytic potential.
- Drugs known to prolong QTcF
- Drugs known to interact with primaquine or chloroquine.

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

See Appendix 5 in Section 11.5 for a non-exhaustive list of prohibited medicines for guidance.

5.7. Treatment after the End of the Study

There is no extension study planned and thus no post study treatment will be offered except for subjects diagnosed with malaria at the end of the study who will receive rescue medication outlined in Section 5.6.1.2.

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

5.8. Treatment of Study Treatment Overdose

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

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.

Chloroquine

No specific antidote for chloroquine 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.

Drowsiness, blurred vision, diplopia, blindness, tinnitus, convulsions and coma can occur with overdose. Chloroquine is a known cardiovascular toxin thus cardiac monitoring and resuscitation facilities are essential. Thus in addition to dizziness, nausea, vomiting, diarrhea and headache hypotension, cardiogenic shock and cardiac arrest may occur. The 12 lead ECG may demonstrate decreased T waves, widening of the QRS complex, which may lead to ventricular tachycardia and/or fibrillation.

Primaquine

No specific antidote for primaquine has been identified. In the event that overdose or toxicity 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 primaquine overdose include abdominal cramps, vomiting, burning epigastric pain, central nervous system and cardiovascular disturbances, cyanosis, methemoglobinemia (see tafenoquine overdose guidelines), moderate leukocytosis or leukopenia and anemia.

6. STUDY ASSESSMENTS AND PROCEDURES

Table 2 Time and Events

Protocol Activity	Visit Day															
	Screening/Treatment Period[a]							Follow-Up Period							Relapse Visit[b]	Withdrawal Visit[c]
	Day 1[d]	Day 2	Day 3	Day 5	day 8	Day 11	Day 15	Day 22	Day 29	Day 60	Day 90	Day 120	Day 150	Day 180	Relapse	Withdrawal
Window				+1d	-/+1d	-/+1d	-/+2d	-/+3d	-/+3d	-/+7d	-/+7d	-/+10d	-/+10d	-14/+21d		
Informed Consent Process	X															
Demographic Information	X															
Initial History Only [e]	X															
Physician Assess. Malaria Signs & Symptoms	X															
Inclusion/Exclusion Criteria	X															
Efficacy Assessments																
Parasitological Assessment (blood smear)	X[f]	X[f]	X[f]		X		X	X	X	X	X	X	X	X	X	X
Plasmodium PCR Genotyping	X														X	
Plasmodium whole genome sequencing	X														X	
Safety Assessments																
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs [g]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X		X		X	X	X	X	X	X	X	X	X	X

Protocol Activity	Visit Day															
	Screening/Treatment Period[a]							Follow-Up Period							Relapse Visit[b]	Withdrawal Visit[c]
	Day 1[d]	Day 2	Day 3	Day 5	day 8	Day 11	Day 15	Day 22	Day 29	Day 60	Day 90	Day 120	Day 150	Day 180	Relapse	Withdrawal
Window				+1d	-/+1d	-/+1d	-/+2d	-/+3d	-/+3d	-/+7d	-/+7d	-/+10d	-/+10d	-14/+21d		
ECG w/ Interpret. & Report [h]	X	X							X						X	X
Adverse Events Assessment [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
G6PD (phenotyping) [k]	X									X		X				
G6PD and CYP2D6 (genotyping)		X														
Ophthalmological Exam (qualified sites only)	X								X		X			X[l]		X
Laboratory Assessments																
Hematology [m]	X		X[n]	X	X	X	X	X	X	X	X	X			X	X
Clinical Chemistry [o]	X		X[n]	X	X	X	X	X	X	X	X	X			X	X
Methemoglobin	X	X	X	X	X	X	X	X	X	X		X			X	X
Urinalysis [p]	X		X	X	X	X	X	X	X	X	X	X			X	X
Blood Draw for PGx		X[q]														
Pregnancy Test [r]	X						X		X	X				X	X	X
Health Outcomes																
Health Outcomes Assessments [s]	X						X	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]
Pharmacokinetic Assessments																
PK/PD Sampling [u]		X	X		X		X		X	X					X	

Protocol Activity	**Visit Day**																
	Screening/Treatment Period[a]							**Follow-Up Period**							**Relapse Visit[b]**	**Withdrawal Visit[c]**
	Day 1[d]	**Day 2**	**Day 3**	**Day 5**	**day 8**	**Day 11**	**Day 15**	**Day 22**	**Day 29**	**Day 60**	**Day 90**	**Day 120**	**Day 150**	**Day 180**	**Relapse**	**Withdrawal**
Window				**+1d**	**-/+1d**	**-/+1d**	**-/+2d**	**-/+3d**	**-/+3d**	**-/+7d**	**-/+7d**	**-/+10d**	**-/+10d**	**-14/+21d**		
Investigational Product																
Dispense Open Label Chloroquine	X	X	X													
Dispense Blinded Study Medication	X[v]	X[v]														
Treatment Compliance Int. - Invest.	X	X	X	X	X	X	X									
IVRS Registration	X															

a All subjects must remain hospitalized for Days 1 through 3.

b Subjects who relapse will continue to be monitored for safety and efficacy at all scheduled visits through day 180. Relapse is defined by a positive blood smear with or without vivax symptoms.

c If subjects withdraw from blinded study medication, all scheduled follow-up visits should be performed to conduct safety assessments up to and including Day 180.

d Visit Day 1 includes all screening procedures and the first day of treatment with study medication.

e Includes medical, disease and therapy histories.

f Blood smears are to be taken twice a day, 6-12 hours apart for the first 3 days, or until 2 consecutive negative thick blood smears are obtained.

g Vital signs include height and weight (screening only), blood pressure, temperature, heart rate and respiratory rate. Vital signs are to be performed twice a day on Days 1 through 3, at least 4 hours apart, and immediately prior to PK measurements.

h ECGs are to be performed at screening (in triplicate), 12 hours after the first dose of blinded study medication, and on Day 29.

i Adverse events are recorded from the time of the first dose of study medication.

j Serious adverse events are recorded from the time of consent in order to fulfil international regulatory requirements.

k G6PD phenotyping to be performed by both quantitative spectrophotometric analysis and rapid point of care test.

l Only if Day 90 ophthalmological exam shows abnormalities.

m Hematology includes hemoglobin, hematocrit, red blood cell/white blood cell/platelet counts, mean cell volume, white blood cell differential and reticulocyte count.

n Hematology and clinical chemistry on Day 3 must be reviewed prior to discharge from the hospital.

o Clinical Chemistry includes CPK, BUN, serum creatinine, total and indirect bilirubin and liver clinical chemistry.

p Mid-stream urine will be analyzed for protein, glucose, ketones, bilirubin, blood, nitrates, urobilinogen and leukocyte esterase by dipstick method.

q The pharmacogenetics sample must be collected at the earliest opportunity after randomization and during the in-clinic treatment visit (Days 1-3).

Protocol Activity	Visit Day															
	Screening/Treatment Period[a]							Follow-Up Period							Relapse Visit[b]	Withdrawal Visit[c]
	Day 1[d]	Day 2	Day 3	Day 5	day 8	Day 11	Day 15	Day 22	Day 29	Day 60	Day 90	Day 120	Day 150	Day 180	Relapse	Withdrawal
Window				+1d	-/+1d	-/+1d	-/+2d	-/+3d	-/+3d	-/+7d	-/+7d	-/+10d	-/+10d	-14/+21d		

r Serum or urine pregnancy test that is routinely used at site with a test sensitivity for hCG level ≤ 25 mIU/mL. FSH serum test only for post-menopausal females with less than 6 months spontaneous amenorrhea.

s Refer to Section 6.5 of the protocol for details on health outcome data collection.

t Health outcomes assessments will only be collected at these visits from subjects with confirmed parasitemia or from subjects with clinically relevant hemolysis.

u Day 2 and Day 3 PK samples must be taken 6-12 hours and 24-48 hours post TQ dose. ECGs should be taken within 10 minutes prior to the Day 2 and Day 3 PK sampling.

v Treatment with blinded study medication will begin on either Day 1 or Day 2.

6.1. Critical Baseline Assessments

Written, dated informed consent must be obtained from each potentially eligible subject (or his/her legal representative) by study site personnel **prior** to the initiation of any screening procedures.

Clinical and laboratory assessments will be conducted at screening **(prior to first dose of the study medication)** as detailed in the Time and Events (Table 2).

- Demographic data will be collected to include details of date of birth, gender, race and ethnicity
- Medical history will be collected

- A physical examination will be conducted including:
    - Cardiovascular examination
    - Abdominal examination including assessment of splenomegaly
    - Respiratory examination

- Vital signs will be assessed. These include height, weight, temperature (oral, axillary or tympanic), heart rate, respiratory rate, systolic and diastolic blood pressure

- 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 6.3 and the SPM for further details).

- A blood sample will be collected on a filter paper and stored for future plasmodium genotyping analysis. An additional blood sample will be collected to conduct exploratory plasmodium whole genome sequencing.

- Current and prior medications will be reviewed including any anti-malarial medication that has been used.

- G6PD status will be assessed using quantitative spectrophotometric analysis (further instructions can be found in the SPM). The quantitative analysis will be used to determine the subject's eligibility for the study. One or more G6PD rapid point of care tests may also be performed at baseline.
    - Periodic external quality assurance testing will be performed to ensure high quality G6PD assay data. Procedures for quality assurance will be described in detail in the SPM.

- A blood sample will be collected on Day 2 for G6PD and CYP2D6 genotyping.

- Laboratory Assessments:
    - Hematology analysis will include: Hb, hematocrit (Hct), red blood cells (RBC), mean cell volume (MCV), differentiated white blood cells (WBC), platelets and reticulocytes (for conversion to absolute).
    - Clinical chemistry evaluations will include: blood urea nitrogen (BUN), serum creatinine, total and indirect bilirubin and liver chemistries (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and creatine phosphokinase (CPK))

- A serum or urine pregnancy test will be performed that is routinely used at the site, provided the test has a sensitivity for hCG of ≤ 25 mIU/mL. A FSH serum test will be performed only for post-menopausal females with less than 6 months spontaneous amenorrhea.

- Methemoglobin levels will be assessed using a non-invasive signal extraction CO-Oximeter handheld machine.

- 12 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 hear rate, RR interval, QRS duration, QT interval and QTcF (QT corrected by Friderica's formula) will be calculated from automated ECG readings and abnormal findings will be recorded. The mean value recorded pre-dose will be classified as baseline.

- A subset of qualified sites will perform the following ophthalmic assessments during in-patient stay and prior to randomization:
    - Visual acuity and color vision will be assessed by standard methods
    - Humphrey 10-2 visual field in order to determine the threshold sensitivity of specific loci in the central retina, detection and definition of relative or absolute scotomas.
    - Slit lamp examination of the cornea (to document and grade any corneal deposits), lens and retina.
    - Retinal digital photography for the documentation of changes in the retinal morphology.

6.2. Unscheduled Visits

Subjects who have one or more visits outside the allowable time window defined for each scheduled visit (see Table 2) will undergo all the procedures and assessments described in Table 2 with the exception of assessments performed only at screening and the PK assessments. Subjects should be able and/or encouraged to return to the clinic for unscheduled visits at anytime during the 180-day study period. **In addition, subjects must return to the clinic anytime they are experiencing a recurrence of malaria symptoms.**

6.3. Efficacy

Parasitology

Asexual parasite counts:

Microscope blood slides will be prepared pre-dose at screening on Day 1, post-dose on Day 1, 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 CQ <6 hours from midnight on day 1 a post dose slide can be taken early on day 2. Microscope blood slides will be prepared at subsequent visits on Days 8, 15, 22, 29, 60, 90, 120, 150 and 180. In addition, blood films should be obtained whenever parasitological re-assessment is required and at the relapse visit or withdrawal visit as applicable. At each time point two thick and one thin film slide should be prepared on separate slides and one additional unstained slide with both thick and thin films retained for quality control. For detailed instructions on the methodology for staining and counting please refer to the SPM.

In summary:

Thick film parasitemia (malaria parasite density) should be calculated first, using the subjects' actual white blood cell count (WBC). Aim to count the number of parasites per 200-250 WBCs:

> i.e., D1 parasitemia/µL = (number of D1 parasites/D1 WBC counted) x D1 WBC count

If after 200 WBCs have been counted, 9 or fewer parasites have been identified, continue counting until reaching 500 WBCs.

If the thick film contains > 250 asexual parasites per 50 WBC (i.e. 5 parasites per WBC, equivalent to 40,000 asexual parasites/µL), 8 high power fields on the thin film should be read and parasites counted against (assuming 250 RBC per high powered field = 2000) red blood cells counted (RBCs).

Parasitemia from thin films is then calculated as:

> Parasitemia/µL = (number of parasites in 8 high powered fields / RBC counted = 2000) x 4,000,000 [assumed RBC]

The calculated parasitemia/µL will be recorded into the eCRF for each time point. See SPM for quality control procedures.

Local quality control of slides is performed by reading of the slide by 2 different qualified microscopists. If the results from the two readings are within 20% of each other for the parasite count and the two readers agree on the species identification then the average result from the two microscopists is computed and recorded in the eCRF.

If the results from the two microscopists are different by more than 20 % or they disagree on the species identification then a third independent reader is required who will read both slides. The average count from the third independent reader is compared with results from the first two readers. The count of the first two readers closest to the average count of the third independent reader is regarded as final and should be recorded in the eCRF. The third reader should therefore be a highly experienced malaria microscopist.

Slides are considered negative after review of 100 high-power fields.

Gametocyte counts

In the same way, thick film slides will be read for gametocytes on Day 1 (pre-dose and post-dose) and then twice daily for the remainder of the in-patient stay. Slides will be prepared at subsequent visits on Days 8, 15, 22, 29, 60, 90, 120, 150 and 180 (and relapse and withdrawal visits if applicable).). If gametocytes are present they will be counted against a 200-250 WBCs and their density calculated as follows:

Gametocytes/µL = (number of gametocytes/WBC counted) x WBC count

Parasite Genotyping

Two drops of peripheral blood will be collected onto pre-printed filter paper for subsequent DNA extraction and PCR analysis of *Plasmodium* species on all subjects at screening (Day 1; pre-dose), at subsequent visits on Days 5, 8, 11, 15, 22, 29, 60, 90, 120, 150 and 180, and at all times of potential recrudescence/relapse or re-infection.

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.

Parasite whole genome sequencing

Four milliliters of blood will be taken for subsequent parasite exploratory whole genome sequencing at baseline and at the relapse visit. If the time taken to transport samples to the central laboratory leads to poor yields of high quality sequencing data (judged after n=50 samples have been analyzed) then this exploratory sample will no longer be taken.

External quality control

External quality control of slide readings will be conducted by an independent laboratory. The external quality control will be blinded to the treatment assignment. They will

examine a proportion of slides from each study site. The procedure for quality control will be described in the SPM.

6.4. Safety

The timing and details of all safety assessments are provided in the Time and Events table in Section 6. Additional details on specific assessments are provided below. Blinded safety information will be reviewed on a monthly basis by a GSK/MMV safety review team.

There are two co-primary safety endpoints in this study: clinically relevant hemolysis will be compared between the two treatment groups in all subjects, and in 50 female subjects with moderate G6PD deficiency (≥40% to <70% of the median site value).

Information on concomitant medication will be collected daily while the subject is an in-patient, at all scheduled treatment and follow-up visits, and if there is a relapse or premature withdrawal visit.

Physical examinations will be performed daily during in-patient days, on each scheduled treatment and follow-up visit at Days 8,15, 22, 29, 60, 90, 120, 150 and 180 and if there is a relapse or premature withdrawal visit.

Vital signs will be performed twice daily whilst an in-patient and on follow-up visits at Days 8, 11, 15, 22, 29, 60, 90, 120, 150 and 180 and if there is a relapse or premature withdrawal visit.

12-lead ECG will be performed at screening, 12 hours (± 30 minutes) after the first dose of blinded study medication, and at Day 29. ECG assessments will also be conducted in cases of relapse or early withdrawal. ECGs will be performed in triplicate at screening but single ECGs will be performed subsequently as indicated in Table 2 unless prolonged QTc is seen.

Clinical chemistry and hematology samples will be analyzed by local laboratories. Evaluations will be made at screening, treatment Days 3, 5, 8,11,15 and follow-up Days 22, 29, 60, 90, and 120. These assessments will also be performed if there is a relapse or withdrawal visit. The panel of tests to be analyzed are detailed below in Table 3 and Table 4. 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 Hct measurements that deviate substantially from previous readings should be immediately repeated via venous sampling. If a significant drop in Hb or Hct is observed upon repeat testing, all additional hematology and 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 3 Hematology Tests

Hemoglobin	Hematocrit	Platelets	MCV
WBC	RBC	Reticulocyte	WBC Differential

Table 4 Clinical Chemistry Tests

Creatinine	BUN	Total bilirubin	Indirect bilirubin
AST	ALT	ALP	CPK

Urinalysis will be conducted by local laboratories at screening, Days 3, 5, 8, 11, 15, 22, 29, 60, 90, and 180 (and at the withdrawal and relapse visits if applicable). Urine (approximately 20mL mid-stream urine) will be analyzed for protein, glucose, ketones, bilirubin, blood, nitrates, urobilinogen and leukocyte esterase 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 during the in-patient stay, at all out-patient treatment visits (Days 5, 8, 11 and 15) and at selected follow-up visits (Days 22, 29, 60 and 120) as well as at the relapse and withdrawal visits if applicable. 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).

Ophthalmic assessments will be performed at selected sites prior to randomization then at Days 29 and 90 and at the withdrawal follow-up visit. Assessments will also be carried out at Day 180 (and up to resolution) if the Day 90 assessments show abnormalities. Subjects who do not receive the assessment prior to randomization should not receive any subsequent ophthalmic exams.

6.4.1. Liver chemistry stopping and follow up criteria

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

Phase III-IV liver chemistry stopping criteria 1-5 are defined below and are presented in a figure in Appendix 3 (Section 11.3):

1. ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT ≥ 3xULN and INR>1.5, if INR measured)

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT ≥ 8xULN.
3. ALT ≥ 5xULN but <8 xULN persists for ≥2 weeks
4. ALT ≥ 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
5. ALT ≥ 5xULN but <8 xULN and cannot be monitored weekly for ≥2 weeks

When any of the liver chemistry stopping criteria 1-5 is met, do the following:

- **Immediately** withdraw study medication for that subject
- Report the event to GSK **within 24 hours** of learning its occurrence
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN **and** INR>1.5, if INR measured); INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Do not restart study medication

In addition, for criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values

For criteria 2, 3, 4 and 5:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (see below)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilise or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Subjects with ALT ≥5xULN and <8xULN which exhibit a decrease to ALT x≥3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, 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
- Subjects can continue study medication
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

For criteria 1-5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - 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
- Blood sample for PK analysis, obtained as soon as possible and within 24 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study medication 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 SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form.

- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form.

The following are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and 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]).
- 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. **NOTE**: 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].
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease.

6.4.2. Hemoglobin Stopping Criteria

Study medication will be stopped immediately if the subject's Hb decreases ≥30% or >3 g/dL from baseline; or, the subject's Hb value drops below 6.0 g/dL.

Once the Hb drop is noted and study medication is stopped, the following hematology and clinical chemistry tests should be performed immediately:

Hematology

- Hb
- Hct
- Platelets
- WBC
- RBC
- Reticulocytes
- Haptoglobin

Clinical Chemistry

- Creatinine
- BUN
- Total bilirubin

- Indirect bilirubin
- AST
- ALT
- ALP
- CPK
- LDH
- Visual inspection & Urine dipstick

In addition, MetHb status must be assessed. The subject should continue to attend all visits through Day 180 so that Hb status can continue to be monitored.

6.4.3. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

6.4.3.1. Definition of an AE

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. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- 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.

The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events that **do not** meet the definition of an AE include:

- 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
- 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

6.4.3.2. Definition of an SAE

A serious adverse event is 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 hospitalisation or prolongation of existing hospitalisation

   NOTE: In general, hospitalisation 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 hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

   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. 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 hospitalisation but may jeopardise 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 hospitalisation, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

   NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

PROTOCOL-DEFINED SAE

Hemoglobin decreases of ≥30% of >3 g/dL from baseline; or, an overall drop in Hb below 6.0 g/dL in the first 15 days of the study should be reported as an SAE (see Hb stopping criteria in Section 6.4.2).

6.4.4. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

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 judgment of the investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs (see Section 6.4.7).

6.4.5. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools 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 thrombosis
- Deep Venous Thrombosis
- Revascularization

This information should be recorded within one week of when the AE/SAE(s) are first reported.

6.4.6. Death Events

In addition, all deaths will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

This information should be recorded within one week of when the death is first reported.

6.4.7. 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 Section 6.4.11) 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.

6.4.8. Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

6.4.8.1. Time period for collecting pregnancy information

Information on the occurrence of new pregnancies will be collected over the period starting at screening (Day 1) and ending at the Day 90 follow-up assessment. Only those pregnancies that occur following the first dose of study medication will be reported to GSK. Follow-up information will be collected for pregnancies occurring throughout the study.

6.4.9. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of study treatment and until the follow up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, 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 reported to GSK within 24 hours, as indicated in Section 6.4.11.

6.4.10. Method of Detecting AEs and SAEs

Care must 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?" or for pediatric studies, "How does your child seem to feel?"

"Have you had any (other) medical problems since your last visit/contact?" or for pediatric studies, "Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?"

"Have you taken any new medicines, other than those provided in this study, since your last visit/contact?" or for pediatric studies, "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?"

6.4.11. Prompt Reporting of Serious Adverse Events and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	"SAE" data collection tool "CV events" and/or "death" data collection tool(s) if applicable	24 hours	Updated "SAE" data collection tool "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	2 weeks	"Pregnancy Notification Form"	2 weeks	"Pregnancy Follow-up Form"
QTcF stopping criteria	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Hematological toxicity criteria	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
DRE	2 weeks	DRE CRF page	2 weeks	Updated DRE CRF page

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	Time Frame	Documents	Time Frame	Documents
Liver chemistry abnormalities:				
ALT≥3xULN and Bilirubin≥2xULN (>35% direct) (or ALT≥3xULN and INR>1.5, if INR measured)[1]	24 hours[2]	"SAE" data collection tool. "Liver Event CRF" and "Liver Imaging" and/or "Liver Biopsy" CRFs, if applicable[3]	24 hours	Updated "SAE" data collection tool/"Liver Event" Documents[3]
ALT≥8xULN; ALT≥3xULN with hepatitis or rash or ≥3xULN and <5xULN that persists≥4 weeks	24 hours[2]	"Liver Event" Documents (defined above) [3]	24 hours	Updated "Liver Event" Documents[3]
ALT≥5xULN plus bilirubin <2xULN	24 hours[2]	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks[3]	24 hours	Updated "Liver Event" Documents, if applicable[3]
ALT≥5xULN and bilirubin <2xULN that persists ≥2 weeks	24 hours[2]	"Liver Event" Documents (defined above) [3]	24 hours	Updated "Liver Event" Documents[3]
ALT≥3xULN and <5x ULN and bilirubin <2xULN	24 hours[2]	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[3]	24 hours	Updated "Liver Event" Documents, if applicable[3]

1. INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants.
2. GSK must be contacted at onset of liver chemistry elevations to discuss subject safety
3. Liver Event Documents (i.e., "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible.

The method of recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

6.4.11.1. Regulatory reporting requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects 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.

6.5. Health Outcomes

Data will be collected to enable a descriptive analysis of the impact of *P.vivax* malaria and clinically relevant hemolysis on healthcare and other costs. Healthcare resource use (*i.e.*, clinic visits) resulting from trial procedures will be excluded.

6.5.1. Health Outcome Assessments Included as Secondary Endpoints

The following data will be collected at study enrolment (for the primary *P. vivax* infection), the Day 15 visit, and at study visits from Day 22 onwards for subjects with confirmed *P. vivax* parasitemia. In addition, the same data will be collected for subjects with clinically relevant hemolysis:

- Healthcare resource use (excluding clinic visits scheduled as part of the study)
- Over-the-counter medications purchased
- Any travel or other costs incurred in seeking or receiving healthcare (excluding travel for clinic visits scheduled as part of the study)
- Time lost from normal occupation (excluding time lost to attend clinic visits scheduled as part of study)

6.6. Pharmacokinetics/Pharmacodynamics

6.6.1. Blood Sample Collection for Pharmacokinetics/Pharmacodynamics

Blood samples for PK analysis will be collected for each patient at the time points indicated in the Time and Events Table (Section 6). Samples should be taken 6 to 12 hours and 24 to 48 hours after TQ dosing and a concurrent set of vital signs should also be obtained. The only exception to this is the sample that is collected when a subject relapses; this sample should be collected as near to the time of relapse as possible. 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.

Details of the PK blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SPM.

6.6.2. Pharmacokinetic/Pharmacodynamic Sample Analysis

Plasma sample analysis will be performed under the management of Worldwide Bioanalysis, DMPK, GlaxoSmithKline. Concentrations of TQ will be determined using the currently approved analytical methodology. In addition, concentrations of CQ and desethylchloroquine will be determined in both treatment arms of the study. Raw data will be stored in the GLP Archives, GlaxoSmithKline.

6.7. Pharmacogenetic Research

A 10 mL pharmacogenetics blood sample collected at the earliest opportunity after randomization and during the in-clinic treatment visit (Days 1 – 3) will be used for potential exploratory pharmacogenetics research aimed at understanding variation in subject response to TQ, PQ or CQ. Additional information regarding pharmacogenetic research is included in Appendix 1. The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments (i.e., approval of Appendix 1). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

7. DATA MANAGEMENT

For this study subject data will be entered into GSK defined electronic case report forms (eCRFs), 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 and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug. eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

Tafenoquine 300mg is not expected to be superior to PQ (15mg/day × 14 days) on the primary endpoint, and feasibility issues meant that it would not be possible to power the study to show non-inferiority. Instead, an estimation approach will be used.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

The sample size of 300 is based on the regulatory requirement to obtain an appropriate total safety database in subjects treated with TQ/CQ at the selected dose, given that subjects are randomized to TQ/CQ: PQ/CQ on a 2:1 ratio.

Included in this sample is a key subgroup of a minimum of 50 female subjects with moderate (40-70%) G6PD enzyme activity. This subgroup will be used to assess the risk to G6PD heterozygous deficient females who may be misclassified by a G6PD POCT and inadvertently treated with TQ.

The proportion of heterozygous subjects in this subgroup who will meet the primary endpoint of clinically relevant hemolysis when treated with either TQ or PQ is assumed to be 50%. A sample size of 30 such subjects treated with TQ will provide precision of 18% for the 95% confidence interval. Similarly, sample size of 15 subjects treated with PQ will provide a precision of 25%.

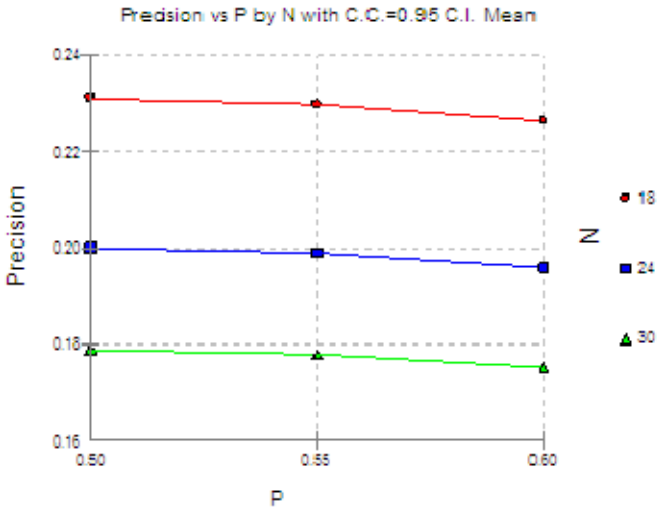
With 50% of the subjects in the subgroup and none of the other subjects assumed to meet the primary endpoint, we expect 8% of the total cohort to have a clinically relevant hemolysis. The 200 subjects in the TQ group will provide a precision of 4% and the 100 subjects in the PQ group precision of 5% for the 95% CI.

The power for testing a difference in proportion between the two treatment groups will be provided retrospectively.

8.2.2. Sample Size Sensitivity

If fewer than 50 subjects are enrolled into the subgroup or if the rate of hemolysis in the subgroup is higher than 50%, then the precision will be affected. We expect most, but not all subjects enrolled into the subgroup to be heterozygous. For total subgroup sizes of 30 and 40, we expect the number of heterozygous females in the TQ arm to be 18 and 24 respectively. For these n's in the TQ arm and for the rates of hemolysis at 50%, 55% and

60%, the corresponding precision for the 95% CI for the estimates rate of hemoslysis is given below:



8.3. Data Analysis Considerations

8.3.1. 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 medication. 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.

Microbiologic Intent to Treat (mITT) Population: all randomized subjects who receive at least one dose of blinded study medication and have microscopically-confimed vivax parasitemia. 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 mITT population for whom there were no major protocol violations (MPVs will be defined in the reporting and analysis plan [RAP]). This population will be used for sensitivity/supporting analyses of efficacy data only.

PK Concentration Population: this population will include all subjects who underwent plasma PK sampling. It will be used for the summarization, listing and plotting of concentration-time profiles.

PK Parameter Population: this population will include all subjects for whom valid PK parameter values were derived. It will be used for the analysis, summary tables, and listing of PK parameters.

PK/PD Population: this population will include all subjects for whom PK and PD were collected, and will be used for any exploratory analysis of PK/PD endpoints.

8.3.2. Analysis Data Sets

Data sets will contain a flag to identify for which analysis population subjects are eligible. Full details of these analysis datasets will be given in the RAP.

8.3.3. Treatment Comparisons

8.3.3.1. Primary Comparisons of Interest

The primary comparisons of interest between the two treatment arms are the proportion of all subjects with *P. vivax* experiencing clinically relevant hemolysis, and the proportions in the subgroup of females with *P. vivax* and moderate G6PD deficiency.

8.3.3.2. Other Comparisons of Interest

Other comparisons include clinical and parasitological efficacy, safety and tolerability of TQ compared to PQ as a radical cure for adult subjects with *P. vivax* malaria when co-administered with CQ.

8.3.4. Key Elements of Analysis Plan

Centers will be pooled for assessing the primary assessment of incidence of clinically relevant hemolysis. Data will be allocated to visit windows using actual visit dates rather than nominal visit numbers. Data collected from extra visits within a window will be listed and will be included in the derivation of the time to relapse, but summary tables will only use the data captured closest to the target visit date. Detailed explanations of the derivation of visit windows will be included in the RAP.

8.3.4.1. Primary Safety Analysis

The proportion and 95% confidence intervals of clinically relevant hemolysis in all subjects and in the subset of females with moderate G6PD deficiency, defined as a decrease in Hb of ≥30% or >3 g/dL from baseline (or an overall drop in Hb below 6.0 g/dL will be estimated separately for TQ and PQ treatment groups. In addition, a 95% confidence interval for the difference in proportions will be provided.

8.3.4.2. Secondary Safety Analyses

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

8.3.4.2.1. Extent of Exposure

The extent of exposure will be the number of doses of study medication administered to the subject (regardless of whether vomited). The duration of exposure to study medication will be defined as date of last dose of active study medication – date of first

dose of study medication + 1. Extent and duration of exposure will be summarized using a frequency distribution for number of doses and number of days.

8.3.4.2.2. Adverse Events

Adverse Event reporting will be performed using the MedDRA (Medical Dictionaries for Regulatory Activities) coding system. Each AE coded using the MedDRA system can be associated with more than one system organ class (SOC). However, for reporting purposes, an AE will be associated with the primary system organ class only.

Counting of AEs will be based on the number of subjects – not the number of AEs. For example, if a subject reports the same AE on three occasions within a time interval, that AE will only be counted once. Subjects reporting more than one AE in a system organ class will only be counted once in the system organ class total. Adverse Events will be summarized by preferred term and SOC, in descending order of frequency, and by maximum severity (mild, moderate or severe).

Adverse Events considered by the investigator to have a reasonable possibility of being related to treatment (drug-related AEs) will be summarized by preferred term and SOC.

Adverse Events leading to premature withdrawal from treatment and or study will be summarized by preferred term and SOC.

Adverse Events that are considered to be GI-related (i.e abdominal pain, heartburn, diarrhea, constipation, nausea and vomiting) will be summarized.

Adverse Events that are considered to be hematologically-related (i.e clinically relevant drops in Hb or Hct or other complications) will be summarized.

Serious adverse events will be summarized by preferred term and SOC.

8.3.4.2.3. Clinical Laboratory Evaluations

Clinical laboratory data (clinical chemistry and haematology) will be summarized by the mean, median, standard deviation, minimum and maximum values by treatment group and time point.

Laboratory data will also be evaluated by tabulating the number and percentage of subjects in each treatment group with values outside specified threshold values of clinical concern. (These may include values outside of the normal range, outer range of clinical concern, and other values of clinical concern.) These safety analyses will be defined in the RAP as appropriate.

8.3.4.2.4. Changes in Methemoglobin

The changes in MetHb will be will be summarized by the mean, median standard deviation, minimum and maximum values by treatment group and time point.

8.3.4.2.5. Ophthalmic Assessments

The ophthalmic assessments of keratopathy, retinopathy and visual field will be summarized.

8.3.4.2.6. QTcF Assessments

ECG results will be summarized accordingly. In addition, an outlier analysis to determine the number and percentage of subjects who have QTcF values and/or an increase from baseline in QTcF that are of clinical concern will be conducted.

8.3.4.3. Secondary Efficacy Analyses

The proportion of patients with relapse-free efficacy at four months and six months will be summarized by treatment group and analyzed using Kaplan-Meier methodology where subjects with missing data are censored, and by separate Fisher's Exact analyses where subjects are classified as a treatment failure if they do not have a six month result or took any drug with activity against *P.vivax*.

The time to relapse, parasite clearance time, fever clearance time and time to gametocyte clearance will be compared using the Kaplan-Meier method and summarized and listed by treatment group.

The incidence rates of genetically homologous and genetically heterologous *P. vivax* infection determined by PCR as well as recrudescence, defined as any *P. vivax* parasitemia occurring on or before Day 29 (*i.e.*, blood stage treatment failure), will be summarized and listed by treatment group.

Subjects will be assessed for clearance times against the following definitions:

Parasite Clearance Time (PCT): Time needed to clear asexual parasite from the blood defined as parasite numbers falling below the limit of detection in the thick blood smear and remaining undetectable 6-12 hours later.

Fever Clearance Time (FCT): Time from first dose of treatment to the time when body temperature falls to normal and remains normal for at least 48 hours.

Gametocyte Clearance Time (GCT): Time from first dose until the first slide that was gametocyte negative and remained so at the next slide reading. Subjects with no gametocytes at baseline will be censored, with a time to clearance of zero.

8.3.4.4. Health Outcomes Analyses

Descriptive summaries of the secondary endpoints on health outcomes will be produced.

8.3.4.5. Pharmacokinetic Analyses

Population PK analysis will be the responsibility of the Clinical Pharmacology Modelling and Simulation department within GlaxoSmithKline. All PK data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Plasma concentration data for TQ will be displayed in tables and/or graphs. Individual plasma concentration-time data may be pooled with previous data from studies containing robust PK sampling. Data permitting, a population PK model will be developed using software such as NONMEM or other currently available methods. Population PK parameters of tafenoquine such as oral clearance (CL/F) and volume of distribution (V/F) will be determined. In addition, the influence of various covariates (e.g. age, weight, and race) on the PK parameters will be examined.

Plasma concentration data for CQ and desethylchloroquine may be displayed in tables and/or graphs. A population PK model will be developed for CQ and/or desethylchloroquine data if safety or efficacy results from phase II studies indicate that PK/PD analyses are needed.

8.3.4.6. Pharmacokinetic/Pharmacodynamic Analyses

If data permit, exploratory PK/PD analyses for TQ data may be undertaken to examine any relationship between PK parameters (e.g. systemic exposure) and/or clinical outcome (relapse-free efficacy) or safety parameters (e.g. change in MetHb). Similarly, exploratory PK/PD analyses for chloroquine and/or desethylchloroquine data will be undertaken only if safety or efficacy results indicate that these data are needed to understand the PK/PD relationships for TQ.

8.3.4.7. Exploratory G6PD & CYP-2D6 Genotype Analyses

All treated female and any male subjects meeting the pre-specified criteria for Hb deficiency (Hb decrease ≥30% or ≥3.0 g/dL, or an overall drop below 6 g/dL) will be examined for mutations in the G6PD gene to investigate the relationship between G6PD enzyme level, Hb and genotype. Genetic strategies most likely to be used include single nucleotide polymorphism (SNP) genotyping and/or direct DNA sequencing of subject DNA samples. The same genetic approaches may be used to investigate G6PD genotype in subjects that do not meet the pre-specified criteria for G6PD deficiency to allow relationships between G6PD enzyme level, Hb and genotype to be explored.

In addition, exploratory CYP-2D6 genotype analyses will be undertaken to test the hypothesis that null and/or intermediate metabolisers of 8-aminoquinoline drugs are more at risk of *P. vivax* relapse [Bennett, 2013].

8.3.4.8. Pharmacogenetic Analyses

See Section 11.1 (Appendix 1) for details about the Pharmacogenetics Analysis Plan.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

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

9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, 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.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., PGx assessments described in Appendix 1, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

For adolescents who are not legally able to give consent, written informed consent is obtained from their Legally Authorized Representative (LAR) in accordance with applicable laws or regulations. The investigator is encouraged to obtain assent from adolescents in addition to the consent provided by the LAR.

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors 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 include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study to ensure 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.

9.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK 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.

9.5. Study and Site Closure

Upon completion or termination of the study, the GSK monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the investigator or 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 easily accessible 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 the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must 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. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

9.7. Provision of Study Results to Investigators, Posting of Information on Publicly 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 results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

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

9.8. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter, which is available upon request.

10. REFERENCES

Barcus MJ, Basri H, Picarima H et al. Demographic Risk Factors for Severe and Fatal Vivax and Falciparum Malaria Among Hospital Admissions in Northeastern Indonesian Papua. Am J Trop Med Hyg 2007;77(5):984-991.

Bennett JW, Pybus BS, Yadava A, Tosh D, Sousa JC. Primaquine failure and cytochrome P-450 2D6 in *Plasmodium vivax* malaria. N Engl J Med 2013;369(14): 1381-1382.

Fernando D, Rodrigo C, Rajapakse S. Primaquine in vivax malaria: an update and review on management issues. Malar J 2011;10:351.

Gething PW, Elyazar IRF, Moyes CL et al. A Long Neglected World Malaria Map: *Plasmodium vivax* Endemicity in 2010. PLoS Negl Trop Dis 2012;6(9): e1814. doi:10.1371/journal.pntd.0001814

GlaxoSmithKline Document Number GM2007/00152/06. SB-252263 Investigator's Brochure. Effective Date: 22nd November 2012.

GlaxoSmithKline Document Number RM2007/00309/00 Study ID SB-252263/047. A dose ranging study for the safety and efficacy of WD238605/SB252263 in the prevention and relapse of *Plasmodium vivax* infection in Thailand. Effective Date: 25th February 2010.

GlaxoSmithKline Document Number UM2004/00017/00 Study ID SB-252263/058. A randomized, active-control, double-blind, double-dummy study to evaluate the efficacy and safety of Tafenoquine for the treatment of *Plasmodium vivax* in adults. Effective Date: 26th September 2006.

GlaxoSmithKline Document Number WD2009/01503/00 Study ID TAF106491. Safety, tolerability and pharmacokinetic study of concomitant chloroquine and tafenoquine in healthy volunteers. Effective Date: 16th October 2009.

Hill DR, Baird JK, Parise ME, Lewis LS, Ryan ET, Magill AJ. Primaquine: Report From CDC Expert Meeting on Malaria Chemoprophylaxis I. Am J Trop Med Hyg 2006;75(3):402-415.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Protein Adducts in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009;37(8): 1779-1784.

Kochar DK, Das A, Kochar SK et al. Severe *Plasmodium vivax* Malaria: A Report on Serial Cases from Bikaner in Northwestern India. Am J Trop Med Hyg 2009;80(2):194-198.

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. Clin Microbiol 2005;43(5):2363–2369.

Price RN, Tjitra E, Guerra CA, Yeung S, White NJ, Anstey NM. Vivax Malria: Neglected and Not Benign. Am J Trop Med Hyg 2007;77(Suppl 6):79-87.

White NJ, Imwong M. Relapse (Chapter Two). Adv Parasitol 2012;80:113-150.

WHO Guidelines for the Treatment of Malaria - 2nd Edition, 2010, ISBN 9789241547925.

11. APPENDICES

11.1. Appendix 1: Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	HLA-B* *57:01 (Human Leukocyte Antigen B)*	Carriage of the HLA-B**57:01* variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective HLA-B**57:01* screening and exclusion of HLA-B**57:01* positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective HLA-B**57:01* screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. HLA-B**57:01* screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia Chung, 2010; Ferrell, 2008	HLA-B*15:02	Independent studies indicated that patients of East Asian ancestry who carry HLA-B**57:02* are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of HLA-B**57:02* prior to initiating treatment with carbamazepine.

Drug	Disease	Gene Variant	Outcome
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	UGT1A1*28	Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular UGT1A1 gene variation might be too high for another patient without this variation, raising the risk of certain side-effects, that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the UGT1A1*28 variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no a priori hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to tafenoquine or chloroquine.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to tafenoquine or chloroquine. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with tafenoquine or chloroquine, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Pharmacokinetics and/or pharmacodynamics of study treatment
- Safety and/or tolerability
- Efficacy

Study Population

Any subject, who is enrolled in the clinical study, can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

Blood samples can be taken for Deoxyribonucleic acid (DNA) extraction and used in PGx assessments.

In addition to any blood samples taken for the clinical study, a whole blood sample (~10ml) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

The PGx sample is labelled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or a set of studies) of tafenoquine or chloroquine has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to tafenoquine or chloroquine.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the PGx, if already collected:

- Continue to participate in the PGx research with the PGx sample retained for analysis
- Withdraw from the PGx research and destroy the PGx sample

If a subject withdraws consent for PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. The investigator should forward the Pharmacogenetic Sample Destruction Request Form to GSK as directed on the form. This can be done at any time

when a subject wishes to withdraw from the PGx research or have their sample destroyed whether during the study or during the retention period following close of the main study.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Pharmacogenetics Analyses

- Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to tafenoquine or chloroquine. The genes that may code for these proteins may also be studied.

- Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarised as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research.

Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarise the PGx research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

References

Chung WH, Hung SL, Chen YT. Genetic predisposition of life-threatening antiepileptic-induced skin reactions. Expert Opin. Drug Saf. 2010; 9: 15-21.

Ferrell PB, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics. 2008; 9: 1543-1546.

Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, Lai E, Davies K, Handley A, Dow DJ, Fling ME, Stocum M, Bowman C, Thurmond LM, Roses AD. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet. 2002; 359:1121-1122.

Innocenti F, Undevia SD, Iyer L, Chen PX, Das S, Kocherginsky M, Karrison T, Janisch L, Ramirez J, Rudin CM, Vokes EE, Ratain MJ. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 2004; 22: 1382-1388.

Liu CY, Chen PM, Chiou TJ, Liu JH, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, Wang WS. UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. Cancer. 2008; 112: 1932-1940.

Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, Sayer D, Castley A, Mamotte C, Maxwell D, James I. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet. 2002; 359:727-732.

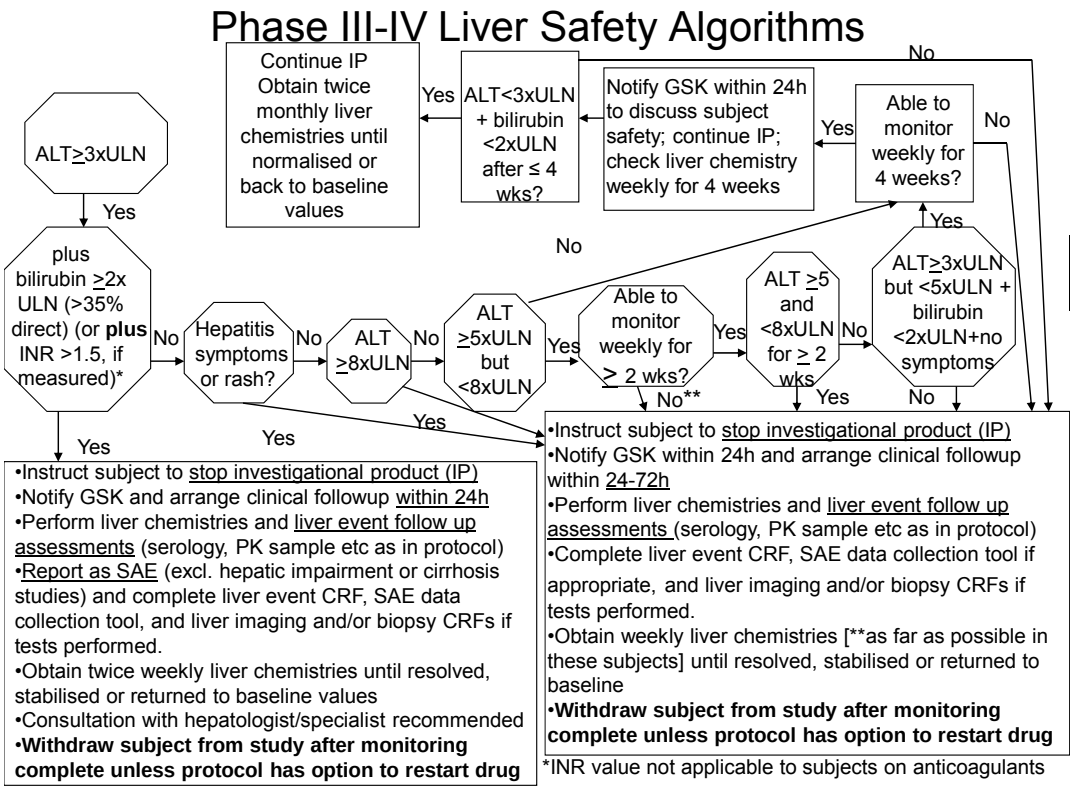
Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, Jägel-Guedes E, Rugina S, Kozyrev O, Cid JF, Hay P, Nolan D, Hughes S, Hughes A, Ryan S, Fitch N, Thorborn D, Benbow A; PREDICT-1 Study Team. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008; 358; 568-579

Schulz C, Heinemann V, Schalhorn A, Moosmann N, Zwingers T, Boeck S, Giessen C, Stemmler HJ. UGT1A1 gene polymorphism: Impact on toxicity and efficacy of irinotecan-based regimens in metastatic colorectal cancer. World J. Gastroenterol. 2009; 15: 5058-5066.

11.2. Appendix 2: Country Specific Requirements

No country-specific requirements exist.

11.3. Appendix 3: Liver Chemistry Stopping and Follow-up Criteria



11.4. 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 oedema and adult respiratory distress syndrome (ARDS)
- Circulatory collapse or shock
- Abnormal bleeding
- Jaundice with organ dysfunction
- Haemoglobinuria
- Hyperparasitaemia (>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.

11.5. Appendix 5: Prohibited Medications for Study Entry

Acetylsalicylic acid. (Paracetamol is the recommended antipyretic agent due to FDA requirement to record times antipyretics are given).

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

Drugs with antimalarial activity:

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

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

Drugs known to cause QTcF prolongation:

- Arsenic trioxide
- Bepridil
- Chlorpromazine
- Cisapride
- Disopyramide
- Dofetilide
- Domperidol
- Droperidol
- Haloperidol
- Ibutilide
- Isotalol
- Levomethadyl
- Lidoflazine
- Macrolides (Azithromycin, Erythromycin, Clarithromycin, Roxithromycin)
- Mesoridazine
- Methadone
- Pentamidine
- Pimozide
- Probucol
- Procainamide hydrochloride
- Terfenadine
- Thioridazine
- Sulfapyridine

Drugs Contraindicated in G6PD deficiency:

- Melarsoprol
- Menadiol
- Methyl dopa-
- Methylthioninium chloride (i.e., Methylene Blue)
- Nalidixic acid
- Niridazole
- Nitrofurantoin

Others-miscellaneous:

- Phenazopyridine
- Phenylhydrazine
- Chloramphenicol

CQ interactions (source eMC):

- Amiodarone
- Antacids (Al, Ca, Mg salts) may cause reduced absorption of CQ. If required therapy must be taken well separated from CQ (at least four hours apart).
- Cimetidine inhibits metabolism of CQ (increases plasma concentration)
- Cyclosporin (CQ interaction)

In addition, refer to locally approved prescribing information.

PQ interactions (source USP):

- Contraindicated with other potentially haemolytic drugs & depressants of myeloid elements of bone marrow.

In addition, refer to locally approved prescribing information.

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

- Penicillins (e.g., Penicillin, Ampicillin, Amoxicillin, Amoxicillin + Clavulanate, Cloxacillin)
- Cephalsoporins (e.g., ceftazidime, Ceftriaxone)
- Aminoglycosides (e.g., Gentamicin)
- Carbapenems (e.g., Meropenem and Imipenem)

TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Randomized, Double-Blind, Double Dummy, Comparative, Multicenter Study to Assess the Incidence of Hemolysis, Safety, and Efficacy of Tafenoquine (SB-252263, WR238605) versus Primaquine in the Treatment of Subjects with *Plasmodium vivax* Malaria.

Compound Number: SB-252263

Development Phase: III

Effective Date: 15-JUL-2015

Protocol Amendment Number: 5

Authors: PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2012N152563_00	2013-NOV-26	Original
2012N152563_01	2014-FEB-20	Amendment No. 1
Remove paragraph in Section 6.4.3.1 regarding "lack of efficacy" being an AE or SAE Regarding urinalysis, change the term "nitrate" to "nitrite" in all places Remove sentence in footnote regarding Day 2 and Day 3 ECG measurements		
2012N152563_02	2014-OCT-15	Amendment No. 2
This is a site-specific amendment for two centers in Thailand, and includes the following: The objectives of the study are being revised to correlate with the research methodology being used. The term "subgroup" has been removed from the primary objective to describe females with moderate glucose-6-phosphate dehydrogenase (G6PD) deficiency. The hemoglobin stopping criteria is being revised to raise the absolute minimum hemoglobin value allowed from 6 g/dL to 7 g/dL. This also requires that the minimum hemoglobin value for entry of G6PD normal subjects (≥70% G6PD activity) into the study must be raised from 7 g/dL to 8 g/dL for all subjects (G6PD normal and deficient).		
2012N152563_03	2014-OCT-21	Amendment No. 2 (Re-publishing)
Amendment was made to correct the typographical error on title page		
2012N152563_04	2014-NOV-19	Amendment No. 3
Tafenoquine has been shown to inhibit the renal transporters OCT2, MATE1 and MATE2-K. The following drugs have been added to the prohibited medications list that are excreted via these transporters: phenformin, buformin, dofetilide, procainamide, pilsicainide. The list of prohibited medication has been updated to include albendazole (due to its known anti-malarial activity), and ketoconazole (due to its known QT-prolonging effect). Metformin should be stopped if the subject has renal impairment. There is no need to adjust the dose of metformin provided the subject has a serum creatinine below the upper limit of normal. Also refer to contraindications and cautions listed in the prescribing information for metformin.		

A change is made to the secondary contact medical monitor. The monitoring period for recrudescence is extended from 29 to 32 days. Female subjects who screen fail sister Study TAF112582 due to G6PD deficiency may enroll in this study using TAF112582 screening labs. To clarify that rapid point of care G6PD test(s) may be performed at baseline (Day 1) only. Parasite genotyping will only be performed at screening and at the time of recrudescence/relapse or re-infection. Urinalysis will be conducted by local laboratories on Day 120, not Day 180. The haptoglobin test was removed from required hematology tests for hemoglobin stopping criteria. A spelling error in the protocol-defined SAE has been corrected that may otherwise lead to confusion. The period for collecting pregnancy information will end at the 180 day follow up assessment, not the 90 day follow up assessment. Details were inserted on the PK analysis of primaquine and carboxy-primaquine levels.		
2012N152563_05	2015-MAR-31	Amendment No. 4
Add and describe an additional 250mg formulation of chloroquine that may be used during the conduct of the study. Revise the inclusion criterion for age to indicate that in Ethiopia only subjects ≥18 years of age will be enrolled. Revise the SAE Case Management details.		
2012N152563_06	2015-JUL-15	Amendment No. 5
Change in medical monitor Change to SAE Case Management Details Company and tablet description details have been removed for the comparator primaquine. A typographical error was corrected in the Amendment section of the Appendix.		

SPONSOR SIGNATORY

PPD

15 July 2015

Gavin CKW Koh MB BChir MRCP PhD DTM&H
Director, Clinical Development

Date

SPONSOR INFORMATION PAGE

Clinical Study Identifier: 116564

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Sponsor Contact Address:

GlaxoSmithKline Research & Development Limited
1250 South Collegeville Road
Collegeville, PA 19426, USA
Telephone Number: PPD

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Sponsor Medical Monitor and Serious Adverse Event (SAE) Contact Information:

PPD
GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BT, UK
Telephone: PPD
Mobile: PPD

Secondary Contact:

PPD
GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: PPD
Mobile: PPD

SAE Case Management Details:

SAE's should be reported via Inform database. If InForm is unavailable, SAE CRF pages and supporting documents should be sent to GSK GCSP Case Management either by email to PPD or by fax to PPD
SAE data should be entered into Inform once available.

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol TAF116564

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

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline phosphotase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CL/F	Oral clearance
CPK	Creatine phosphokinase
CQ	Chloroquine
CV	Cardiovascular
DRE	Disease-Related Event
ECG	Electrocardiogram
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
G6PD	Glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GCSP	Global Clinical Safety & Pharmacovigilance
g/dL	grams per deciliter
GSK	GlaxoSmithKline
Hct	Hematocrit
Hb	Hemoglobin
HPLC	High pressure liquid chromatography
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LDH	Lactate dehydrogenase
LSLV	Last subject last visit
MPV	Major Protocol Violation
MSDS	Material Safety Data Sheet
MCV	Mean Cell Volume
MetHb	Methemoglobinemia
mITT	Microbiologic Intent To Treat
µL	Microliter
mg	Milligram
msec	Millisecond
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PGx	Pharmacogenetics
PK	Pharmacokinetics
PP	Per Protocol
PQ	Primaquine
RAMOS	Registration and Medication Ordering System
RBC	Red blood cell

RAP	Reporting & Analysis Plan
SAE	Serious Adverse Event
SPM	Study Procedures Manual
SOC	System Organ Class
TQ	Tafenoquine
ULN	Upper Limit of Normal
V/F	Volume of distribution
WBC	White blood cell
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

PROTOCOL SUMMARY

Rationale

The global disease burden of malaria due to *Plasmodium vivax* is significant. There are up to 391 million persons infected annually, with an estimated 2.49 billion individuals living at risk of *P. vivax* infection. *P. vivax* has the largest geographic distribution of human malarias, extending well beyond the distribution for *P. falciparum*. Infection with *P. vivax* presents in the majority of cases as an acute but uncomplicated febrile illness; however, recent work has demonstrated that the risk of fatal outcome in patients with severe malaria was indistinguishable between those with *P. falciparum* versus *P. vivax* malaria.

P. vivax presents an added challenge to malaria eradication efforts, and that is its ability to establish a dormant liver stage, the hypnozoite. Relapsing *P. vivax* malaria is caused by hypnozoite activation after the initial infection. Left untreated, tropical *P. vivax* strains can relapse in 3 to 6 week intervals, whereas strains from temperate regions can stay dormant for 1 year or longer. The only widely available drug for the prevention of *P. vivax* relapse is primaquine (PQ), an 8-aminoquinoline derivative.

Tafenoquine (TQ, SB-252263 and WR 238605) is a novel 8-aminoquinoline anti-malarial drug being co-developed by GlaxoSmithKline and the Medicines for Malaria Venture with the assistance and historic support of the Walter Reed Army Institute of Research. It is a synthetic analog of PQ and is currently being developed for the radical cure of *P. vivax* malaria, to be co-administered as a single dose with standard doses of chloroquine (CQ).

All members of the 8-aminoquinoline class of drugs induce hemolysis in subjects with glucose-6-phosphate dehydrogenase (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. Therefore, it is important that the dose of TQ selected is not only effective but also minimizes the hemolytic potential of the drug in this population.

The primary objectives of this study is to characterize the incidence of hemolysis with TQ/CQ and compare this to the incidence of hemolysis with PQ/CQ; both in all subjects, as well as in the subset of female subjects that display a moderate deficiency in G6PD activity. The efficacy and safety of TQ/CQ will be studied in comparison to PQ/CQ, and the socioeconomic impact of infection and relapse due to *P. vivax* will be studied. In addition, a pharmacokinetic/pharmacodynamic analysis will be conducted in all subjects receiving TQ.

Objective(s)

Primary Objective(s)

- To investigate the occurrence of clinically relevant hemolysis in adult subjects with *P. vivax*. The incidence of hemolysis in the subgroup of female patients with moderate (40-70%) G6PD activity is of particular interest.

Secondary Objective(s)

- To compare the clinical and parasitological efficacy, safety and tolerability of tafenoquine to primaquine as a radical cure for adult subjects with *P. vivax* malaria when co-administered with chloroquine.
- To characterize the socioeconomic impact of *P. vivax* relapse.
- To evaluate the pharmacokinetics of tafenoquine in the treatment of adult subjects with *P. vivax* malaria.
- To characterize the pharmacokinetic/pharmacodynamic relationship in this study population.

Study Design

In this prospective, double-blind, double-dummy design, a total of 300 subjects will be randomized to treatment on Day 1, of which a minimum of 50 female subjects must be enrolled that display moderate G6PD deficiency (≥40% - <70% of the site median G6PD value). Subjects must have a blood smear that is positive for *P. vivax* at entry. Subjects must remain in the hospital for a minimum of the first 3 days of the study to monitor study medication compliance and infection status, and will continue on treatment as an outpatient for an additional 12 days. Subjects will be monitored up to day 32 for recrudescence, then continue to be monitored up to 180 days post-randomization for evidence of relapsing infection.

During the 180 day study period subjects must attend screening and randomization to treatment (Day 1), three in-hospital days (Days 1-3), four out-patient visits while on treatment with study medication (Days 5, 8, 11 and 15) and seven follow-up visits (Days 22, 29, 60, 90, 120, 150 and 180).

All subjects will receive open label CQ for the first 3 days of the study to treat the blood stage of the infection. Beginning on Day 1 or Day 2, subjects will receive TQ or the active comparator, PQ, and the corresponding placebo for treatment of the liver stage of infection. Primaquine was selected as the comparator for this study as PQ plus CQ is the current standard of care for radical cure of *P. vivax* malaria in the majority of endemic countries.

An independent data monitoring committee will be established to monitor, in an unblinded manner, safety in general and females with moderate G6PD deficiency in particular. The latter will ensure the frequency and severity of any hemoglobin declines in females remains as expected and remains clinically acceptable. This will include the

use of pre-defined criteria for evaluating early stopping of recruitment of subjects with moderate G6PD deficiency.

Study Endpoints/Assessments

Primary

- Occurrence of clinically relevant hemolysis in all subjects; defined as, a decrease in hemoglobin of ≥30% or >3 g/dL from baseline; or, an overall drop in hemoglobin below 6.0 g/dL.
- Occurrence of clinically relevant hemolysis in female subjects with moderate (40-70%) G6PD deficiency; defined as, a decrease in hemoglobin of ≥30% or >3 g/dL from baseline; or, an overall drop in hemoglobin below 6.0 g/dL.

Secondary

- Relapse-free efficacy six months post-dosing
- Relapse-free efficacy four months post-dosing
- Time to relapse
- Parasite clearance time
- Fever clearance time
- Gametocyte clearance time
- Recrudescence, defined as any *P. vivax* parasitemia occurring on or before Day 32 (i.e., blood stage treatment failure).
- Incidence of genetically homologous and genetically heterologous *P. vivax* infections (determined by PCR)
- Characterization of healthcare resource use and socio-economic impact of *P. vivax* relapses and adverse events caused by treatment to prevent *P. vivax* relapses, especially hemolytic anemia.
- PK and selected PD endpoints (e.g., relapse-free efficacy, change in methemoglobin) if appropriate
- Population PK parameters for tafenoquine including but not limited to oral clearance (CL/F) and volume of distribution (V/F)
- Safety evaluation of data from clinical laboratory tests, urinalysis, spontaneous/elicited adverse event reporting, ECGs and vital signs in all subjects who received at least one dose of study medication.
- Incidence of *P. falciparum* malaria

1. INTRODUCTION

1.1. Background

The global disease burden of malaria due to *Plasmodium vivax* is significant. There are up to 391 million persons infected annually, with an estimated 2.49 billion individuals living at risk of *P. vivax* infection [Gething, 2012; Price, 2007]. *P. vivax* has the largest geographic distribution of human malarias, extending well beyond the distribution for *P. falciparum* [Gething, 2012]. The majority of cases occur in Asia, with the remainder occurring in Central and South America, Oceania and Africa. Infection with *P. vivax* presents in the majority of cases as an acute but uncomplicated febrile illness, and it was long thought that *P. vivax* infection could not cause severe disease. Recent work has demonstrated that the risk of fatal outcome in patients with severe malaria was indistinguishable between those with *P. falciparum* versus *P. vivax* malaria [Barcus, 2007]. In addition, using molecular diagnostic techniques, it has been shown that *P. vivax* monoinfection can be responsible for multiple organ dysfunction and severe, life-threatening malarial disease [Kochar, 2009].

P. vivax presents an added challenge to malaria eradication efforts, and that is its ability to establish a dormant liver stage, the hypnozoite. Relapsing *P. vivax* malaria is caused by hypnozoite activation after the initial infection. Left untreated, tropical *P. vivax* strains can relapse in 3 to 6 week intervals, whereas strains from temperate regions can stay dormant for 1 year or longer [White, 2012]. The latter explains *P. vivax* prevalence in areas where the Anopheles vector is not present at all times of the year. The only widely available drug for the prevention of *P. vivax* relapse is primaquine (PQ), an 8-aminoquinoline derivative. Primaquine was approved by the FDA for the treatment of malaria in 1952, and remains the only licensed drug that can eliminate all liver stages of *P. vivax* [Hill, 2006]

The current gold standard for treatment of *P. vivax* malaria in many areas of the world is chloroquine (CQ) for clearance of the acute parasitemia, immediately followed by PQ 15 mg once daily x 14 days to clear the liver stages of the parasite and prevent disease relapse [WHO, 2010]. In some regions the PQ dose is increased to 22.5 mg or 30 mg once daily x 14 days where PQ tolerant hypnozoites are present. The 14-day regimen for PQ has presented major compliance problems, resulting in a significant degree of *P. vivax* malaria relapses in treated populations. Shorter courses (e.g., 5 or 7 days) have been studied, but results have been variable. Consequently, anti-relapse therapy for *P. vivax* malaria is impractical in most epidemic regions due to duration of treatment resulting in poor compliance [WHO, 2010]. In addition, recent evidence suggests that cytochrome P450 2D6 might have a role in PQ metabolism and treatment efficacy, and as such will be investigated in this study [Bennett, 2013].

1.2. Rationale

Tafenoquine (TQ, SB-252263 and WR 238605) is a novel 8-aminoquinoline anti-malarial drug being co-developed by GlaxoSmithKline and the Medicines for Malaria Venture with the assistance and historic support of the Walter Reed Army Institute of

Research. It is a synthetic analog of PQ and is currently being developed for the radical cure of acute *P. vivax* malaria, to be co-administered as a single dose with standard doses of CQ. Tafenoquine has shown to be well-tolerated in the treatment and prevention of plasmodial infections in pre-clinical models and during Phase I, II and III clinical studies in >4000 subjects. Of note, TQ possesses activity against all stages of the Plasmodium life cycle, including the dormant *P. vivax* hypnozoite.

All members of the 8-aminoquinoline class of drugs induce hemolysis in subjects with glucose-6-phosphate dehydrogenase (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. Therefore, it is important that the dose of TQ selected is not only effective but also minimizes the hemolytic potential of the drug in this population.

Historical data indicate that the degree of hemolysis observed with PQ is dose-dependent as well as dependent on the severity of G6PD deficiency [Fernando, 2011]. In many areas of the world, standard doses of PQ are routinely used to treat *P. vivax* malaria without testing for G6PD deficiency. This is done with full knowledge that the average decline in hemoglobin is approximately 25-30% in WHO class III (mild to moderate) G6PD-deficient variants, a decline that is considered clinically acceptable in *P. vivax* malaria endemic regions.

Therefore, the primary objectives of this study are to characterize the incidence of hemolysis with TQ/CQ and compare this to the incidence of hemolysis with PQ/CQ. The objectives will be studied in all subjects, and in the subset of female subjects that display a moderate deficiency in G6PD activity. In addition, the efficacy and safety of TQ/CQ will be studied in comparison to PQ/CQ, the socioeconomic impact of infection and relapse due to *P. vivax* will be studied, and a pharmacokinetic/pharmacodynamic (PK/PD) analysis will be conducted in all subjects receiving TQ.

The efficacy data produced from this study will support the results for sister study TAF112582, the pivotal phase III efficacy and safety study of the tafenoquine program. The primary safety data collected in study TAF116564 will help to understand the hemolysis risk to both G6PD-normal and G6PD-deficient subjects. The information from G6PD-deficient subjects will be particularly useful should patients inadvertently be dosed with tafenoquine who do not know or are misinformed as to their G6PD status. This study also supports the regulatory requirement of randomizing a minimum of 500 subjects in the phase III program to receive the target dose of TQ.

1.3. Benefit:Risk Assessment

1.3.1. Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with TQ can be found in the Investigator Brochure (IB) [GlaxoSmithKline Document Number GM2007/00152/06]

The current key risk associated with the development and use of tafenoquine in this study is hemolysis in moderately deficient G6PD subjects. Since TQ is to be contraindicated in cases of moderate and severe G6PD deficiency, the most severe G6PD subjects, hemizygous males and homozygous females, will not be recruited into this study. Table 1 below outlines the risk assessment and mitigation strategy for this protocol.

Table 1 Risk Assessment for Tafenoquine (SB-252263)

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation
Hemolysis in G6PD-deficient patients	Tafenoquine is an 8-aminoquinoline, 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 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.	A quantitative spectrophotometric phenotype assay will be used to determine G6PD status based on levels of enzyme activity. Levels will be compared to a normal range set by the laboratory conducting the assay in males representing the study population pool. Study exclusion are set by % activity of median of normal range. Males with <70% and females with <40% G6PD activity are excluded. Protocol-defined SAE criteria will be adopted, defined as ≥ 3.0 g/dL or 30% decline in Hb from the baseline value to aid in safety monitoring. Subjects will be closely monitored around the expected time of nadir of Hb drop to enable investigators to intervene if required.
Hemoglobin changes	Integrated clinical safety data and data from thorough QT study data indicate a dose related trend for mild decrease in Hb in non-G6PD deficient patients.	The hematological effects of TQ in G6PD normal subjects will be included as part of activities conducted to investigate risk in G6PD deficient patients. Risk mitigation is covered by the activities described for hemolysis in G6PD-deficient patients above.

Potential Risk of Clinical Significance	**Data/Rationale for Risk**	**Mitigation**
Methemoglobinemia (MetHb)	Methemoglobinemia has been observed in previous studies associated with larger total doses of TQ than are being considered for clinical investigation. Risk factors have been assessed and include a strong relationship between MetHb development, TQ dose, and body surface area.	Methemoglobinemia will be monitored instream. Data will be collected to support tolerance in female heterozygous carriers of G6PD deficiency. An assessment will be made to determine if there is any relationship between Hb decline and Methb.
Retinal Toxicity	No ophthalmological changes have been observed with TQ in preclinical species or in any of the TQ-treated subjects in previous studies. Irreversible retinopathy has been reported with the combination partner CQ. The effects with CQ are dose related and have been observed following cumulative total doses of >1g base/kg body weight. CQ dose used in treatment of *P.vivax* is a total of 25mg/kg over 3 days. Retinopathy associated with severe malaria is reported in the literature.	In a subset of the study population, anatomical and functional ophthalmic tests will be conducted, including digital retinal photo and macular function test (Humphrey 10-2 visual field). Assessments will be taken at baseline (Day 1), Day 29 and Day 90 of the study. For any abnormality subjects will be followed for outcome.

Potential Risk of Clinical Significance	**Data/Rationale for Risk**	**Mitigation**
Keratopathy	No ophthalmological changes were observed in preclinical species. Reversible vortex keratopathy was observed in previous TQ clinical trials.	Appropriate sites will conduct slit lamp procedure and be provided with standardized photos of keratopathy to capture grades of keratopathy consistently. Assessments will be taken at baseline (Day 1), Day 29 and Day 90 of the study.
QTcF	Preclinical studies determined that TQ has a low potential for QTcF prolongation. Chloroquine does have a propensity to cause QTcF prolongation. A previous TQ drug-drug interaction study concluded that whilst there was no trend over time for increased QTcF intervals in those treated with TQ alone those treated with CQ did experience QTcF prolongation. In those treated with a combination of CQ/TQ there did not appear to be a trend over time for increased QTcF intervals in the CQ/TQ arm beyond those observed on CQ alone. In addition, a TQ thorough QT study did not show elongation of the QTcF at clinical doses.	Conduct ECG monitoring in this study and all phase III studies.

Potential Risk of Clinical Significance	**Data/Rationale for Risk**	**Mitigation**
Liver Transaminase Elevations	Preclinical repeat dose toxicology studies observed liver changes that were fully or partially reversible. During a TQ thorough QT study two subjects receiving 1200 mg TQ experienced transient elevations in liver transaminases. It was concluded that high doses of TQ appeared to be associated with transient increases in transaminases.	Conduct liver function testing in this study and all phase III studies.
Renal Function	Transient increases in serum creatinine have been observed in clinical studies in adults. A renal safety study was conducted and concluded that TQ, when given as 200 mg x 3 days loading dose followed by weekly 200 mg dosing for 6 months was non-inferior to placebo when comparing mean change from baseline glomerular filtration rate. In TAF112582 study part 1 outliers were characterized by isolated transient rises in creatinine with rapid recovery and no consistent time to onset at a particular dose for the outliers. An *in vitro* study conducted to better understand and investigate the possible mechanisms involved showed that tafenoquine is an inhibitor of three renal transporters (OCT2, MATE1 and	Conduct renal function testing in this study and in all phase III studies. Contra-indicate the use of phenformin, buformin, dofetilide, procainamide and pilsicainide. Exclude subjects taking metformin if the subject has a serum creatinine above the upper limit of normal.

Potential Risk of Clinical Significance	**Data/Rationale for Risk**	**Mitigation**
	MATE2. Inhibition of these transporters may explain mild, transient, asymptomatic increases of creatinine observed in previous clinical studies and also may lead to increased exposure to medications excreted via these transporters.	
Use in pregnancy and lactation	Preclinical data reported no adverse effects on fertility, embryofetal development or on post-natal survival. No clinical studies have been conducted in humans during pregnancy. There may be concern about risk to a fetus who is G6PD deficient and risk to breastfed infants whose G6PD status may be unknown.	Pregnant or lactating women are excluded from this study.
Phototoxicity	Preclinical studies have been conducted to assess TQ photoirritancy factor. The conclusion of these studies was that tafenoquine was "probably" phototoxic. A review of Integrated clinical safety data (>4000 subjects) has not determined any discernible pattern of incidence of rash associated with TQ treatment.	The incidence and frequency of rash will continue to be reviewed for signs of photoirritancy in this patient population.

1.3.2. Benefit Assessment

In the absence of radical cure treatment, a percentage of patients with *P. vivax* malaria will relapse due to the liver being infected with hypnozoites (the dormant form of the parasite). *P. vivax* malaria is most prevalent primarily in Asia, Asia-Pacific and Latin American countries and frequency of relapse rates may impact product use. Relapse rates vary with strain and are difficult to measure due to confounding by re-infection. The WHO have generalized relapse rates in the following countries as: India (15-20%), Indonesia (30%) and South East Asia (50-60%). *P. vivax* can cause a debilitating fever and as it preferentially invades reticulocytes, 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, especially in children. Consequences are loss of work or school days (e.g. 5.4 days school absenteeism per episode) and hospitalization (especially children) due to vomiting, dehydration and anemia (resulting in transfusion).

Due to its long half life, tafenoquine can be administered as a single oral dose and is therefore a more convenient treatment regimen with the potential to improve patient compliance. Improved compliance could also lead to improved clinical outcomes for patients with *P. vivax* malaria by further reducing relapse rates.

1.3.3. Overall Benefit:Risk Conclusion

Tafenoquine is being developed with the aim of a benefit:risk profile which is as least as good as the current gold standard therapy PQ. Our intent is to evaluate whether improved compliance could also lead to improved clinical outcomes for patients. Tafenoquine should have no clinically significant side effects that will restrict its use as a first line agent in treatment of *P.vivax* malaria when used in combination with a G6PD test and recommended therapies to treat the blood stages of infection. With specific regard to this study, the overall benefit:risk is favorable to all subjects, given that all are receiving active treatment.

2. OBJECTIVES & ENDPOINTS

Objectives	Endpoints
Primary	
To investigate the occurrence of clinically relevant hemolysis in adult subjects with *P. vivax*. The incidence of hemolysis in the subgroup of female patients with moderate (40-70%) G6PD activity is of particular interest.	• Occurrence of clinically relevant hemolysis in all subjects; defined as, a decrease in hemoglobin of ≥30% or >3 g/dL from baseline; or, an overall drop in hemoglobin below 6.0 g/dL. • Occurrence of clinically relevant hemolysis in female subjects with moderate (40-70%) G6PD deficiency; defined as, a decrease in hemoglobin of ≥30% or >3 g/dL from baseline; or, an overall drop in hemoglobin below 6.0 g/dL.
Secondary	
To compare the clinical and parasitological efficacy, safety and tolerability of tafenoquine to primaquine as a radical cure for adult subjects with *P. vivax* malaria when co-administered with chloroquine.	• Relapse-free efficacy six months post-dosing • Relapse-free efficacy four months post-dosing • Time to relapse • Parasite clearance time • Fever clearance time • Gametocyte clearance time • Recrudescence, defined as any *P. vivax* parasitemia occurring on or before Day 32 (i.e., blood stage treatment failure). • Incidence of genetically homologous and genetically heterologous *P. vivax* infections (determined by PCR) • Safety evaluation of data from clinical laboratory tests, urinalysis, spontaneous/elicited adverse event reporting, ECGs and vital signs in all subjects who received at least one dose of study medication. • Incidence of *P. falciparum* malaria

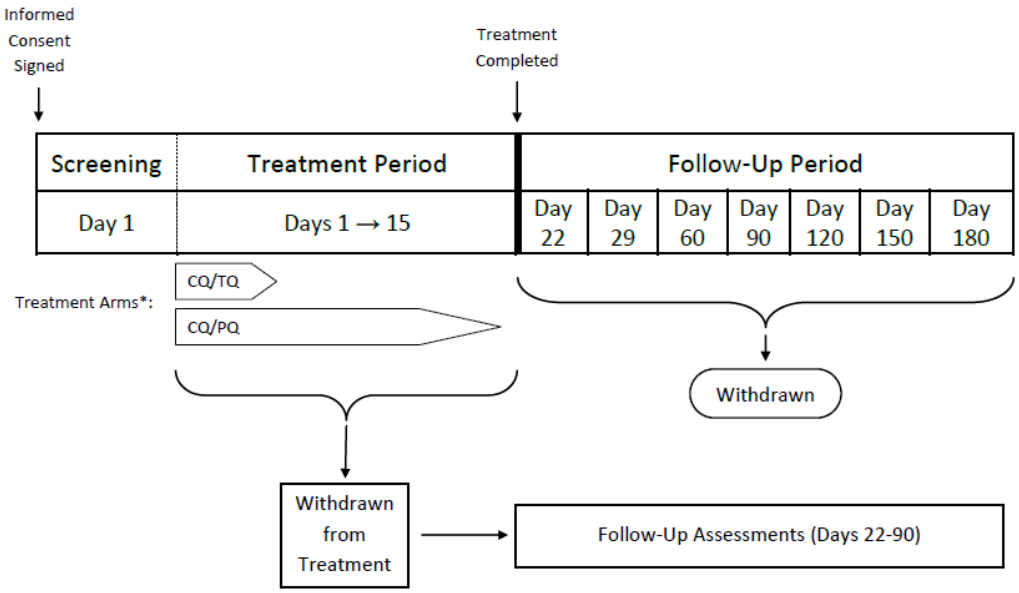
Objectives	Endpoints
To characterize the socioeconomic impact of *P. vivax* relapse.	• Characterization of healthcare resource use and socio-economic impact of *P. vivax* relapses and adverse events caused by treatment to prevent *P. vivax* relapses, especially hemolytic anemia.
To evaluate the pharmacokinetics of tafenoquine in the treatment of 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)
To characterize the pharmacokinetic/pharmacodynamic relationship in this study population.	• PK and selected PD endpoints (e.g., relapse-free efficacy, change in methemoglobin) if appropriate

With regard to the secondary efficacy endpoints, it should be noted that it is not possible to determine if a subject's recurrence of malaria is a relapse or a re-infection. For the purposes of this protocol, the term "relapse" will be used to describe any recurrence of malaria that occurs after Day 32 of the study. "Recrudescence" applies to the term relating to recurrence for Days 1 to 32 of the study where, although a genetically homologous parasite is highly suggestive of recrudescence and thus blood stage treatment failure, it is not absolute as re-infection is technically possible; the probability of which is related to the overall background incidence of the homologous parasite in the mosquito population.

3. INVESTIGATIONAL PLAN

Study TAF116564 is a prospective, double-blind, double-dummy, multicenter, comparative study, enrolling 300 subjects and consisting of a 3 day in-patient hospital stay and 11 further on-treatment and follow-up study visits distributed over 180 days. The study schematic diagram in Section 3.1 summarizes the study visits.

3.1. Study Design Schema



CQ/TQ = Chloroquine 600mg OD Days 1 & 2; 300mg OD Day 3 / Tafenoquine 300mg single dose Day 2
CQ/PQ = Chloroquine 600mg OD Days 1 & 2; 300mg OD Day 3 / Primaquine 15mg OD Days 2-15

3.2. Study Design

- Study TAF116564 is a prospective, double-blind, double-dummy, multicenter, comparative study.
- A total of 300 subjects will be randomized 2:1 to receive TQ/CQ or the active comparator PQ/CQ. All subjects will receive CQ on Days 1 to 3 followed by TQ or PQ and matching placebo beginning on Day 1 or 2. Tafenoquine, or matching placebo, will be given as a single, 300mg dose. Subjects will receive PQ (15mg once daily) or matching placebo for 14 days.
- The duration of the study is 180 days, including screening and randomization to treatment (Day 1), three in-hospital days (Days 1-3), four out-patient visits while on treatment with study medication (Days 5, 8, 11 and 15) and seven follow-up visits (Days 22, 29, 60, 90, 120, 150 and 180).
- Subjects must have a blood smear that is positive for *P. vivax* at entry. Blood smears will be taken for parasitological assessment twice a day for the first 3 days of the study, or until two consecutive thick blood smears are negative for *P. vivax*. Additional parasitological assessments will be conducted throughout the treatment and follow-up periods.
- Subjects are required to remain in the hospital for the first three days of the study, in order to ensure clinical improvement, to monitor early study medication compliance, and so that parasitological assessments can readily be taken twice a day. Subjects may need to remain in the hospital longer than 3 days if two consecutive thick blood smears negative for *P. vivax* are not obtained within the 3 day timeframe.
- At the Day 1 visit subjects will be screened for G6PD deficiency by a quantitative assay and the result will be determined as a percentage of the predetermined median enzyme activity of the site. Female subjects must have a minimum G6PD assay value of 40% to be enrolled, and male subjects must have a minimum G6PD assay value of 70% to be enrolled. In addition, a minimum of 50 female subjects must be enrolled that display ≥40% - <70% of the site median G6PD enzyme activity.
- The status of methemoglobin, an oxidized and inactive form of hemoglobin, will be assessed at selected visits.
- An independent data monitoring committee will be established to monitor, in an unblinded manner, safety in general and females with moderate G6PD deficiency in particular. The latter will ensure the frequency and severity of any hemoglobin declines in females remains as expected and remains clinically acceptable.
- The primary analysis population will be the Microbiologic Intent To Treat (mITT) population, defined as all randomized subjects who receive at least one dose of blinded study medication and have microscopically-confirmed vivax parasitemia.

- Selected investigator centers will perform ophthalmic safety assessments at selected visits to monitor subjects for changes in the eye.
- Healthcare resource use and socio-economic impact data will be collected to characterize *P. vivax* relapse and adverse events caused by treatment to prevent *P. vivax* relapse, with particular attention to hemolytic anemia.
- Blood samples will be collected on Days 2, 3, 8, 15, 29 and 60 of the study for pharmacokinetic and pharmacodynamic analyses.

Subjects are considered to have completed the study if they meet all inclusion/exclusion criteria, are considered compliant with all study medication, complete the 3 day hospital stay, and attend the Day 180 visit.

Protocol waivers or exemptions are not allowed; therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

3.3. Discussion of Design

The design of TAF116564 has been made purposely similar to Part 2 of sister study TAF112582, the pivotal phase III efficacy and safety study of the tafenoquine program. The overall design of the studies is based on FDA guidance for the radical cure of malaria due to *P. vivax*. In this double-blind, double-dummy design, subjects will be screened and randomized to treatment on Day 1, and will remain in the hospital for the first 3 days of the study, or until two consecutive thick blood smears are negative for *P. vivax,* to monitor study medication compliance and infection status. Subjects will continue on treatment for the first 15 days of the study and will be monitored up to day 32 for recrudescence. Subjects will continue to be monitored up to 180 days post-randomization for evidence of relapsing infection. In all subjects, PCR analysis of *Plasmodium* species will be conducted to investigate the genetic constitution of *P. vivax* recurrences during the study.

All subjects will receive open label CQ for the first 3 days of the study to treat the blood stage of the infection. Beginning on Day 1 or Day 2, subjects will receive TQ or the active comparator, PQ, and the corresponding placebo for treatment of the liver stage of infection. Primaquine was selected as the comparator for this study as PQ plus CQ is the current standard of care for radical cure of *P. vivax* malaria in the majority of endemic countries.

3.3.1. Dose Rationale

Tafenoquine has demonstrated preliminary efficacy following 1-3 days of dosing, which is further supported by a prolonged half-life of 15-19 days. This shorter course of therapy should significantly improve compliance and thus effectiveness of relapse prevention.

Two separate exploratory clinical studies have demonstrated TQ's utility for the treatment and radical cure of *P. vivax* malaria: Study SB-252263/047 [GlaxoSmithKline Document Number RM2007/00309/00] was conducted in two parts, and tafenoquine was administered following chloroquine treatment of blood schizonts. Tafenoquine was found to be highly efficacious across the entire 500 mg to 3000 mg dose range. In study SB-252263/058 [GlaxoSmithKline Document Number UM2004/00017/00], a total dose of 1200 mg tafenoquine was administered over 3 days. Tafenoquine resulted in 100% relapse prevention, however, the tafenoquine monotherapy regimen exhibited slow parasite and fever clearance times relative to the CQ+PQ control. In conclusion, TQ's long half-life supported a 1 to 3 day treatment regimen when co-administered with a second blood schizonticidal drug, such as CQ.

A two-part drug-drug interaction study [GlaxoSmithKline Document Number WD2009/01503/00; Study TAF106491] has also been conducted to investigate the interaction between TQ and CQ in healthy volunteers. Part 1 was a three arm, open label pilot study to evaluate the safety and pharmacokinetics of a low dose CQ co-administered with TQ. Part 2 was a double-blind study to assess the drug-drug interaction, safety (including ECG effects), tolerability and pharmacokinetic parameters of CQ co-administered with TQ. Based on the PK results from the pivotal Part 2 portion of this study, there appears to be a short term significant effect on TQ PK (Day 2 Cmax and AUC(0-24)) when co-administered with CQ with no significant effect on the full PK profile (AUC(0-∞) and t1/2). TQ had no significant effect on the PK of CQ and desethylchloroquine. Taken together, these results suggest that there is no clinically significant pharmacokinetic interaction with concomitant administration of TQ and CQ.

A thorough QT study (TAF114582) was recently completed that studied two therapeutic doses (300mg and 600mg; single dose) and one supratherapeutic dose (1200mg; 400mg x 3) of tafenoquine. The therapeutic doses of tafenoquine had no marked effect on QTcF prolongation. In the 1200mg group, a mean effect of 6.6 msec in QTcF prolongation was observed, just within the 10 msec safety margin set out in E14 ICH guidelines.

Throughout the tafenoquine program, subjects have been evaluated for changes in Hb following treatment with TQ. In G6PD-normal subjects only small decreases in Hb have been observed. These changes were not considered clinically significant, and were only seen in subjects receiving doses of TQ much higher than what had been considered for clinical investigation. In studies where G6PD-deficient subjects have been included, significant Hb decreases have been observed. A study was recently completed (TAF110027) that assessed the hemolytic risk of TQ in female healthy volunteers with moderate G6PD deficiency (40%-60% of site median normal value). Results indicated a TQ dose response for hemolysis, and the highest dose of TQ tested, 300mg, resulted in Hb declines similar to daily dosing of 15mg PQ. This data factored greatly into determining a dose to take forward into phase III.

Tafenoquine was recently investigated in part 1 of TAF112582, a seamless Phase II/III study. The phase II portion (part 1) was a dose-ranging study assessing the efficacy and safety of four doses of TQ in subjects with *P. vivax* malaria. The goal was to select an efficacious and well-tolerated dose of TQ to be co-administered with CQ. The long half-life of TQ allowed it to be delivered as a single dose. The 300mg dose achieved highly significant improvements ($p<0.0001$) in relapse-free efficacy compared to CQ alone. Treatment differences (TQ/CQ - CQ) ranged from 45% for the most conservative analyses to 61%. Small declines in Hb were seen; approximately 30% of subjects in the 300mg TQ dose experienced a decline in Hb of >1.5 g/dL and <2.5 g/dL. Only 2 (4%) subjects experienced a Hb drop >2.5 g/dL. All other treatment groups experienced similar Hb drops, and all were considered disease-related. At the conclusion of Phase II, the single 300mg dose of TQ was selected to carry forward to the Phase III program.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

Subjects who have a blood smear positive for a single species infection with *P. vivax* and meet all other eligibility criteria qualify for entry into the study. A total of 300 subjects will be randomized into the study, and 50 of these will be females with G6PD enzyme levels consistent with moderate G6PD deficiency. The primary study population is the mITT population, and includes all subjects who meet all eligibility criteria and receive at least one dose of blinded study medication.

4.1. Number of Subjects

Randomized: 300

Subject Screening Failures: 150

Number of Evaluable Subjects: 300

Number of Screened Subjects: 450

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study medication that may impact subject eligibility is provided in the Tafenoquine Investigator Brochure [GlaxoSmithKline Document Number GM2007/00152/06], and the locally-approved product labels for Chloroquine and Primaquine.

Deviations from inclusion 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.

Subjects eligible for enrolment in the study must meet all of the following criteria:

Safety

1. A female is eligible to enter and participate in the study if she is non-pregnant, non-lactating and if she is of:

   a. Non-childbearing potential defined as: post-menopausal (12 months of spontaneous amenorrhea or <6 months of spontaneous amenorrhea with serum FSH >40 mIU/mL), or pre-menopausal and has had a hysterectomy or a bilateral oophorectomy (removal of the ovaries) or a bilateral tubal ligation, negative pregnancy test or,

   b. Child-bearing potential, has a negative pregnancy test at screening, and agrees to comply with one of the following during the treatment stage of the study and for a period of 90 days after stopping study medication:
      - Use of oral contraceptive, either combined or progestogen alone used in conjunction with double barrier method as defined below.
      - Use of an intrauterine device with a documented failure rate of <1% per year
      - Use of depo provera injection
      - Double barrier method consisting of spermicide with either condom or diaphragm
      - Male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female.
      - Complete abstinence from intercourse for 2 weeks prior to administration of study medication, throughout the study and for a period of 90 days after stopping study medication.

2. The subject has a glucose 6-phosphate dehydrogenase (G6PD) value (measured by a quantitative spectrophotometric phenotype assay) as follows:

   - **Female subjects** must have an enzyme level ≥40% of the site median value for G6PD normal males.
   - **Male subjects** must have an enzyme level ≥70% of the site median value for G6PD normal males.

3. The subject has a screening hemoglobin (Hb) value as follows:

   •Any subject with a G6PD value ≥70% of the site median value must have a screening Hb value ≥7 g/dL.

   •Female subjects with a G6PD value is ≥40% - <70% of the site median value must have a screening Hb value ≥8 g/dL.

4. 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 or manual over-read.

Efficacy

5. The subject has a positive malarial smear for *P. vivax*.
6. The subject has a parasite density of >100 and <100,000/µL.

Other

7. Male or female subject aged 16 years or older (18 years or older in Ethiopia) at the time of signing the informed consent.
8. The subject agrees to G6PD genotyping.
9. The subject is willing and able to comply with the study protocol.
10. The subject or parent/legal guardian, as applicable, has given written informed, dated consent; and the subject has given written assent, if applicable, to participate in the study.

4.2.2. Exclusion Criteria

Deviations from 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.

Subjects meeting any of the following criteria must not be enrolled in the study:

Safety

1. The subject has a mixed malaria infection (identified by a malarial smear or rapid diagnostic test).
2. The subject has severe *P. vivax* malaria as defined by WHO criteria.
3. The subject has a history of allergy to chloroquine, mefloquine, tafenoquine, primaquine, or to any other 4- or 8-aminoquinoline.

Hepatic Disease

4. The subject has a liver ALT >2 x ULN.

Concurrent Disease

5. The subject has severe vomiting (no food or inability to take food during the previous 8 hours).
6. The subject has a clinically significant concurrent illness (e.g., pneumonia, septicemia), pre-existing condition (e.g., renal disease, malignancy), condition that

may affect absorption of study medication (e.g., vomiting, severe diarrhea), or clinical signs and symptoms of severe cardiovascular disease (e.g., uncontrolled congestive heart failure, severe coronary artery disease).

7. The subject has a history of porphyria, psoriasis, or epilepsy.
8. The subject has a history of significant ocular disease (e.g. surgery to the globe, glaucoma, diabetic retinopathy) or has evidence of corneal or retinal abnormalities identified in the clinical screening ophthalmologic examination.

Concurrent Medication

9. The subject has taken anti-malarials (e.g., artemisinin-based combination therapies, mefloquine, primaquine, or any other 4- or 8-aminoquinoline) within 30 days prior to study entry.
10. The subject has taken or will likely require during the study the use of medications from the following classes:

    - Histamine-2 blockers and antacids
    - Drugs with hemolytic potential
    - Drugs known to prolong the QTcF interval
    - The biguanides phenformin and buformin (but excluding metformin)
    - Drugs that are substrates of the renal transporters OCT2, MATE1 and MATE-2K and have a narrow therapeutic index (for example, the anti-arrhythmic agents dofetilide, procainamide and pilsicainide)

Other

11. The subject has received treatment with any investigational drug within 30 days of study entry, or within 5 half-lives, whichever is longer.
12. The subject has a recent history of illicit drug abuse or heavy alcohol intake, such that full participation in the study could be compromised.

NOTES ON ELIGIBILITY CRITERIA:

- See Appendix 4 (Section 11.4) for the WHO definition of severe malaria.
- Ophthalmic safety assessments will only be conducted at appropriately qualified investigator sites. Therefore, exclusion criterion 8 only applies to those pre-selected sites. A subject may be excluded from the ophthalmic assessments at one of these sites but still participate in the main portion of the study.
- For centers participating in this study and sister Study TAF112582: if female subjects screen fail Study TAF112582 due to being G6PD deficient, they may enrol in this study using the screening labs and procedures from the TAF112582 screening process.

4.3. Withdrawal Criteria

- Adverse event
- Protocol deviation
- Study closed/terminated
- Lost to follow-up
- Consent withdrawal
- Subject or investigator non-compliance
- At the request of the subject, investigator, or sponsor
- Pregnancy

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at their discretion, discontinue the subject from participating in this study at any time. A subject is considered to be withdrawn prematurely from the study if they do not complete the Day 180 assessment. A subject may withdraw or be prematurely withdrawn for any of the reasons presented in the list above. If a subject withdraws consent the site should offer to conduct safety assessments through Day 90.

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 must make every effort to perform the study evaluations as specified in Table 2 for the Relapse or Withdrawal visit as applicable.

4.4. Premature Withdrawal of Study Medication

If a subject prematurely discontinues from blinded study medication, the reason for withdrawal from medication should be recorded in the eCRF. As useful safety and efficacy information can still be obtained for these patients, the investigator should continue following subjects for all protocol assessments, up to and including day 180. The subject should be offered/given appropriate rescue medication as detailed in Section 5.6.1.2 if they get a recurrence of malaria due to inability to take blinded study medication.

Subjects who withdraw from open label CQ (and prior to receiving blinded study medication) will not continue in the study and should be offered alternative treatment in accordance with site (local) or national treatment guidelines for *P. vivax* malaria. These subjects should be followed up until resolution of the malaria infection.

In addition, subjects should discontinue taking study medication if they meet any of the following criteria:

- Any grade 4 AE or toxicity in the absence of compelling evidence that the AE is not related to study medication

- Clinically significant laboratory results considered by the investigator to warrant withdrawal from the study
- QT stopping criteria as defined below:
    - QTcF > 500msec
    - Uncorrected QT > 600msec

      These criteria should be based on the average QTcF value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTcF values of the three ECGs to determine whether the patient should be discontinued from the study.
    - For subjects with underlying Bundle Branch Block, the criterion is ≥ 530 msec.
- Liver chemistry stopping criteria as specified in Section 6.4.1
- Given the hemolytic potential of TQ and PQ in subjects with G6PD deficiency, study specific hemoglobin stopping criteria will be employed. Refer to Section 6.4.2 for details.

When QT or hematologic stopping criteria are met, this must be promptly reported by the investigator to GSK (see Section 6.4.11)

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

Throughout the protocol, study treatments will be defined and described as follows:

- "Study medication" refers to all drugs and placebos used in the study
- "Blinded study medication" refers to tafenoquine, primaquine and the corresponding placebos

The contents of the study medication labels will be in accordance with all applicable regulatory requirements. All study medication is being supplied by GlaxoSmithKline.

5.1.1. Tafenoquine

Tafenoquine will be supplied as a dark pink, 17.1mm × 9.0mm, capsule-shaped, film-coated tablet that is plain on both sides. Each tablet will contain 150mg tafenoquine.

5.1.2. Tafenoquine Placebo

Placebo tafenoquine tablets will be supplied as a dark pink, 17.1mm × 9.0mm, capsule-shaped, film-coated tablet that is plain on both sides, with common excipients of appropriate quality.

5.1.3. Chloroquine

One of two formulations of commercially available generic chloroquine may be utilized in this study:

1. tablets containing 500 mg chloroquine phosphate (equivalent to 300 mg chloroquine free base); or,
2. tablets containing 250 mg chloroquine phosphate (equivalent to 155 mg chloroquine free base).

5.1.4. Primaquine

Commercially available primaquine phosphate tablets containing primaquine phosphate 26.3 mg (equivalent to primaquine base 15 mg) over-encapsulated in a Swedish orange capsule will be utilized in this study.

5.1.5. Primaquine Placebo

Placebo to match primaquine will be supplied as Swedish orange capsules with common excipients of appropriate quality.

5.1.6. Handling and Storage of Investigational Product

Under normal conditions of handling and administration, investigational product is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product at a temperature up to 30°C (87°F). Access to and administration of the investigational product will be limited to the investigator and authorized site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

A temperature log must be maintained at all study sites where study medication is stored.

Following full drug accountability, all used study medication should be destroyed at site according to local guidelines.

5.1.7. Duration of Treatment of Active Study Medication

The total duration of treatment is 15 days.

Chloroquine will be dosed orally once daily for three days starting on Day 1 of the study.

Tafenoquine will be dosed orally as a single dose on Day 1 or Day 2 of the study.

Primaquine will be given as a 14-dose course administered orally once daily for 14 days starting from Day 1 or Day 2 of the study.

5.1.8. Dose and Administration

Study medication should be administered with food. If the subject vomits within 1 hour following dosing, a repeat dose should be given. If a subject sequentially vomits two doses of study medication he/she will be considered intolerant to study medication. These subjects will be withdrawn from study medication and be given appropriate rescue medication as outlined in Section 5.6.1.2. Subjects and all site staff will be blinded to the study treatment.

Subjects will be randomized into one of two treatment arms. Subjects that receive the 500 mg CQ tablet (300 mg CQ free base) will receive the following number of CQ tablets, TQ/placebo tablets and PQ/placebo capsules:

Treatment Arm	**Day 1**	**Day 2**	**Day 3**	**Days 4 – 15**
tafenoquine	2×CQ 300mg	2×CQ 300mg + 2×TQ 150mg + 1×PQ placebo	1×CQ 300mg + 1×PQ placebo	1×PQ placebo
primaquine	2×CQ 300mg	2×CQ 300mg + 2×TQ placebo + 1×PQ 15mg	1×CQ 300mg + 1×PQ 15mg	1×PQ 15mg
Total number of capsules/tablets per treatment arm	**2 tablets**	**4 tablets + 1 capsule**	**1 tablet + 1 capsule**	**1 capsule × 12 days**

NOTE: subjects may begin blinded study medication (TQ or PQ and corresponding placebo) on Day 1 or Day 2 of the study.

Subjects that receive the 250 mg CQ tablet (155 mg CQ free base) will receive the following number of CQ tablets, TQ/placebo tablets and PQ/placebo capsules:

Treatment Arm	Day 1	Day 2	Day 3	Days 4 – 15
tafenoquine	4×CQ 155mg	4×CQ 155mg + 2×TQ 150mg + 1×PQ placebo	2×CQ 155mg + 1×PQ placebo	1×PQ placebo
primaquine	4×CQ 155mg	4×CQ 155mg + 2×TQ placebo + 1×PQ 15mg	2×CQ 155mg + 1×PQ 15mg	1×PQ 15mg
Total number of capsules/tablets per treatment arm	**4 tablets**	**6 tablets + 1 capsule**	**2 tablet + 1 capsule**	**1 capsule × 12 days**

NOTE: subjects may begin blinded study medication (TQ or PQ and corresponding placebo) on Day 1 or Day 2 of the study.

5.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule generated prior to the start of the study by the study statistician, using the validated internal software RANDALL.

Each subject scheduled to receive study medication will receive a treatment allocation number when randomized. The randomization number will indicate which therapy the subject will receive, the treatment allocation ratio will be 2:1 (TQ/CQ: PQ/CQ). Once a randomization number has been allocated to a subject, it cannot be re-assigned to any other subject.

5.3. Blinding

This is a double-blind study and both subject and study staff will remain blinded to treatment.

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. It is preferred (but not required) that the investigator first contacts the GSK Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment. If GSK study personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible, 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 appropriate data collection tool.

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 clinical investigators in accordance with local regulations and/or GSK policy.

5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

5.5. Treatment Compliance

Compliance with study medication will be assessed in all subjects by directly observing the taking of medication for days 1-3 of the study. Compliance with respect to PQ medication/placebo in the subgroup of female subjects with moderate G6PD deficiency will be assessed for days 4-15 also by directly observing the taking of study medication. In all other subjects, outpatient compliance will be assessed by pill count and will be evaluated using details of dose administration recorded in the eCRF.

As part of the assessment of PQ compliance, levels of PQ and 7-carboxy PQ will be measured on Days 2, 3, 8 and 15 using TQ pharmacokinetic samples (see Section 6 and Section 6.6.1). Refer to the SPM for detailed methodology on measuring PQ and 7-carboxy PQ in these samples.

5.6. Concomitant Medications and Non-Drug Therapies

5.6.1. Permitted Medications and Non-Drug Therapies

5.6.1.1. Concomitant Medication

All subjects can be given paracetamol during the study but administration time must be recorded in the eCRF. Allowable antibiotics are penicillins, cephalosporins, carbapenems and aminoglycosides.

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

5.6.1.2. Rescue Medication

Subjects requiring rescue medication will be given appropriate medication in accordance with site (local) or national treatment guidelines for *P. vivax* malaria or; e.g., *P. falciparum* malaria, whichever is applicable. Subjects offered rescue medication should be followed up for safety assessment until resolution of the malaria infection.

Details of rescue medication including reason for the rescue medication offered (e.g. withdrawal from study, treatment failure) should be recorded in the eCRF.

5.6.2. Prohibited Medications and Non-Drug Therapies

The following drugs are prohibited for use from 30 days prior to entry in the study through Day 180:

- Anti-malarials and other medicines with known anti-malarial activity.
- Drugs with hemolytic potential.
- Drugs known to prolong QTcF
- Drugs known to interact with primaquine or chloroquine.

Results from an *in vitro* renal transporters study showed that TQ 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 prohibited for a period of 21 days immediately following the blinded dose of tafenoquine.

- The following anti-diabetic drugs of the biguanide class:
  - Phenformin
  - Buformin
- The following 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 is to be avoided. However, if taken this should be recorded in the eCRF under concomitant medication.

See Appendix 5 in Section 11.5 for a non-exhaustive list of prohibited medicines for guidance.

5.7. Treatment after the End of the Study

There is no extension study planned and thus no post study treatment will be offered except for subjects diagnosed with malaria at the end of the study who will receive rescue medication outlined in Section 5.6.1.2

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

5.8. Treatment of Study Treatment Overdose

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

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.

Chloroquine

No specific antidote for chloroquine 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.

Drowsiness, blurred vision, diplopia, blindness, tinnitus, convulsions and coma can occur with overdose. Chloroquine is a known cardiovascular toxin thus cardiac monitoring and resuscitation facilities are essential. Thus in addition to dizziness, nausea, vomiting, diarrhea and headache hypotension, cardiogenic shock and cardiac arrest may occur. The 12 lead ECG may demonstrate decreased T waves, widening of the QRS complex, which may lead to ventricular tachycardia and/or fibrillation.

Primaquine

No specific antidote for primaquine has been identified. In the event that overdose or toxicity 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 primaquine overdose include abdominal cramps, vomiting, burning epigastric pain, central nervous system and cardiovascular disturbances, cyanosis, methemoglobinemia (see tafenoquine overdose guidelines), moderate leukocytosis or leukopenia and anemia.

6. STUDY ASSESSMENTS AND PROCEDURES

Table 2 Time and Events

Protocol Activity	Visit Day															
	Screening/Treatment Period[a]							Follow-Up Period							Relapse Visit[b]	Withdrawal Visit[c]
	Day 1[d]	Day 2	Day 3	Day 5	day 8	Day 11	Day 15	Day 22	Day 29	Day 60	Day 90	Day 120	Day 150	Day 180	Relapse	Withdrawal
Window				+1d	-/+1d	-/+1d	-/+2d	-/+3d	-/+3d	-/+7d	-/+7d	-/+10d	-/+10d	-14/+21d		
Informed Consent Process	X															
Demographic Information	X															
Initial History Only [e]	X															
Physician Assess. Malaria Signs & Symptoms	X															
Inclusion/Exclusion Criteria	X															
Efficacy Assessments																
Parasitological Assessment (blood smear)	X[f]	X[f]	X[f]		X		X	X	X	X	X	X	X	X	X	X
Plasmodium PCR Genotyping	X														X	
Plasmodium whole genome sequencing	X														X	
Safety Assessments																
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs [g]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X

Protocol Activity	**Visit Day**															
	Screening/Treatment Period[a]							**Follow-Up Period**							**Relapse Visit[b]**	**Withdrawal Visit[c]**
	Day 1[d]	**Day 2**	**Day 3**	**Day 5**	**day 8**	**Day 11**	**Day 15**	**Day 22**	**Day 29**	**Day 60**	**Day 90**	**Day 120**	**Day 150**	**Day 180**	**Relapse**	**Withdrawal**
Window				**+1d**	**-/+1d**	**-/+1d**	**-/+2d**	**-/+3d**	**-/+3d**	**-/+7d**	**-/+7d**	**-/+10d**	**-/+10d**	**-14/+21d**		
Physical Examination	X	X	X		X		X	X	X	X	X	X	X	X	X	X
ECG w/ Interpret. & Report [h]	X	X							X						X	X
Adverse Events Assessment [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
G6PD (phenotyping) [k]	X									X		X				
G6PD and CYP2D6 (genotyping)		X														
Ophthalmological Exam (qualified sites only)	X								X		X			X[l]		X
Laboratory Assessments																
Hematology [m]	X		X[n]	X	X	X	X	X	X	X	X	X			X	X
Clinical Chemistry [o]	X		X[n]	X	X	X	X	X	X	X	X	X			X	X
Methemoglobin	X	X	X	X	X	X	X	X	X	X		X			X	X
Urinalysis [p]	X		X	X	X	X	X	X	X	X	X	X			X	X
Blood Draw for PGx		X[q]														
Pregnancy Test [r]	X						X		X	X				X	X	X
Health Outcomes																
Health Outcomes Assessments [s]	X						X	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]

Protocol Activity	Visit Day															
	Screening/Treatment Period[a]							Follow-Up Period							Relapse Visit[b]	Withdrawal Visit[c]
	Day 1[d]	Day 2	Day 3	Day 5	day 8	Day 11	Day 15	Day 22	Day 29	Day 60	Day 90	Day 120	Day 150	Day 180	Relapse	Withdrawal
Window				+1d	-/+1d	-/+1d	-/+2d	-/+3d	-/+3d	-/+7d	-/+7d	-/+10d	-/+10d	-14/+21d		
Pharmacokinetic Assessments																
PK/PD Sampling [u]		X	X		X		X		X	X					X	
Investigational Product																
Dispense Open Label Chloroquine	X	X	X													
Dispense Blinded Study Medication	X[v]	X[v]														
Treatment Compliance Int. - Invest.	X	X	X	X	X	X	X									
IVRS Registration	X															

a All subjects must remain hospitalized for Days 1 through 3.
b Subjects who relapse will continue to be monitored for safety and efficacy at all scheduled visits through day 180. Relapse is defined by a positive blood smear with or without vivax symptoms.
c If subjects withdraw from blinded study medication, all scheduled follow-up visits should be performed to conduct safety assessments up to and including Day 180.
d Visit Day 1 includes all screening procedures and the first day of treatment with study medication.
e Includes medical, disease and therapy histories.
f Blood smears are to be taken twice a day, 6-12 hours apart for the first 3 days, or until 2 consecutive negative thick blood smears are obtained.
g Vital signs include height and weight (screening only), blood pressure, temperature, heart rate and respiratory rate. Vital signs are to be performed twice a day on Days 1 through 3, at least 4 hours apart, and immediately prior to PK measurements.
h ECGs are to be performed at screening (in triplicate), 12 hours after the first dose of blinded study medication, and on Day 29.
i Adverse events are recorded from the time of the first dose of study medication.
j Serious adverse events are recorded from the time of consent in order to fulfil international regulatory requirements.
k G6PD phenotyping to be performed by quantitative spectrophotometric analysis. One or more G6PD rapid point of care tests may be performed at baseline (Day 1) only.
l Only if Day 90 ophthalmological exam shows abnormalities.
m Hematology includes hemoglobin, hematocrit, red blood cell/white blood cell/platelet counts, mean cell volume, white blood cell differential and reticulocyte count.

n Hematology and clinical chemistry on Day 3 must be reviewed prior to discharge from the hospital.
o Clinical Chemistry includes CPK, BUN, serum creatinine, total and indirect bilirubin and liver clinical chemistry.
p Mid-stream urine will be analyzed for protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen and leukocyte esterase by dipstick method.
q The pharmacogenetics sample must be collected at the earliest opportunity after randomization and during the in-clinic treatment visit (Days 1-3).
r Serum or urine pregnancy test that is routinely used at site with a test sensitivity for hCG level ≤ 25 mIU/mL. FSH serum test only for post-menopausal females with less than 6 months spontaneous amenorrhea.
s Refer to Section 6.5 of the protocol for details on health outcome data collection.
t Health outcomes assessments will only be collected at these visits from subjects with confirmed parasitemia or from subjects with clinically relevant hemolysis.
u Day 2 and Day 3 PK samples must be taken 6-12 hours and 24-48 hours post TQ dose.
v Treatment with blinded study medication will begin on either Day 1 or Day 2.

6.1. Critical Baseline Assessments

Written, dated informed consent must be obtained from each potentially eligible subject (or his/her legal representative) by study site personnel **prior** to the initiation of any screening procedures.

Clinical and laboratory assessments will be conducted at screening **(prior to first dose of the study medication)** as detailed in the Time and Events (Table 2).

- Demographic data will be collected to include details of date of birth, gender, race and ethnicity
- Medical history will be collected

- A physical examination will be conducted including:
    - Cardiovascular examination
    - Abdominal examination including assessment of splenomegaly
    - Respiratory examination

- Vital signs will be assessed. These include height, weight, temperature (oral, axillary or tympanic), heart rate, respiratory rate, systolic and diastolic blood pressure

- 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 6.3 and the SPM for further details).

- A blood sample will be collected on a filter paper and stored for future plasmodium genotyping analysis. An additional blood sample will be collected to conduct exploratory plasmodium whole genome sequencing.

- Current and prior medications will be reviewed including any anti-malarial medication that has been used.

- G6PD status will be assessed using quantitative spectrophotometric analysis (further instructions can be found in the SPM). The quantitative analysis will

be used to determine the subject's eligibility for the study. One or more G6PD rapid point of care tests may also be performed at baseline.
    - Periodic external quality assurance testing will be performed to ensure high quality G6PD assay data. Procedures for quality assurance will be described in detail in the SPM.

- A blood sample will be collected on Day 2 for G6PD and CYP2D6 genotyping.

- Laboratory Assessments:
    - Hematology analysis will include: Hb, hematocrit (Hct), red blood cells (RBC), mean cell volume (MCV), differentiated white blood cells (WBC), platelets and reticulocytes (for conversion to absolute).
    - Clinical chemistry evaluations will include: blood urea nitrogen (BUN), serum creatinine, total and indirect bilirubin and liver chemistries (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and creatine phosphokinase (CPK))

- A serum or urine pregnancy test will be performed that is routinely used at the site, provided the test has a sensitivity for hCG of ≤ 25 mIU/mL. A FSH serum test will be performed only for post-menopausal females with less than 6 months spontaneous amenorrhea.

- Methemoglobin levels will be assessed using a non-invasive signal extraction CO-Oximeter handheld machine.

- 12 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 hear rate, RR interval, QRS duration, QT interval and QTcF (QT corrected by Friderica's formula) will be calculated from automated ECG readings and abnormal findings will be recorded. The mean value recorded pre-dose will be classified as baseline.

- A subset of qualified sites will perform the following ophthalmic assessments during in-patient stay and prior to randomization:
    - Visual acuity and color vision will be assessed by standard methods

- Humphrey 10-2 visual field in order to determine the threshold sensitivity of specific loci in the central retina, detection and definition of relative or absolute scotomas.
- Slit lamp examination of the cornea (to document and grade any corneal deposits), lens and retina.
- Retinal digital photography for the documentation of changes in the retinal morphology.

6.2. Unscheduled Visits

Subjects who have one or more visits outside the allowable time window defined for each scheduled visit (see Table 2) will undergo all the procedures and assessments described in Table 2 with the exception of assessments performed only at screening and the PK assessments. Subjects should be able and/or encouraged to return to the clinic for unscheduled visits at anytime during the 180-day study period. **In addition, subjects must return to the clinic anytime they are experiencing a recurrence of malaria symptoms.**

6.3. Efficacy

Parasitology

Asexual parasite counts:

Microscope blood slides will be prepared pre-dose at screening on Day 1, post-dose on Day 1, 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 CQ <6 hours from midnight on day 1, a post dose slide can be taken early on day 2. Microscope blood slides will be prepared at subsequent visits on Days 8, 15, 22, 29, 60, 90, 120, 150 and 180. In addition, blood films should be obtained whenever parasitological re-assessment is required and at the relapse visit or withdrawal visit as applicable. At each time point two thick and one thin film slide should be prepared on separate slides and one additional unstained slide with both thick and thin films retained for quality control. For detailed instructions on the methodology for staining and counting please refer to the SPM.

In summary:

Thick film parasitemia (malaria parasite density) should be calculated first, using the subjects' actual white blood cell count (WBC). Aim to count the number of parasites per 200-250 WBCs:

> i.e., D1 parasitemia/µL = (number of D1 parasites/D1 WBC counted) x D1 WBC count

If after 200 WBCs have been counted, 9 or fewer parasites have been identified, continue counting until reaching 500 WBCs.

If the thick film contains > 250 asexual parasites per 50 WBC (i.e. 5 parasites per WBC, equivalent to 40,000 asexual parasites/µL), 8 high power fields on the thin film should be

read and parasites counted against (assuming 250 RBC per high powered field = 2000) red blood cells counted (RBCs).

Parasitemia from thin films is then calculated as:

> Parasitemia/µL = (number of parasites in 8 high powered fields / RBC counted = 2000) x 4,000,000 [assumed RBC]

The calculated parasitemia/µL will be recorded into the eCRF for each time point. See SPM for quality control procedures.

Local quality control of slides is performed by reading of the slide by 2 different qualified microscopists. If the results from the two readings are within 20% of each other for the parasite count and the two readers agree on the species identification then the average result from the two microscopists is computed and recorded in the eCRF.

If the results from the two microscopists are different by more than 20 % or they disagree on the species identification then a third independent reader is required who will read both slides. The average count from the third independent reader is compared with results from the first two readers. The count of the first two readers closest to the average count of the third independent reader is regarded as final and should be recorded in the eCRF. The third reader should therefore be a highly experienced malaria microscopist.

Slides are considered negative after review of 100 high-power fields.

Gametocyte counts

In the same way, thick film slides will be read for gametocytes on Day 1 (pre-dose and post-dose) and then twice daily for the remainder of the in-patient stay. Slides will be prepared at subsequent visits on Days 8, 15, 22, 29, 60, 90, 120, 150 and 180 (and relapse and withdrawal visits if applicable). If gametocytes are present they will be counted against a 200-250 WBCs and their density calculated as follows:

Gametocytes/µL = (number of gametocytes/WBC counted) x WBC count

Parasite Genotyping

Two drops of peripheral blood will be collected onto pre-printed filter paper 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 recrudescence/relapse or re-infection.

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.

Parasite whole genome sequencing

Four milliliters of blood will be taken for subsequent parasite exploratory whole genome sequencing at baseline and at the relapse visit. If the time taken to transport samples to

the central laboratory leads to poor yields of high quality sequencing data (judged after n=50 samples have been analyzed) then this exploratory sample will no longer be taken.

External quality control

External quality control of slide readings will be conducted by an independent laboratory. The external quality control will be blinded to the treatment assignment. They will examine a proportion of slides from each study site. The procedure for quality control will be described in the SPM.

6.4. Safety

The timing and details of all safety assessments are provided in the Time and Events table in Section 6. Additional details on specific assessments are provided below. Blinded safety information will be reviewed on a monthly basis by a GSK/MMV safety review team.

There are two co-primary safety endpoints in this study: clinically relevant hemolysis will be compared between the two treatment groups in all subjects, and in 50 female subjects with moderate G6PD deficiency (≥40% to <70% of the median site value).

Information on concomitant medication will be collected daily while the subject is an in-patient, at all scheduled treatment and follow-up visits, and if there is a relapse or premature withdrawal visit.

Physical examinations will be performed daily during in-patient days, on each scheduled treatment and follow-up visit at Days 8,15, 22, 29, 60, 90, 120, 150 and 180 and if there is a relapse or premature withdrawal visit.

Vital signs will be performed twice daily whilst an in-patient and on follow-up visits at Days 8, 11, 15, 22, 29, 60, 90, 120, 150 and 180 and if there is a relapse or premature withdrawal visit.

12-lead ECG will be performed at screening, 12 hours (± 30 minutes) after the first dose of blinded study medication, and at Day 29. ECG assessments will also be conducted in cases of relapse or early withdrawal. ECGs will be performed in triplicate at screening but single ECGs will be performed subsequently as indicated in Table 2 unless prolonged QTc is seen.

Clinical chemistry and hematology samples will be analyzed by local laboratories. Evaluations will be made at screening, treatment Days 3, 5, 8, 11, 15 and follow-up Days 22, 29, 60, 90, and 120. These assessments will also be performed if there is a relapse or withdrawal visit. The panel of tests to be analyzed are detailed below in Table 3 and Table 4. 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 Hct measurements that deviate substantially from previous readings should be immediately repeated via venous sampling. If a significant drop in Hb or Hct is observed upon repeat testing, all additional hematology and 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 3 Hematology Tests

Hemoglobin	Hematocrit	Platelets	MCV
WBC	RBC	Reticulocyte	WBC Differential

Table 4 Clinical Chemistry Tests

Creatinine	BUN	Total bilirubin	Indirect bilirubin
AST	ALT	ALP	CPK

Urinalysis will be conducted by local laboratories at screening, Days 3, 5, 8, 11, 15, 22, 29, 60, 90, and 120 (and at the withdrawal and relapse visits if applicable). Urine (approximately 20mL mid-stream urine) will be analyzed for protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen and leukocyte esterase 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 during the in-patient stay, at all out-patient treatment visits (Days 5, 8, 11 and 15) and at selected follow-up visits (Days 22, 29, 60 and 120) as well as at the relapse and withdrawal visits if applicable. 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).

Ophthalmic assessments will be performed at selected sites prior to randomization then at Days 29 and 90 and at the withdrawal follow-up visit. Assessments will also be carried out at Day 180 (and up to resolution) if the Day 90 assessments show abnormalities. Subjects who do not receive the assessment prior to randomization should not receive any subsequent ophthalmic exams.

6.4.1. Liver chemistry stopping and follow up criteria

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

Phase III-IV liver chemistry stopping criteria 1-5 are defined below and are presented in a figure in Appendix 3 (Section 11.3):

1. ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT ≥ 3xULN and INR>1.5, if INR measured)

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT ≥ 8xULN.
3. ALT ≥ 5xULN but <8 xULN persists for ≥2 weeks
4. ALT ≥ 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
5. ALT ≥ 5xULN but <8 xULN and cannot be monitored weekly for ≥2 weeks

When any of the liver chemistry stopping criteria 1-5 is met, do the following:

- **Immediately** withdraw study medication for that subject
- Report the event to GSK **within 24 hours** of learning its occurrence
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN **and** INR>1.5, if INR measured); INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Do not restart study medication

In addition, for criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring
- A specialist or hepatology consultation is recommended

- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values

For criteria 2, 3, 4 and 5:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (see below)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilise or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Subjects with ALT ≥5xULN and <8xULN which exhibit a decrease to ALT x≥3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, 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
- Subjects can continue study medication
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

For criteria 1-5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - 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
- Blood sample for PK analysis, obtained as soon as possible and within 24 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study medication 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 SPM.

- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form.

The following are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and 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]).
- 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. **NOTE**: 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].
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease.

6.4.2. Hemoglobin Stopping Criteria

Study medication will be stopped immediately if the subject's Hb decreases ≥30% or >3 g/dL from baseline; or, the subject's Hb value drops below 6.0 g/dL.

Once the Hb drop is noted and study medication is stopped, the following hematology and clinical chemistry tests should be performed immediately:

Hematology

- Hb
- Hct
- Platelets
- WBC
- RBC
- Reticulocytes

Clinical Chemistry

- Creatinine
- BUN
- Total bilirubin
- Indirect bilirubin
- AST
- ALT
- ALP
- CPK
- LDH
- Visual inspection & Urine dipstick

In addition, MetHb status must be assessed. The subject should continue to attend all visits through Day 180 so that Hb status can continue to be monitored.

6.4.3. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

6.4.3.1. Definition of an AE

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. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- 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 that **do not** meet the definition of an AE include:

- 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
- 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

6.4.3.2. Definition of an SAE

A serious adverse event is 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 hospitalisation or prolongation of existing hospitalisation

   NOTE: In general, hospitalisation 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 hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

   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. 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 hospitalisation but may jeopardise 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 hospitalisation, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

   NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

PROTOCOL-DEFINED SAE

Hemoglobin decreases of ≥30% or >3 g/dL from baseline; or, an overall drop in Hb below 6.0 g/dL in the first 15 days of the study should be reported as an SAE (see Hb stopping criteria in Section 6.4.2)

6.4.4. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

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 judgment of the investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs (see Section 6.4.7)

6.4.5. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools 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 thrombosis
- Deep Venous Thrombosis
- Revascularization

This information should be recorded within one week of when the AE/SAE(s) are first reported.

6.4.6. Death Events

In addition, all deaths will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

This information should be recorded within one week of when the death is first reported.

6.4.7. 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 Section 6.4.11) 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.

6.4.8. Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

6.4.8.1. Time period for collecting pregnancy information

Information on the occurrence of new pregnancies will be collected over the period starting at screening (Day 1) and ending at the Day 180 follow-up assessment. Only those pregnancies that occur following the first dose of study medication will be reported to GSK. Follow-up information will be collected for pregnancies occurring throughout the study.

6.4.9. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of study treatment and until the follow up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, 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 reported to GSK within 24 hours, as indicated in Section 6.4.11

6.4.10. Method of Detecting AEs and SAEs

Care must 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?" or for pediatric studies, "How does your child seem to feel?"

"Have you had any (other) medical problems since your last visit/contact?" or for pediatric studies, "Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?"

"Have you taken any new medicines, other than those provided in this study, since your last visit/contact?" or for pediatric studies, "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?"

6.4.11. Prompt Reporting of Serious Adverse Events and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool "CV events" and/or "death" data collection tool(s) if applicable	24 hours	Updated "SAE" data collection tool "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	2 weeks	"Pregnancy Notification Form"	2 weeks	"Pregnancy Follow-up Form"
QTcF stopping criteria	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Hematological toxicity criteria	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
DRE	2 weeks	DRE CRF page	2 weeks	Updated DRE CRF page

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
Liver chemistry abnormalities:				
ALT≥3xULN and Bilirubin≥2xULN (>35% direct) (or ALT≥3xULN and INR>1.5, if INR measured)[1]	24 hours[2]	"SAE" data collection tool. "Liver Event CRF" and "Liver Imaging" and/or "Liver Biopsy" CRFs, if applicable[3]	24 hours	Updated "SAE" data collection tool/"Liver Event" Documents[3]
ALT≥8xULN; ALT≥3xULN with hepatitis or rash or ≥3xULN and <5xULN that persists≥4 weeks	24 hours[2]	"Liver Event" Documents (defined above) [3]	24 hours	Updated "Liver Event" Documents[3]
ALT≥5xULN plus bilirubin <2xULN	24 hours[2]	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 2 weeks or subject cannot be monitored weekly for 2 weeks[3]	24 hours	Updated "Liver Event" Documents, if applicable[3]
ALT≥5xULN and bilirubin <2xULN that persists ≥2 weeks	24 hours[2]	"Liver Event" Documents (defined above) [3]	24 hours	Updated "Liver Event" Documents[3]
ALT≥3xULN and <5x ULN and bilirubin <2xULN	24 hours[2]	"Liver Event" Documents (defined above) do not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[3]	24 hours	Updated "Liver Event" Documents, if applicable[3]

1. INR measurement is not required; if measured, the threshold value stated will not apply to patients receiving anticoagulants.
2. GSK must be contacted at onset of liver chemistry elevations to discuss subject safety
3. Liver Event Documents (i.e., "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible.

The method of recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

6.4.11.1. Regulatory reporting requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects 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.

6.5. Health Outcomes

Data will be collected to enable a descriptive analysis of the impact of *P.vivax* malaria and clinically relevant hemolysis on healthcare and other costs. Healthcare resource use (*i.e.*, clinic visits) resulting from trial procedures will be excluded.

6.5.1. Health Outcome Assessments Included as Secondary Endpoints

The following data will be collected at study enrolment (for the primary *P. vivax* infection), the Day 15 visit, and at study visits from Day 22 onwards for subjects with confirmed *P. vivax* parasitemia. In addition, the same data will be collected for subjects with clinically relevant hemolysis:

- Healthcare resource use (excluding clinic visits scheduled as part of the study)
- Over-the-counter medications purchased
- Any travel or other costs incurred in seeking or receiving healthcare (excluding travel for clinic visits scheduled as part of the study)
- Time lost from normal occupation (excluding time lost to attend clinic visits scheduled as part of study)

6.6. Pharmacokinetics/Pharmacodynamics

6.6.1. Blood Sample Collection for Pharmacokinetics/Pharmacodynamics

Blood samples for PK analysis will be collected for each patient at the time points indicated in the Time and Events Table (Section 6). Samples should be taken 6 to 12 hours and 24 to 48 hours after TQ dosing and a concurrent set of vital signs should also be obtained. The only exception to this is the sample that is collected when a subject relapses; this sample should be collected as near to the time of relapse as possible. 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.

Details of the PK blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SPM.

6.6.2. Pharmacokinetic/Pharmacodynamic Sample Analysis

Plasma sample analysis will be performed under the management of PTS-DMPK/Scinovo, , GlaxoSmithKline. Concentrations of TQ will be determined using the currently approved analytical methodology. In addition, concentrations of CQ and desethylchloroquine will be determined in both treatment arms of the study. PQ and carboxy-PQ levels will be measured from the PK samples collected on Days 1-3, Day 8 and Day 15. If the actual collection day of the Day 15 sample is later than Day 15, PQ/carboxy-PQ levels will not be assessed. Raw data will be archived at the bioanalytical site (detailed in the Study Procedures Manual).

6.7. Pharmacogenetic Research

A 10 mL pharmacogenetics blood sample collected at the earliest opportunity after randomization and during the in-clinic treatment visit (Days 1 – 3) will be used for potential exploratory pharmacogenetics research aimed at understanding variation in subject response to TQ, PQ or CQ. Additional information regarding pharmacogenetic research is included in Appendix 1. The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments (i.e., approval of Appendix 1). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

7. DATA MANAGEMENT

For this study subject data will be entered into GSK defined electronic case report forms (eCRFs), 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 and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug. eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

Tafenoquine 300mg is not expected to be superior to PQ (15mg/day × 14 days) on the primary endpoint, and feasibility issues meant that it would not be possible to power the study to show non-inferiority. Instead, an estimation approach will be used.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

The sample size of 300 is based on the regulatory requirement to obtain an appropriate total safety database in subjects treated with TQ/CQ at the selected dose, given that subjects are randomized to TQ/CQ: PQ/CQ on a 2:1 ratio.

Included in this sample is a key subgroup of a minimum of 50 female subjects with moderate (40-70%) G6PD enzyme activity. This subgroup will be used to assess the risk to G6PD heterozygous deficient females who may be misclassified by a G6PD POCT and inadvertently treated with TQ.

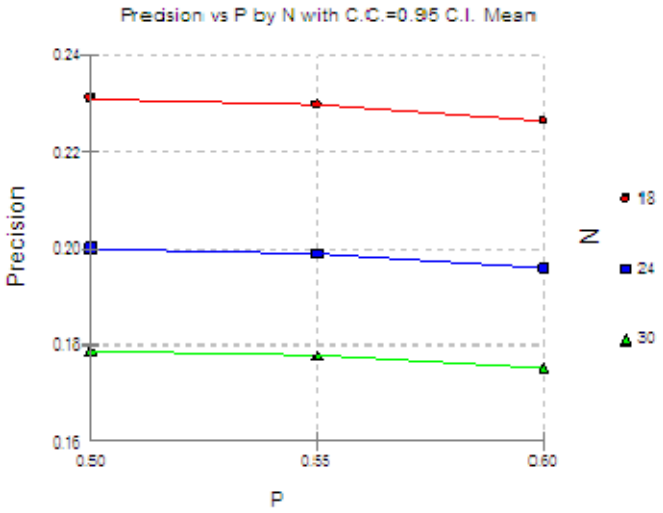
The proportion of heterozygous subjects in this subgroup who will meet the primary endpoint of clinically relevant hemolysis when treated with either TQ or PQ is assumed to be 50%. A sample size of 30 such subjects treated with TQ will provide precision of 18% for the 95% confidence interval. Similarly, sample size of 15 subjects treated with PQ will provide a precision of 25%.

With 50% of the subjects in the subgroup and none of the other subjects assumed to meet the primary endpoint, we expect 8% of the total cohort to have a clinically relevant hemolysis. The 200 subjects in the TQ group will provide a precision of 4% and the 100 subjects in the PQ group precision of 5% for the 95% CI.

The power for testing a difference in proportion between the two treatment groups will be provided retrospectively.

8.2.2. Sample Size Sensitivity

If fewer than 50 subjects are enrolled into the subgroup or if the rate of hemolysis in the subgroup is higher than 50%, then the precision will be affected. We expect most, but not all subjects enrolled into the subgroup to be heterozygous. For total subgroup sizes of 30 and 40, we expect the number of heterozygous females in the TQ arm to be 18 and 24 respectively. For these n's in the TQ arm and for the rates of hemolysis at 50%, 55% and 60%, the corresponding precision for the 95% CI for the estimates rate of hemoslysis is given below:



8.3. Data Analysis Considerations

8.3.1. 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 medication. 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.

Microbiologic Intent to Treat (mITT) Population: all randomized subjects who receive at least one dose of blinded study medication and have microscopically-confimed vivax parasitemia. 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 mITT population for whom there were no major protocol violations (MPVs will be defined in the reporting and analysis plan [RAP]). This population will be used for sensitivity/supporting analyses of efficacy data only.

PK Concentration Population: this population will include all subjects who underwent plasma PK sampling. It will be used for the summarization, listing and plotting of concentration-time profiles.

PK Parameter Population: this population will include all subjects for whom valid PK parameter values were derived. It will be used for the analysis, summary tables, and listing of PK parameters.

PK/PD Population: this population will include all subjects for whom PK and PD were collected, and will be used for any exploratory analysis of PK/PD endpoints.

8.3.2. Analysis Data Sets

Data sets will contain a flag to identify for which analysis population subjects are eligible. Full details of these analysis datasets will be given in the RAP.

8.3.3. Treatment Comparisons

8.3.3.1. Primary Comparisons of Interest

The primary comparisons of interest between the two treatment arms are the proportion of all subjects with *P. vivax* experiencing clinically relevant hemolysis, and the proportions in the subgroup of females with *P. vivax* and moderate G6PD deficiency.

8.3.3.2. Other Comparisons of Interest

Other comparisons include clinical and parasitological efficacy, safety and tolerability of TQ compared to PQ as a radical cure for adult subjects with *P. vivax* malaria when co-administered with CQ.

8.3.4. Key Elements of Analysis Plan

Centers will be pooled for assessing the primary assessment of incidence of clinically relevant hemolysis. Data will be allocated to visit windows using actual visit dates rather than nominal visit numbers. Data collected from extra visits within a window will be listed and will be included in the derivation of the time to relapse, but summary tables will only use the data captured closest to the target visit date. Detailed explanations of the derivation of visit windows will be included in the RAP.

8.3.4.1. Primary Safety Analysis

The proportion and 95% confidence intervals of clinically relevant hemolysis in all subjects and in the subset of females with moderate G6PD deficiency, defined as a

decrease in Hb of ≥30% or >3 g/dL from baseline (or an overall drop in Hb below 6.0 g/dL will be estimated separately for TQ and PQ treatment groups. In addition, a 95% confidence interval for the difference in proportions will be provided.

8.3.4.2. Secondary Safety Analyses

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

8.3.4.2.1. Extent of Exposure

The extent of exposure will be the number of doses of study medication administered to the subject (regardless of whether vomited). The duration of exposure to study medication will be defined as date of last dose of active study medication – date of first dose of study medication + 1. Extent and duration of exposure will be summarized using a frequency distribution for number of doses and number of days.

8.3.4.2.2. Adverse Events

Adverse Event reporting will be performed using the MedDRA (Medical Dictionaries for Regulatory Activities) coding system. Each AE coded using the MedDRA system can be associated with more than one system organ class (SOC). However, for reporting purposes, an AE will be associated with the primary system organ class only.

Counting of AEs will be based on the number of subjects – not the number of AEs. For example, if a subject reports the same AE on three occasions within a time interval, that AE will only be counted once. Subjects reporting more than one AE in a system organ class will only be counted once in the system organ class total. Adverse Events will be summarized by preferred term and SOC, in descending order of frequency, and by maximum severity (mild, moderate or severe).

Adverse Events considered by the investigator to have a reasonable possibility of being related to treatment (drug-related AEs) will be summarized by preferred term and SOC.

Adverse Events leading to premature withdrawal from treatment and or study will be summarized by preferred term and SOC.

Adverse Events that are considered to be GI-related (i.e abdominal pain, heartburn, diarrhea, constipation, nausea and vomiting) will be summarized.

Adverse Events that are considered to be hematologically-related (i.e clinically relevant drops in Hb or Hct or other complications) will be summarized.

Serious adverse events will be summarized by preferred term and SOC.

8.3.4.2.3. Clinical Laboratory Evaluations

Clinical laboratory data (clinical chemistry and haematology) will be summarized by the mean, median, standard deviation, minimum and maximum values by treatment group and time point.

Laboratory data will also be evaluated by tabulating the number and percentage of subjects in each treatment group with values outside specified threshold values of clinical concern. (These may include values outside of the normal range, outer range of clinical concern, and other values of clinical concern.) These safety analyses will be defined in the RAP as appropriate.

8.3.4.2.4. Changes in Methemoglobin

The changes in MetHb will be will be summarized by the mean, median standard deviation, minimum and maximum values by treatment group and time point.

8.3.4.2.5. Ophthalmic Assessments

The ophthalmic assessments of keratopathy, retinopathy and visual field will be summarized.

8.3.4.2.6. QTcF Assessments

ECG results will be summarized accordingly. In addition, an outlier analysis to determine the number and percentage of subjects who have QTcF values and/or an increase from baseline in QTcF that are of clinical concern will be conducted.

8.3.4.3. Secondary Efficacy Analyses

The proportion of patients with relapse-free efficacy at four months and six months will be summarized by treatment group and analyzed using Kaplan-Meier methodology where subjects with missing data are censored, and by separate Fisher's Exact analyses where subjects are classified as a treatment failure if they do not have a six month result or took any drug with activity against *P.vivax*.

The time to relapse, parasite clearance time, fever clearance time and time to gametocyte clearance will be compared using the Kaplan-Meier method and summarized and listed by treatment group.

The incidence rates of genetically homologous and genetically heterologous *P. vivax* infection determined by PCR as well as recrudescence, defined as any *P. vivax* parasitemia occurring on or before Day 32 (*i.e.*, blood stage treatment failure), will be summarized and listed by treatment group.

Subjects will be assessed for clearance times against the following definitions:

Parasite Clearance Time (PCT): Time needed to clear asexual parasite from the blood defined as parasite numbers falling below the limit of detection in the thick blood smear and remaining undetectable 6-12 hours later.

Fever Clearance Time (FCT): Time from first dose of treatment to the time when body temperature falls to normal and remains normal for at least 48 hours.

Gametocyte Clearance Time (GCT): Time from first dose until the first slide that was gametocyte negative and remained so at the next slide reading. Subjects with no gametocytes at baseline will be censored, with a time to clearance of zero.

8.3.4.4. Health Outcomes Analyses

Descriptive summaries of the secondary endpoints on health outcomes will be produced.

8.3.4.5. Pharmacokinetic Analyses

Population PK analysis will be the responsibility of the Clinical Pharmacology Modelling and Simulation department within GlaxoSmithKline. All PK data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

Plasma concentration data for TQ will be displayed in tables and/or graphs. Individual plasma concentration-time data may be pooled with previous data from studies containing robust PK sampling. Data permitting, a population PK model will be developed using software such as NONMEM or other currently available methods. Population PK parameters of tafenoquine such as oral clearance (CL/F) and volume of distribution (V/F) will be determined. In addition, the influence of various covariates (e.g. age, weight, and race) on the PK parameters will be examined.

Plasma concentration data for CQ and desethylchloroquine may be displayed in tables and/or graphs. A population PK model will be developed for CQ and/or desethylchloroquine data if safety or efficacy results from phase II studies indicate that PK/PD analyses are needed.

8.3.4.6. Pharmacokinetic/Pharmacodynamic Analyses

If data permit, exploratory PK/PD analyses for TQ data may be undertaken to examine any relationship between PK parameters (e.g. systemic exposure) and/or clinical outcome (relapse-free efficacy) or safety parameters (e.g. change in MetHb). Similarly, exploratory PK/PD analyses for chloroquine and/or desethylchloroquine data will be undertaken only if safety or efficacy results indicate that these data are needed to understand the PK/PD relationships for TQ.

8.3.4.7. Exploratory G6PD & CYP-2D6 Genotype Analyses

All treated female and any male subjects meeting the pre-specified criteria for Hb deficiency (Hb decrease ≥30% or ≥3.0 g/dL, or an overall drop below 6 g/dL) will be examined for mutations in the G6PD gene to investigate the relationship between G6PD

enzyme level, Hb and genotype. Genetic strategies most likely to be used include single nucleotide polymorphism (SNP) genotyping and/or direct DNA sequencing of subject DNA samples. The same genetic approaches may be used to investigate G6PD genotype in subjects that do not meet the pre-specified criteria for G6PD deficiency to allow relationships between G6PD enzyme level, Hb and genotype to be explored.

In addition, exploratory CYP-2D6 genotype analyses will be undertaken to test the hypothesis that null and/or intermediate metabolisers of 8-aminoquinoline drugs are more at risk of *P. vivax* relapse [Bennett, 2013].

8.3.4.8. Pharmacogenetic Analyses

See Section 11.1 (Appendix 1) for details about the Pharmacogenetics Analysis Plan.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

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

9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, 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.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., PGx assessments described in Appendix 1, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

For adolescents who are not legally able to give consent, written informed consent is obtained from their Legally Authorized Representative (LAR) in accordance with applicable laws or regulations. The investigator is encouraged to obtain assent from adolescents in addition to the consent provided by the LAR.

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors 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 include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study to ensure 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.

9.4. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK 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.

9.5. Study and Site Closure

Upon completion or termination of the study, the GSK monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the investigator or 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 easily accessible 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 the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must 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. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

9.7. Provision of Study Results to Investigators, Posting of Information on Publicly 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 results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

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

9.8. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter, which is available upon request.

10. REFERENCES

Barcus MJ, Basri H, Picarima H et al. Demographic Risk Factors for Severe and Fatal Vivax and Falciparum Malaria Among Hospital Admissions in Northeastern Indonesian Papua. Am J Trop Med Hyg 2007;77(5):984-991.

Bennett JW, Pybus BS, Yadava A, Tosh D, Sousa JC. Primaquine failure and cytochrome P-450 2D6 in *Plasmodium vivax* malaria. N Engl J Med 2013;369(14): 1381-1382.

Fernando D, Rodrigo C, Rajapakse S. Primaquine in vivax malaria: an update and review on management issues. Malar J 2011;10:351.

Gething PW, Elyazar IRF, Moyes CL et al. A Long Neglected World Malaria Map: *Plasmodium vivax* Endemicity in 2010. PLoS Negl Trop Dis 2012;6(9): e1814. doi:10.1371/journal.pntd.0001814

GlaxoSmithKline Document Number 2012N152563_02. A Randomized, Double-Blind, Double Dummy, Comparative, Multicenter Study to Assess the Incidence of Hemolysis, Safety, and Efficacy of Tafenoquine (SB-252263, WR238605) versus Primaquine in the Treatment of Subjects with Plasmodium vivax Malaria. Amendment Number 2. Effective Date: 15-OCT-2014.

GlaxoSmithKline Document Number GM2007/00152/06. SB-252263 Investigator's Brochure. Effective Date: 22-NOV-2012.

GlaxoSmithKline Document Number RM2007/00309/00 Study ID SB-252263/047. A dose ranging study for the safety and efficacy of WD238605/SB252263 in the prevention and relapse of *Plasmodium vivax* infection in Thailand. Effective Date: 25-FEB-2010.

GlaxoSmithKline Document Number UM2004/00017/00 Study ID SB-252263/058. A randomized, active-control, double-blind, double-dummy study to evaluate the efficacy and safety of Tafenoquine for the treatment of *Plasmodium vivax* in adults. Effective Date: 26-SEP-2006.

GlaxoSmithKline Document Number WD2009/01503/00 Study ID TAF106491. Safety, tolerability and pharmacokinetic study of concomitant chloroquine and tafenoquine in healthy volunteers. Effective Date: 16-OCT- 2009.

Hill DR, Baird JK, Parise ME, Lewis LS, Ryan ET, Magill AJ. Primaquine: Report From CDC Expert Meeting on Malaria Chemoprophylaxis I. Am J Trop Med Hyg 2006;75(3):402-415.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Protein Adducts in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009;37(8): 1779-1784.

Kochar DK, Das A, Kochar SK et al. Severe *Plasmodium vivax* Malaria: A Report on Serial Cases from Bikaner in Northwestern India. Am J Trop Med Hyg 2009;80(2):194-198.

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. Clin Microbiol 2005;43(5):2363–2369.

Price RN, Tjitra E, Guerra CA, Yeung S, White NJ, Anstey NM. Vivax Malria: Neglected and Not Benign. Am J Trop Med Hyg 2007;77(Suppl 6):79-87.

White NJ, Imwong M. Relapse (Chapter Two). Adv Parasitol 2012;80:113-150.

WHO Guidelines for the Treatment of Malaria - 2nd Edition, 2010, ISBN 9789241547925.

11. APPENDICES

11.1. Appendix 1: Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	HLA-B* *57:01 (Human Leukocyte Antigen B)*	Carriage of the HLA-B**57:01* variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective HLA-B**57:01* screening and exclusion of HLA-B**57:01* positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective HLA-B**57:01* screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. HLA-B**57:01* screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia Chung, 2010; Ferrell, 2008	HLA-B*15:02	Independent studies indicated that patients of East Asian ancestry who carry HLA-B**57:02* are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of HLA-B**57:02* prior to initiating treatment with carbamazepine.

Drug	Disease	Gene Variant	Outcome
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	UGT1A1*28	Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular UGT1A1 gene variation might be too high for another patient without this variation, raising the risk of certain side-effects, that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the UGT1A1*28 variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no a priori hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to tafenoquine or chloroquine.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to tafenoquine or chloroquine. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with tafenoquine or chloroquine, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Pharmacokinetics and/or pharmacodynamics of study treatment
- Safety and/or tolerability
- Efficacy

Study Population

Any subject, who is enrolled in the clinical study, can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

Blood samples can be taken for Deoxyribonucleic acid (DNA) extraction and used in PGx assessments.

In addition to any blood samples taken for the clinical study, a whole blood sample (~10ml) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

The PGx sample is labelled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or a set of studies) of tafenoquine or chloroquine has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to tafenoquine or chloroquine.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the PGx, if already collected:

- Continue to participate in the PGx research with the PGx sample retained for analysis
- Withdraw from the PGx research and destroy the PGx sample

If a subject withdraws consent for PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. The investigator should forward the Pharmacogenetic Sample Destruction Request Form to GSK as directed on the form. This can be done at any time

when a subject wishes to withdraw from the PGx research or have their sample destroyed whether during the study or during the retention period following close of the main study.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Pharmacogenetics Analyses

- Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to tafenoquine or chloroquine. The genes that may code for these proteins may also be studied.

- Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarised as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research.

Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarise the PGx research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

References

Chung WH, Hung SL, Chen YT. Genetic predisposition of life-threatening antiepileptic-induced skin reactions. Expert Opin. Drug Saf. 2010; 9: 15-21.

Ferrell PB, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics. 2008; 9: 1543-1546.

Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, Lai E, Davies K, Handley A, Dow DJ, Fling ME, Stocum M, Bowman C, Thurmond LM, Roses AD. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet. 2002; 359:1121-1122.

Innocenti F, Undevia SD, Iyer L, Chen PX, Das S, Kocherginsky M, Karrison T, Janisch L, Ramirez J, Rudin CM, Vokes EE, Ratain MJ. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 2004; 22: 1382-1388.

Liu CY, Chen PM, Chiou TJ, Liu JH, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, Wang WS. UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. Cancer. 2008; 112: 1932-1940.

Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, Sayer D, Castley A, Mamotte C, Maxwell D, James I. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet. 2002; 359:727-732.

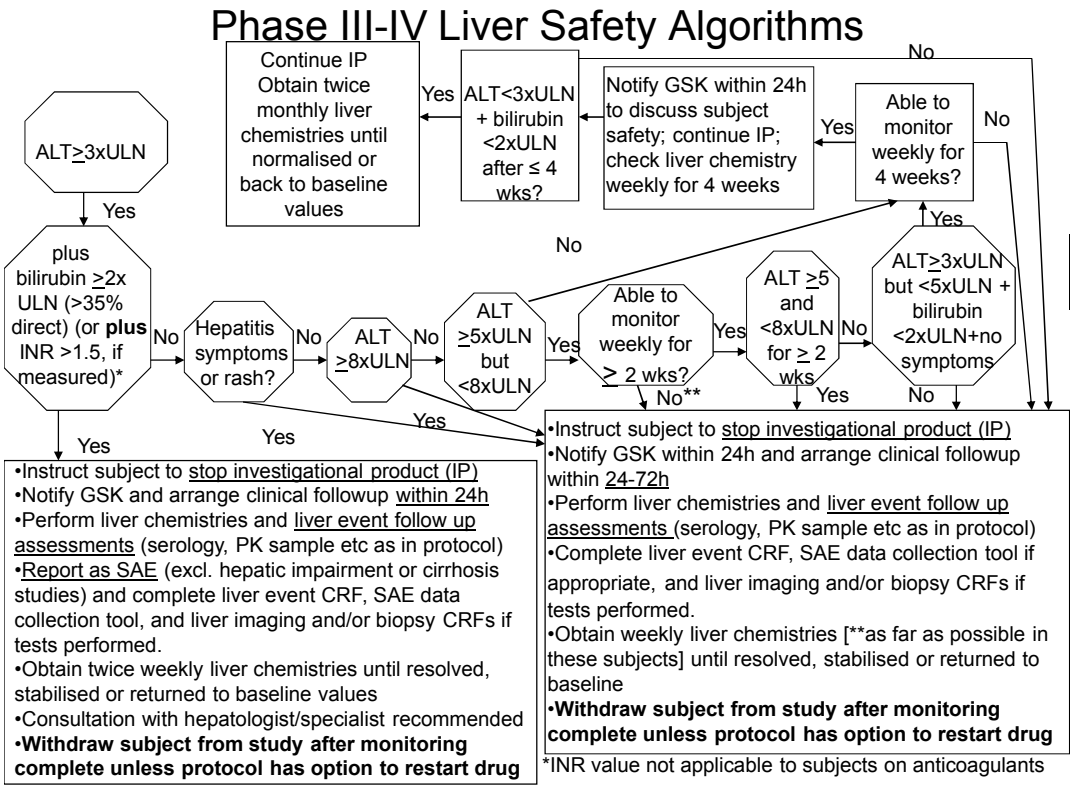
Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, Jägel-Guedes E, Rugina S, Kozyrev O, Cid JF, Hay P, Nolan D, Hughes S, Hughes A, Ryan S, Fitch N, Thorborn D, Benbow A; PREDICT-1 Study Team. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008; 358; 568-579

Schulz C, Heinemann V, Schalhorn A, Moosmann N, Zwingers T, Boeck S, Giessen C, Stemmler HJ. UGT1A1 gene polymorphism: Impact on toxicity and efficacy of irinotecan-based regimens in metastatic colorectal cancer. World J. Gastroenterol. 2009; 15: 5058-5066.

11.2. Appendix 2: Country Specific Requirements

No country-specific requirements exist.

11.3. Appendix 3: Liver Chemistry Stopping and Follow-up Criteria



11.4. 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 oedema and adult respiratory distress syndrome (ARDS)
- Circulatory collapse or shock
- Abnormal bleeding
- Jaundice with organ dysfunction
- Haemoglobinuria
- Hyperparasitaemia (>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.

11.5. Appendix 5: Prohibited Medications for Study Entry

Acetylsalicylic acid. (Paracetamol is the recommended antipyretic agent due to FDA requirement to record times antipyretics are given).

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

Drugs with antimalarial activity:

This list serves to provides 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
- Sulfadiazine, Sulfadoxine or Sulfalene/pyrimethamine, Sulfamethoxazole/trimethoprim, Sulfasalazine (and other sulfonamides)
- Sulfacetamide

Drugs known to cause QTcF prolongation:

- Arsenic trioxide
- Bepridil
- Chlorpromazine
- Cisapride
- Disopyramide
- Dofetilide
- Domperidol
- Droperidol
- Haloperidol
- Ibutilide
- Isotalol
- Ketoconazole (oral or IV, topical preparations are allowed)
- Levomethadyl
- Lidoflazine
- Macrolides (Azithromycin, Erythromycin, Clarithromycin, Roxithromycin)
- Mesoridazine
- Methadone
- Pentamidine
- Pimozide
- Probucol
- Procainamide hydrochloride
- Terfenadine
- Thioridazine
- Sulfapyridine

Drugs Contraindicated in G6PD deficiency:

- Melarsoprol
- Menadiol
- Methyl dopa-
- Methylthioninium chloride (i.e., Methylene Blue)

- Nalidixic acid
- Niridazole
- Nitrofurantoin

Drugs excreted via the renal transporters MATE1, MATE2-K AND OCT2:

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

- Phenformin
- Buformin
- Dofetilide
- Procainamide
- Pilsicainide

Metformin is also excreted via MATE1, MATE2-K 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.

Others-miscellaneous:

- Phenazopyridine
- Phenylhydrazine
- Chloramphenicol

CQ interactions (source eMC):

- Amiodarone
- Antacids (Al, Ca, Mg salts) may cause reduced absorption of CQ. If required therapy must be taken well separated from CQ (at least four hours apart).
- Cimetidine inhibits metabolism of CQ (increases plasma concentration)
- Cyclosporin (CQ interaction)

In addition, refer to locally approved prescribing information.

PQ interactions (source USP):

- Contraindicated with other potentially haemolytic drugs & depressants of myeloid elements of bone marrow.

In addition, refer to locally approved prescribing information.

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

- Penicillins (e.g., Penicillin, Ampicillin, Amoxicillin, Amoxicillin + Clavulanate, Cloxacillin)
- Cephalsoporins (e.g., ceftazidime, Ceftriaxone)
- Aminoglycosides (e.g., Gentamicin)
- Carbapenems (e.g., Meropenem and Imipenem)

11.6. Appendix 6: Protocol Amendment Changes

Amendment 1

This amendment applies to all sites in all countries.

The primary reason for this amendment is to remove a paragraph from Section 6.4.3.1, Definition of an AE, that states "lack of efficacy" constitutes an AE or SAE. This paragraph applies to phase IV post-approval studies, and this study is a phase III study. In addition, the term "nitrate" was used in error to describe one of the urinalysis dipstick tests, and this must be changed to the term "nitrite." Lastly, a statement must be removed from a footnote of the Time and Events table referring to Day 2 and Day 3 ECG measurements.

6. STUDY ASSESSMENTS AND PROCEDURES

Table 2, Time and Events, footnote "p"

PREVIOUS TEXT

Mid-stream urine will be analyzed for protein, glucose, ketones, bilirubin, blood, nitrates, urobilinogen and leukocyte esterase by dipstick method.

REVISED TEXT

Mid-stream urine will be analyzed for protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen and leukocyte esterase by dipstick method.

Table 2, Time and Events, footnote "u"

PREVIOUS TEXT

Day 2 and Day 3 PK samples must be taken 6-12 hours and 24-48 hours post TQ dose. ECGs should be taken within 10 minutes prior to the Day 2 and Day 3 PK sampling.

REVISED TEXT

Day 2 and Day 3 PK samples must be taken 6-12 hours and 24-48 hours post TQ dose.

6.4 Safety

PREVIOUS TEXT

Urinalysis will be conducted by local laboratories at screening, Days 3, 5, 8, 11, 15, 22, 29, 60, 90, and 180 (and at the withdrawal and relapse visits if applicable). Urine (approximately 20mL mid-stream urine) will be analyzed for protein, glucose, ketones, bilirubin, blood, nitrates, urobilinogen and leukocyte esterase 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.

REVISED TEXT

Urinalysis will be conducted by local laboratories at screening, Days 3, 5, 8, 11, 15, 22, 29, 60, 90, and 180 (and at the withdrawal and relapse visits if applicable). Urine (approximately 20mL mid-stream urine) will be analyzed for protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen and leukocyte esterase 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.

6.4.3.1 Definition of an AE

PREVIOUS TEXT

The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

REVISED TEXT

Paragraph removed from section.

Amendment 2

This amendment applies to two centers in Thailand. The changes are as follows:

- The objectives of the study are being revised to correlate with the research methodology being used.
- The term "subgroup" has been removed from the primary objective to describe females with moderate glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- The hemoglobin stopping criteria is being revised to raise the absolute minimum hemoglobin value allowed from 6 g/dL to 7 g/dL. This also requires that the minimum hemoglobin value for entry of G6PD normal subjects (≥70% G6PD activity) into the study must be raised from 7 g/dL to 8 g/dL for all subjects (G6PD normal and deficient).

The changes are described in detail in a separate document [GlaxoSmithKline Document Number 2012N152563_02]

Amendment 3

This amendment applies to all sites in all countries.

Tafenoquine has been shown to inhibit the renal transporters MATE1, MATE2-K and OCT2. The primary reason for this amendment is to add drugs to the prohibited medications list that are excreted via these transporters and have a narrow therapeutic index.

Other amendments include:

- The prohibited medications list was also updated to include albendazole (anti-malarial activity) and ketoconazole (QT prolongation).
- A change was made to the secondary contact medical monitor.
- A change was made to the period of monitoring subjects for recrudescence from 29 days to 32 days.
- Text was added that female subjects who screen fail sister Study TAF112582 due to G6PD deficiency may enroll in this study using TAF112582 screening labs.
- A clarification was made that rapid point-of-care tests for G6PD may be performed at baseline (Day 1) only.
- The haptoglobin test was removed from the list of required hematology tests for haemoglobin stopping criteria.
- In the Efficacy section, parasite genotyping will only occur at screening and at recrudescence/relapse or re-infection.
- Urinalysis will be conducted by local laboratories on Day 120, not Day 180.
- A spelling error in the protocol-defined SAE was corrected that may otherwise lead to confusion.
- Details were inserted on the PK analysis of primaquine and carboxy-primaquine levels.
- The period for collecting pregnancy information will end at the 180 day follow up assessment, not the 90 day follow up assessment.

SPONSOR INFORMATION PAGE

PREVIOUS TEXT

Secondary Contact:

PPD
GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: PPD
Mobile: PPD

REVISED TEXT

Secondary Contact:

PPD
GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BT, UK
Telephone: PPD
Mobile: PPD

Protocol Summary, Study Design

PREVIOUS TEXT

In this prospective, double-blind, double-dummy design, a total of 300 subjects will be randomized to treatment on Day 1, of which a minimum of 50 female subjects must be enrolled that display moderate G6PD deficiency (≥40% - <70% of the site median G6PD value). Subjects must have a blood smear that is positive for *P. vivax* at entry. Subjects must remain in the hospital for a minimum of the first 3 days of the study to monitor study medication compliance and infection status, and will continue on treatment as an outpatient for an additional 12 days. Subjects will be monitored up to day 29 for recrudescence, then continue to be monitored up to 180 days post-randomization for evidence of relapsing infection.

REVISED TEXT

In this prospective, double-blind, double-dummy design, a total of 300 subjects will be 21enrolled that display moderate G6PD deficiency (≥40% - <70% of the site median G6PD value). Subjects must have a blood smear that is positive for *P. vivax* at entry. Subjects must remain in the hospital for a minimum of the first 3 days of the study to monitor study medication compliance and infection status, and will continue on treatment as an outpatient for an additional 12 days. Subjects will be monitored up to day 32 for

recrudescence, then continue to be monitored up to 180 days post-randomization for evidence of relapsing infection.

Protocol Summary, Study Endpoints/Assessments

PREVIOUS TEXT

- Recrudescence, defined as any *P. vivax* parasitemia occurring on or before Day 29 (i.e., blood stage treatment failure).

REVISED TEXT

- Recrudescence, defined as any *P. vivax* parasitemia occurring on or before Day 32 (i.e., blood stage treatment failure).

1.3.1 Risk Assessment

Table 1 Risk Assessment for Tafenoquine (SB-252263)

PREVIOUS TEXT

Renal Function	Transient increases in serum creatinine have been observed in clinical studies. Most recent example includes observation of mild, transient, dose related increases in serum creatinine in human volunteers. A renal safety study was conducted and concluded that TQ, when given as 200 mg x 3 days loading dose followed by weekly 200 mg dosing for 6 months was not inferior to placebo when comparing mean change from baseline glomerular filtration rate.	Conduct renal function testing in this study and in all phase III studies.

REVISED TEXT

Renal Function	Transient increases in serum creatinine have been observed in clinical studies in adults. A renal safety study was conducted and concluded that TQ, when given as 200 mg x 3 days loading dose followed by weekly 200 mg dosing for 6 months was non-inferior to placebo when comparing mean change from baseline glomerular filtration rate. In TAF112582 study part 1 outliers were characterized by isolated transient rises in creatinine with rapid recovery and no consistent time to onset at a particular dose for the outliers. An *in vitro* study conducted to better understand and investigate the possible mechanisms involved showed that tafenoquine is an inhibitor of three renal transporters (OCT2, MATE1 and MATE2. Inhibition of these transporters may explain mild, transient, asymptomatic increases of creatinine observed in previous clinical studies and also may lead to increased exposure to medications excreted via these transporters.	Conduct renal function testing in this study and in all phase III studies. Contra-indicate the use of phenformin, buformin, dofetilide, procainamide and pilsicainide. Exclude subjects taking metformin if the subject has a serum creatinine above the upper limit of normal.

2. OBJECTIVES & ENDPOINTS

PREVIOUS TEXT

- Recrudescence, defined as any *P. vivax* parasitemia occurring on or before Day 29 (i.e., blood stage treatment failure).

REVISED TEXT

- Recrudescence, defined as any *P. vivax* parasitemia occurring on or before Day 32 (i.e., blood stage treatment failure).

3.3 Discussion of Design

PREVIOUS TEXT

Subjects will continue on treatment for the first 15 days of the study and will be monitored up to day 29 for recrudescence.

REVISED TEXT

Subjects will continue on treatment for the first 15 days of the study and will be monitored up to day 32 for recrudescence.

3.3.1 Dose Rationale

PREVIOUS TEXT

Based on the PK results from the pivotal Part 2 portion of this study, there appears to be a short term significant effect on TQ PK (Day 2 Cmax and AUC(0-24)) when co-administered with CQ with no significant effect on the full PK profile (AUC(0-) and t1/2).

REVISED TEXT

Based on the PK results from the pivotal Part 2 portion of this study, there appears to be a short term significant effect on TQ PK (Day 2 Cmax and AUC(0-24)) when co-administered with CQ with no significant effect on the full PK profile (AUC(0-∞) and t1/2).

4.2.2. Exclusion Criteria

Concurrent Medication

PREVIOUS TEXT

10. The subject has taken or will likely require during the study the use of medications from the following classes:

- Histamine-2 blockers and antacids
- Drugs with hemolytic potential
- Drugs known to prolong the QTcF interval

REVISED TEXT

10. The subject has taken or will likely require during the study the use of medications from the following classes:

- Histamine-2 blockers and antacids
- Drugs with hemolytic potential
- Drugs known to prolong the QTcF interval
- The biguanides phenformin and buformin (but excluding metformin)
- Drugs that are substrates of the renal transporters OCT2, MATE1 and MATE-2K and have a narrow therapeutic index (for example, the anti-arrhythmic agents dofetilide, procainamide and pilsicainide)

NOTES ON ELIGIBILITY CRITERIA:

ADDED TEXT

- For centers participating in this study and sister Study TAF112582: if female subjects screen fail Study TAF112582 due to being G6PD deficient, they may enrol in this study using the screening labs and procedures from the TAF112582 screening process.

5.6.2 Prohibited Medications and Non-Drug Therapies

ADDED TEXT

Results from an *in vitro* renal transporters study showed that TQ 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 prohibited for a period of 21 days immediately following the blinded dose of tafenoquine.

- The following anti-diabetic drugs of the biguanide class:
    - Phenformin
    - Buformin
- The following 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.

6. STUDY ASSESSMENTS AND PROCEDURES

Table 2, Time & Events , footnote "k"

PREVIOUS TEXT

k G6PD phenotyping to be performed by both quantitative spectrophotometric analysis and rapid point of care test.

REVISED TEXT

k G6PD phenotyping to be performed by quantitative spectrophotometric analysis. One or more G6PD rapid point of care tests may be performed at baseline (Day 1) only.

6.3 Efficacy

Parasite Genotyping

PREVIOUS TEXT

Two drops of peripheral blood will be collected onto pre-printed filter paper for subsequent DNA extraction and PCR analysis of *Plasmodium* species on all subjects at screening (Day 1; pre-dose), at subsequent visits on Days 5, 8, 11, 15, 22, 29, 60, 90, 120, 150 and 180, and at all times of potential recrudescence/relapse or re-infection.

REVISED TEXT

Two drops of peripheral blood will be collected onto pre-printed filter paper 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 recrudescence/relapse or re-infection.

6.4 Safety

PREVIOUS TEXT

Urinalysis will be conducted by local laboratories at screening, Days 3, 5, 8, 11, 15, 22, 29, 60, 90, and 180 (and at the withdrawal and relapse visits if applicable).

REVISED TEXT

Urinalysis will be conducted by local laboratories at screening, Days 3, 5, 8, 11, 15, 22, 29, 60, 90, and 120 (and at the withdrawal and relapse visits if applicable).

6.4.2 Hemoglobin Stopping Criteria

PREVIOUS TEXT

Hematology

- Hb
- Hct
- Platelets
- WBC
- RBC
- Reticulocytes
- Haptoglobin

REVISED TEXT

Hematology

- Hb
- Hct
- Platelets
- WBC
- RBC
- Reticulocytes

6.4.3.2 Definition of an SAE

PREVIOUS TEXT

PROTOCOL-DEFINED SAE

Hemoglobin decreases of ≥30% of >3 g/dL from baseline; or, an overall drop in Hb below 6.0 g/dL in the first 15 days of the study should be reported as an SAE (see Hb stopping criteria in Section 6.4.2).

REVISED TEXT

PROTOCOL-DEFINED SAE

Hemoglobin decreases of ≥30% or >3 g/dL from baseline; or, an overall drop in Hb below 6.0 g/dL in the first 15 days of the study should be reported as an SAE (see Hb stopping criteria in Section 6.4.2).

6.4.8.1 Time period for collecting pregnancy information

PREVIOUS TEXT

Information on the occurrence of new pregnancies will be collected over the period starting at screening (Day 1) and ending at the Day 90 follow-up assessment.

REVISED TEXT

Information on the occurrence of new pregnancies will be collected over the period starting at screening (Day 1) and ending at the Day 180 follow-up assessment.

6.6.2 Pharmacokinetic/Pharmacodynamic Sample Analysis

PREVIOUS TEXT

Plasma sample analysis will be performed under the management of Worldwide Bioanalysis, DMPK, GlaxoSmithKline. Concentrations of TQ will be determined using the currently approved analytical methodology. In addition, concentrations of CQ and desethylchloroquine will be determined in both treatment arms of the study. Raw data will be stored in the GLP Archives, GlaxoSmithKline.

REVISED TEXT

Plasma sample analysis will be performed under the management of PTS-DMPK/Scinovo, , GlaxoSmithKline. Concentrations of TQ will be determined using the currently approved analytical methodology. In addition, concentrations of CQ and desethylchloroquine will be determined in both treatment arms of the study. PQ and carboxy-PQ levels will be measured from the PK samples collected on Days 1-3, Day 8 and Day 15. If the actual collection day of the Day 15 sample is later than Day 15, PQ/carboxy-PQ levels will not be assessed. Raw data will be archived at the bioanalytical site (detailed in the Study Procedures Manual).

8.3.4.3 Secondary Efficacy Analyses

PREVIOUS TEXT

The incidence rates of genetically homologous and genetically heterologous *P. vivax* infection determined by PCR as well as recrudescence, defined as any *P. vivax* parasitemia occurring on or before Day 29 (*i.e.*, blood stage treatment failure), will be summarized and listed by treatment group.

REVISED TEXT

The incidence rates of genetically homologous and genetically heterologous *P. vivax* infection determined by PCR as well as recrudescence, defined as any *P. vivax* parasitemia occurring on or before Day 32 (*i.e.*, blood stage treatment failure), will be summarized and listed by treatment group.

11.5. Appendix 5: Prohibited Medications for Study Entry

PREVIOUS TEXT

Drugs with antimalarial activity:

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

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

Drugs known to cause QTcF prolongation:

- Arsenic trioxide
- Bepridil
- Chlorpromazine
- Cisapride
- Disopyramide
- Dofetilide
- Domperidol

- Droperidol
- Haloperidol
- Ibutilide
- Isotalol
- Levomethadyl
- Lidoflazine
- Macrolides (Azithromycin, Erythromycin, Clarithromycin, Roxithromycin)
- Mesoridazine
- Methadone
- Pentamidine
- Pimozide
- Probucol
- Procainamide hydrochloride
- Terfenadine
- Thioridazine
- Sulfapyridine

REVISED TEXT

Drugs with antimalarial activity:

This list serves to provides 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

- Sulfadiazine, Sulfadoxine or Sulfalene/pyrimethamine, Sulfamethoxazole/trimethoprim, Sulfasalazine (and other sulfonamides)
- Sulfacetamide

Drugs known to cause QTcF prolongation:

- Arsenic trioxide
- Bepridil
- Chlorpromazine
- Cisapride
- Disopyramide
- Dofetilide
- Domperidol
- Droperidol
- Haloperidol
- Ibutilide
- Isotalol
- Ketoconazole (oral or IV, topical preparations are allowed)
- Levomethadyl
- Lidoflazine
- Macrolides (Azithromycin, Erythromycin, Clarithromycin, Roxithromycin)
- Mesoridazine
- Methadone
- Pentamidine
- Pimozide
- Probucol
- Procainamide hydrochloride
- Terfenadine
- Thioridazine
- Sulfapyridine

ADDED TEXT

Drugs excreted via the renal transporters MATE1, MATE2-K AND OCT2:

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

- Phenformin
- Buformin
- Dofetilide
- Procainamide
- Pilsicainide

Metformin is also excreted via MATE1, MATE2-K 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.

AMENDMENT 4

This amendment addresses the need to add an additional 250 mg formulation of chloroquine to the list of study medications that will be utilized. In addition, the inclusion criterion for age must be revised to state that in Ethiopia only subjects ≥18 years may be enrolled. The SAE case management details are also revised.

SPONSOR INFORMATION PAGE

PREVIOUS TEXT

SAE Case Management Details:

SAE CRF pages and supporting documents should be sent to GSK GCSP Case Management either by email to PPD or by fax to PPD

REVISED TEXT

SAE Case Management Details:

SAE's should be reported via Inform database. If Inform is unavailable, complete paper SAE reports and fax or scan and email directly to the US Case Management Group within 24 hours.

Fax: PPD

Email: PPD

SAE data should be entered into Inform once available.

1.1. Background

PREVIOUS TEXT

The current gold standard for treatment of *P. vivax* malaria in many areas of the world is chloroquine (CQ); typically 600 mg day 1, 600 mg day 2 and 300 mg day 3 for clearance of the acute parasitemia, immediately followed by PQ 15 mg once daily x 14 days to clear the liver stages of the parasite and prevent disease relapse [WHO, 2010]. In some regions the PQ dose is increased to 22.5 mg or 30 mg once daily x 14 days where PQ tolerant hypnozoites are present. The 14-day regimen for PQ has presented major compliance problems, resulting in a significant degree of *P. vivax* malaria relapses in treated populations. Shorter courses (e.g., 5 or 7 days) have been studied, but results have been variable. Consequently, anti-relapse therapy for *P. vivax* malaria is impractical in most epidemic regions due to duration of treatment resulting in poor compliance [WHO, 2010]. In addition, recent evidence suggests that cytochrome P450 2D6 might have a role in PQ metabolism and treatment efficacy, and as such will be investigated in this study [Bennett, 2013].

REVISED TEXT

The current gold standard for treatment of *P. vivax* malaria in many areas of the world is chloroquine (CQ) for clearance of the acute parasitemia, immediately followed by PQ 15 mg once daily x 14 days to clear the liver stages of the parasite and prevent disease relapse [WHO, 2010]. In some regions the PQ dose is increased to 22.5 mg or 30 mg once daily x 14 days where PQ tolerant hypnozoites are present. The 14-day regimen for PQ has presented major compliance problems, resulting in a significant degree of *P. vivax* malaria relapses in treated populations. Shorter courses (e.g., 5 or 7 days) have been studied, but results have been variable. Consequently, anti-relapse therapy for *P. vivax* malaria is impractical in most epidemic regions due to duration of treatment resulting in poor compliance [WHO, 2010]. In addition, recent evidence suggests that cytochrome P450 2D6 might have a role in PQ metabolism and treatment efficacy, and as such will be investigated in this study [Bennett, 2013].

3.2. Study Design

PREVIOUS TEXT

- A total of 300 subjects will be randomized 2:1 to receive TQ/CQ or the active comparator PQ/CQ. All subjects will receive CQ on Days 1 to 3 (600mg, 600mg and 300mg each once daily), followed by TQ or PQ and matching placebo beginning on Day 1 or 2. Tafenoquine, or matching placebo, will be given as a single, 300mg dose. Subjects will receive PQ (15mg once daily) or matching placebo for 14 days.

REVISED TEXT

- A total of 300 subjects will be randomized 2:1 to receive TQ/CQ or the active comparator PQ/CQ. All subjects will receive CQ on Days 1 to 3 followed by TQ or PQ and matching placebo beginning on Day 1 or 2. Tafenoquine, or matching placebo, will be given as a single, 300mg dose. Subjects will receive PQ (15mg once daily) or matching placebo for 14 days.

4.2.1. Inclusion Criteria

PREVIOUS TEXT

7. Male or female subject aged 16 years or older at the time of signing the informed consent.

REVISED TEXT

7. Male or female subject aged 16 years or older (18 years or older in Ethiopia) at the time of signing the informed consent.

5.1.3. Chloroquine

PREVIOUS TEXT

Commercially available generic chloroquine tablets containing 500 mg chloroquine phosphate (equivalent to 300 mg chloroquine free base) will be utilized in this study.

REVISED TEXT

One of two formulations of commercially available generic chloroquine may be utilized in this study:

1. tablets containing 500 mg chloroquine phosphate (equivalent to 300 mg chloroquine free base); or,

2. tablets containing 250 mg chloroquine phosphate (equivalent to 155 mg chloroquine free base).

5.1.8 Dose and Administration

PREVIOUS TEXT

Subjects will be randomized into one of two treatment arms and receive the following number of CQ tablets, TQ/placebo tablets and PQ/placebo capsules:

Treatment Arm	**Day 1**	**Day 2**	**Day 3**	**Days 4 – 15**
tafenoquine	2×CQ 300mg	2×CQ 300mg + 2×TQ 150mg + 1×PQ placebo	1×CQ 300mg + 1×PQ placebo	1×PQ placebo
primaquine	2×CQ 300mg	2×CQ 300mg + 2×TQ placebo + 1×PQ 15mg	1×CQ 300mg + 1×PQ 15mg	1×PQ 15mg
Total number of capsules/tablets per treatment arm	**2 tablets**	**4 tablets + 1 capsule**	**1 tablet + 1 capsule**	**1 capsule × 12 days**

NOTE: subjects may begin blinded study medication (TQ or PQ and corresponding placebo) on Day 1 or Day 2 of the study.

REVISED TEXT

Subjects will be randomized into one of two treatment arms. Subjects that receive the 500 mg CQ tablet (300 mg CQ free base) will receive the following number of CQ tablets, TQ/placebo tablets and PQ/placebo capsules:

Treatment Arm	**Day 1**	**Day 2**	**Day 3**	**Days 4 – 15**
tafenoquine	2×CQ 300mg	2×CQ 300mg + 2×TQ 150mg + 1×PQ placebo	1×CQ 300mg + 1×PQ placebo	1×PQ placebo
primaquine	2×CQ 300mg	2×CQ 300mg + 2×TQ placebo + 1×PQ 15mg	1×CQ 300mg + 1×PQ 15mg	1×PQ 15mg
Total number of capsules/tablets per treatment arm	**2 tablets**	**4 tablets + 1 capsule**	**1 tablet + 1 capsule**	**1 capsule × 12 days**

NOTE: subjects may begin blinded study medication (TQ or PQ and corresponding placebo) on Day 1 or Day 2 of the study.

Subjects that receive the 250 mg CQ tablet (155 mg CQ free base) will receive the following number of CQ tablets, TQ/placebo tablets and PQ/placebo capsules:

Treatment Arm	**Day 1**	**Day 2**	**Day 3**	**Days 4 – 15**
tafenoquine	4×CQ 155mg	4×CQ 155mg + 2×TQ 150mg + 1×PQ placebo	2×CQ 155mg + 1×PQ placebo	1×PQ placebo
primaquine	4×CQ 155mg	4×CQ 155mg + 2×TQ placebo + 1×PQ 15mg	2×CQ 155mg + 1×PQ 15mg	1×PQ 15mg
Total number of capsules/tablets per treatment arm	**4 tablets**	**6 tablets + 1 capsule**	**2 tablet + 1 capsule**	**1 capsule × 12 days**

NOTE: subjects may begin blinded study medication (TQ or PQ and corresponding placebo) on Day 1 or Day 2 of the study.

AMENDMENT 5

This amendment includes changes to the medical monitor contacts and the SAE management case details. In addition, company and tablet description details have been removed for the comparator primaquine. A typographical error was corrected in the amendment section of the appendix.

SPONSOR INFORMATION PAGE

PREVIOUS TEXT

Sponsor Medical Monitor and Serious Adverse Event (SAE) Contact Information:

PPD
GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: PPD
Mobile: PPD

Secondary Contact:

PPD
GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BT, UK
Telephone: PPD
Mobile: PPD

REVISED TEXT

Sponsor Medical Monitor and Serious Adverse Event (SAE) Contact Information:

PPD
GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BT, UK
Telephone: PPD
Mobile: PPD

Secondary Contact:

PPD
GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: PPD

Mobile: PPD

PREVIOUS TEXT

SAE Case Management Details:

SAE's should be reported via Inform database. If Inform is unavailable, complete paper SAE reports and fax or scan and email directly to the US Case Management Group within 24 hours.

Fax: PPD

Email: PPD

SAE data should be entered into Inform once available.

REVISED TEXT

SAE Case Management Details:

SAE's should be reported via Inform database. If InForm is unavailable, SAE CRF pages and supporting documents should be sent to GSK GCSP Case Management either by email to PPD or by fax to PPD
SAE data should be entered into Inform once available.

5.1.4 Primaquine

PREVIOUS TEXT

Commercially available primaquine containing primaquine phosphate USP 26.3 mg (equivalent to primaquine base 15 mg) will be utilized in this study. Primaquine, a pink film-coated tablet imprinted W on one side and P97 on the other is made by SANOFI AVENTIS U.S. The primaquine tablets for this study have been over-encapsulated in a Swedish orange size B supro capsule.

REVISED TEXT

Commercially available primaquine phosphate tablets containing primaquine phosphate 26.3 mg (equivalent to primaquine base 15 mg) over-encapsulated in a Swedish orange capsule will be utilized in this study.

5.1.5 Primaquine Placebo

PREVIOUS TEXT

Placebo to match primaquine will be supplied as Swedish orange size B supro capsules with common excipients of appropriate quality.

REVISED TEXT

Placebo to match primaquine will be supplied as Swedish orange capsules with common excipients of appropriate quality.

11.6. Appendix 6: Protocol Amendment Changes

PREVIOUS TEXT

AMENDMENT 7

REVISED TEXT

AMENDMENT 4

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2012N152563_00	2013-NOV-26	Original
2012N152563_01	2014-FEB-20	Amendment No. 1
Remove paragraph in Section 6.4.3.1 regarding "lack of efficacy" being an AE or SAE Regarding urinalysis, change the term "nitrate" to "nitrite" in all places Remove sentence in footnote regarding Day 2 and Day 3 ECG measurements		
2012N152563_02	2014-OCT-15	Amendment No. 2
This is a site-specific amendment for two centers in Thailand, and includes the following: The objectives of the study are being revised to correlate with the research methodology being used. The term "subgroup" has been removed from the primary objective to describe females with moderate glucose-6-phosphate dehydrogenase (G6PD) deficiency. The hemoglobin stopping criteria is being revised to raise the absolute minimum hemoglobin value allowed from 6 g/dL to 7 g/dL. This also requires that the minimum hemoglobin value for entry of G6PD normal subjects (≥70% G6PD activity) into the study must be raised from 7 g/dL to 8 g/dL for all subjects (G6PD normal and deficient).		
2012N152563_03	2014-OCT-21	Amendment No. 2 (Re-publishing)
Amendment was made to correct the typographical error on title page		
2012N152563_04	2014-NOV-19	Amendment No. 3
Tafenoquine has been shown to inhibit the renal transporters OCT2, MATE1 and MATE2-K. The following drugs have been added to the prohibited medications list that are excreted via these transporters: phenformin, buformin, dofetilide, procainamide, pilsicainide. The list of prohibited medication has been updated to include albendazole (due to its known anti-malarial activity), and ketoconazole (due to its known QT-prolonging effect). Metformin should be stopped if the subject has renal impairment. There is no need to adjust the dose of metformin provided the subject has a serum creatinine below the upper limit of normal. Also refer to contraindications and cautions listed in the prescribing information for metformin.		

A change is made to the secondary contact medical monitor. The monitoring period for recrudescence is extended from 29 to 32 days. Female subjects who screen fail sister Study TAF112582 due to G6PD deficiency may enroll in this study using TAF112582 screening labs. To clarify that rapid point of care G6PD test(s) may be performed at baseline (Day 1) only. Parasite genotyping will only be performed at screening and at the time of recrudescence/relapse or re-infection. Urinalysis will be conducted by local laboratories on Day 120, not Day 180. The haptoglobin test was removed from required hematology tests for hemoglobin stopping criteria. A spelling error in the protocol-defined SAE has been corrected that may otherwise lead to confusion. The period for collecting pregnancy information will end at the 180 day follow up assessment, not the 90 day follow up assessment. Details were inserted on the PK analysis of primaquine and carboxy-primaquine levels.		
2012N152563_05	2015-MAR-31	Amendment No. 4
Add and describe an additional 250mg formulation of chloroquine that may be used during the conduct of the study. Revise the inclusion criterion for age to indicate that in Ethiopia only subjects ≥18 years of age will be enrolled. Revise the SAE Case Management details.		
2012N152563_06	2015-JUL-15	Amendment No. 5
Change in medical monitor Change to SAE Case Management Details Company and tablet description details have been removed for the comparator primaquine. A typographical error was corrected in the Amendment section of the Appendix.		

Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for TAF116564: A Randomized, Double-Blind, Double Dummy, Comparative, Multicenter Study to Assess the Incidence of Haemolysis, Safety, and Efficacy of Tafenoquine (SB-252263, WR238605) versus Primaquine in the Treatment of Subjects with *Plasmodium vivax* Malaria.
Compound Number	:	SB-252263
Effective Date	:	21-FEB-2017

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol TAF116564.
- This RAP is intended to describe the planned safety, efficacy, tolerability, pharmacokinetic and pharmacogenetic analyses required for the study.
- This version includes amendments to the originally approved RAP.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

Author's Name and Functional Area:

PPD Statistician, Clinical Statistics	19-APR-2016
PPD Principal Statistician, Clinical Statistics	21-FEB-2017

Approved via e-mail by:

PPD Director, Clinical Statistics	21-FEB-2017

TABLE OF CONTENTS

PAGE

1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol TAF116564. This document will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverables.
Protocol	• This RAP is based on the original protocol amendment 5 (15-JUL-2015) of study TAF116564 [GSK Document Number: 2012N152563_01] and eCRF Version 3.0.
Primary Objective	• To investigate the occurrence of clinically relevant haemolysis in adult subjects with *P. vivax*.
Primary Endpoint	• Occurrence of clinically relevant haemolysis in all subjects; defined as, a decrease in haemoglobin of ≥30% or >30 g/L (>3 g/dL) from baseline; or, an overall drop in haemoglobin below 60 g/L (6.0 g/dL).
Study Design	• Study TAF116564 is a prospective, double-blind, double-dummy, multicenter, comparative study. • The duration of the study is 180 days, including screening and randomization to treatment (Day 1), three in-hospital days (Days 1-3), four out-patient visits while on treatment with study medication (Days 5, 8, 11 and 15) and seven follow-up visits (Days 22, 29, 60, 90, 120, 150 and 180). • A total of 300 subjects will be randomized 2:1 to receive TQ/CQ or the active comparator PQ/CQ.
Planned Analyses	• No interim analysis is planned. • All decisions regarding final analysis, as defined in this RAP document, will be made prior to Database Freeze (unblinding) of the study data.
Analysis Populations	• Safety Population: all randomized subjects who received at least one dose of blinded study medication. 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. • Microbiologic Intent to Treat (mITT) Population: all randomized subjects who receive at least one dose of blinded study medication and have microscopically-confirmed vivax parasitemia. 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 mITT population for whom there were no major protocol violations. This population will be used for sensitivity/supporting analyses of efficacy data only. • Ophthalmic Safety Population: all subjects in the safety population who have results from any eye assessments.
Hypothesis	• There will be no hypotheses tested in this study.

Overview	Key Elements of the RAP
Primary Analyses	• The proportion of subjects with clinically relevant haemolysis in each treatment group will be presented together with a confidence interval based on the Wilson score. • The difference between treatment groups in the proportion of subjects with clinically relevant haemolysis in each treatment group will be presented together with a confidence interval based on the Newcombe method
Secondary Analyses	• All survival efficacy endpoints, e.g. time to relapse, relapse as a success/failure will be analysed by Cox proportional hazards and Kaplan Meier methodology. Binary endpoints, e.g. relapse/no relapse at 6 months, will be analysed by logistic regression. • Other secondary efficacy endpoints will be summarised descriptively by treatment group. • Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. • Pharmacokinetic analyses will be detailed in a separate document. • Pharmacogenetic data will be summarised and an exact logistic regression model will be used to assess the effect of derived CYP2D6 metabolizer class within treatment arm on relapse efficacy six months post-dosing. • Healthcare resource use of *P. vivax* relapses and haemolysis events will be summarised descriptively.

1.1. RAP Amendments

RAP Section	Amendment Details
Reporting and Analysis Plan_StudyTAF115654_Final [05-AUG-2016]	
Reporting and Analysis Plan_StudyTAF115654_Final_Amend 1 [21-FEB-2017]	
1.0, 4, 8.1.2, 10, 13.14.4, 13.14.8	Removal of Pharmacogenetics population – not required. mITT and Safety populations are sufficient as CYP2D6 and G6PD genotyping are collected under the main Informed Consent.
7.1.2	Correction of Newcombe upper confidence limit equation
8.1.2, 13.14.4, 13.14.5, 13.14.11	Secondary Statistical Analyses: Re-design of efficacy analysis tables to display Cox Proportional Hazard and Kaplan-Meier results in one display Sensitivity Analyses: By Genetic Classification: re-design of analyses to look at heterologous and homologous infections separately with new censoring rules Sensitivity Analyses: Chloroquine Supply: Additional analyses included to

RAP Section	Amendment Details
	investigate the effect of chloroquine supplied before and after a cut-off date Secondary Statistical Analyses: Early Failures: Inclusion of category of early failures where the parasite genetics are missing; listing added Secondary Statistical Analyses: CYP2D6: minor changes to the output statistics
8.2.2, 13.14.6	Urine concentration change from baseline removed as no continuous urinalysis data is collected
13.6.3	Laboratory Parameters: Standard text on handling non-detectable lab values added
13.6.4	Relapse-free efficacy at 6 months and 4 months definitions: censoring added to account for subjects that take a concomitant medication with anti-malarial action prior to clearance plus clarification to the time periods assessed for 4 months Genetic classification of relapse definition: added to include censoring rules Recrudescence definition: clearance definition updated in line with other efficacy endpoints Fever clearance definition: updated to reflect Time and Events schedule of temperature collection
13.10.1	Addition of chloroquine supply covariate
Various	Typographical errors corrected

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There are changes or deviations to the originally planned statistical analysis specified in the protocol amendment 5 (Dated: 15-JUL-2015). In the protocol, the primary objectives are:

1. To investigate the occurrence of clinically relevant haemolysis in adult subjects with *P. vivax*.
2. The incidence of haemolysis in the subgroup of female patients with moderate (40-70%) G6PD activity is of particular interest.

Due to difficulties in recruitment of G6PD deficient subjects, this subgroup of subjects will be limited in number and therefore the incidence in this subgroup will not be

estimated. Therefore the only primary objective is the treatment difference of the occurrence of clinically relevant haemolysis in adult subjects with *P. vivax*.

Any subjects who are G6PD deficient will be included in the main analyses unless described otherwise.

The protocol defined subject study completion as: the subject meets all inclusion/ exclusion criteria, is considered compliant with all study medication, completes the 3 day hospital stay, and attends the Day 180 visit; however a more appropriate definition of "a subject that does not withdraw from the study and attends the Day 180 visit" will be used.

The protocol specified that data will be allocated to visit windows using actual visit dates rather than nominal visit numbers, however to remain consistent with study TAF112582, nominal visit will be used. Further details are given in Section 13.3.

Duration of exposure will not be calculated as specified in the protocol as date of last dose of active study medication – date of first dose of study medication + 1, because the date of last dose is not collected. Compliance and exposure will be presented as described in Section 6.6.

Adverse events that are considered to be gastrointestinal-related will not be reported separately as earlier studies have shown these not to be Adverse Events of special interest.

The protocol stated that Fisher's Exact analyses will be performed for the missing=failure analysis of relapse-free efficacy (see Section 8.1.2), but as the number of subjects relapse-free is expected to be large enough, logistic regression will be performed to allow the inclusion of important covariates.

Time to event endpoints will be analysed using Cox proportional hazards methodology, in addition to the Kaplan-Meier methodology described in the protocol.

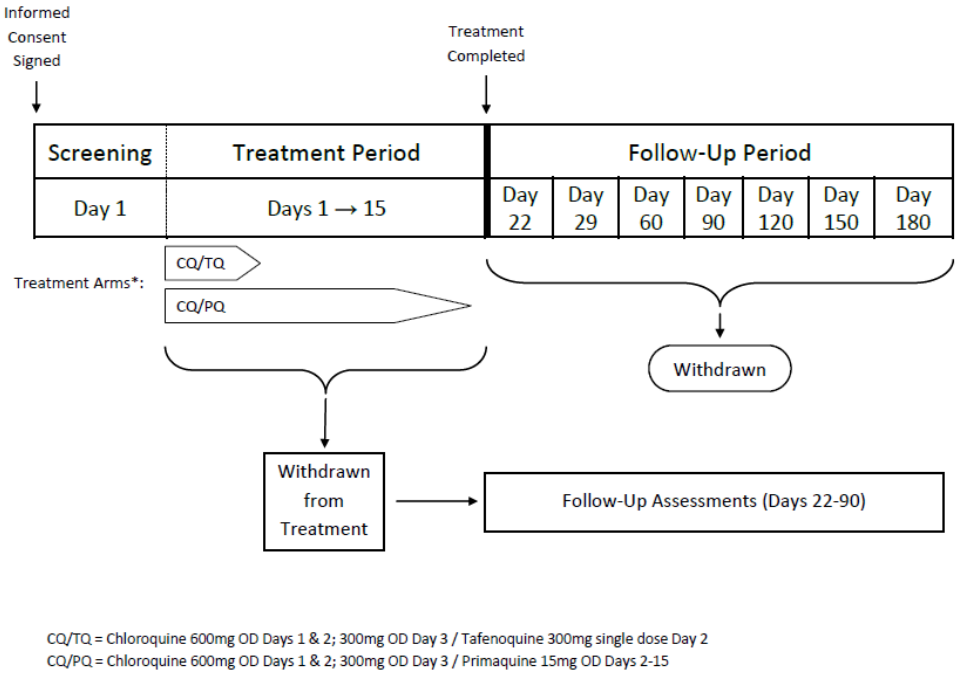
The effect of CYP2D6 metabolism on relapse efficacy within treatment arm and ophthalmic assessments as safety endpoints were not explicitly specified in the protocol as objectives and endpoints. They have been added to the list in Section 2.2.

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To investigate the occurrence of clinically relevant haemolysis in adult subjects with *P. vivax*.	• Occurrence of clinically relevant haemolysis in all subjects; defined as, a decrease in haemoglobin of ≥30% or >30 g/L (>3 g/dL) from baseline; or, an overall drop in haemoglobin below 60 g/L (6.0 g/dL).
Secondary Objectives	**Second Endpoints**
• To compare the clinical and parasitological efficacy, safety and tolerability of tafenoquine to primaquine as a radical cure for	• Relapse-free efficacy six months post-dosing • Relapse-free efficacy four months post-dosing • Time to relapse

Objectives	Endpoints
adult subjects with *P. vivax* malaria when co-administered with chloroquine.	• Parasite clearance time • Fever clearance time • Gametocyte clearance time • Recrudescence, defined as any *P. vivax* parasitemia occurring on or before Day 32 (i.e. blood stage treatment failure). • Incidence of genetically homologous and genetically heterologous *P. vivax* infections (determined by PCR) • Safety evaluation of data from clinical laboratory tests, urinalysis, spontaneous/elicited adverse event reporting, ECGs and vital signs in all subjects who received at least one dose of study medication. • Incidence of *P. falciparum* malaria • Ophthalmic assessments
• To characterize the socioeconomic impact of *P. vivax* relapse.	• Characterization of healthcare resource use and socio-economic impact of *P. vivax* relapses and adverse events caused by treatment to prevent *P. vivax* relapses, especially haemolytic anemia.
• To evaluate the pharmacokinetics of tafenoquine in the treatment of 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)
• To characterize the pharmacokinetic/ pharmacodynamic relationship in this study population.	• PK and selected PD endpoints (e.g. relapse-free efficacy, change in methaemoglobin) if appropriate
• To evaluate the effect of CYP2D6 metabolism on relapse efficacy within treatment arm	• Relapse-free efficacy six months post-dosing

2.3. Study Design

Overview of Study Design and Key Features	
 CQ/TQ = Chloroquine 600mg OD Days 1 & 2; 300mg OD Day 3 / Tafenoquine 300mg single dose Day 2 CQ/PQ = Chloroquine 600mg OD Days 1 & 2; 300mg OD Day 3 / Primaquine 15mg OD Days 2-15	
Design Features	• Study TAF116564 is a prospective, double-blind, double-dummy, multicenter, comparative study. • The duration of the study is 180 days, including screening and randomization to treatment (Day 1), three in-hospital days (Days 1-3), four out-patient visits while on treatment with study medication (Days 5, 8, 11 and 15) and seven follow-up visits (Days 22, 29, 60, 90, 120, 150 and 180). • Subjects will be screened and randomized to treatment on Day 1. Subjects must have a blood smear that is positive for *P. vivax* at entry. Subjects will remain in the hospital for the first 3 days of the study, or until two consecutive thick blood smears are negative for *P. vivax*, to monitor study medication compliance and infection status. Subjects will continue on treatment for the first 15 days of the study and will be monitored up to day 32 for recrudescence. Subjects will continue to be monitored up to 180 days post randomization for evidence of relapsing infection. • All subjects will receive open label CQ (Chloroquine) for the first 3 days of the study to treat the blood stage of the infection. Beginning on Day 1 or Day 2, subjects will receive TQ (Tafenoquine) or the active comparator, PQ (Primaquine), and the

Overview of Study Design and Key Features	
	corresponding placebo for treatment of the liver stage of infection. • At the Day 1 visit subjects will be screened for G6PD deficiency by a quantitative assay and the result will be determined as a percentage of the predetermined median enzyme activity of the site. Female subjects must have a minimum G6PD assay value of 40% to be enrolled, and male subjects must have a minimum G6PD assay value of 70% to be enrolled. • Parasitological assessments will be carried out at each visit in the follow up period. • Other assessments include healthcare resource use and socio-economic data, ophthalmic assessments (selected investigator centres only), vital signs, ECGs, laboratory assessments and blood samples for pharmacokinetic and pharmacodynamic analyses.
Dosing	• All subjects will receive CQ on Study Days 1 to 3, followed by TQ or PQ and matching placebo beginning on Study Day 1 or 2. Tafenoquine, or matching placebo, will be given as a single, 300mg dose. Subjects will receive PQ (15mg once daily) or matching placebo for 14 days.
Treatment Assignment	• A total of 300 subjects (250 with normal G6PD enzyme activity and 50 females with moderate (40-70%) G6PD enzyme activity) were to be randomized 2:1 to receive TQ or the active comparator PQ. • GSK RANDALL NG will be used to generate randomisation schedules. • Treatment allocation will occur by centralised randomisation using GSK RAMOS, accessed by sites via an Interactive Voice Recognition System (IVRS)
Interim Analysis	• No formal interim analyses are planned for this study.
Sample Size	• A sample size of 300 (250 with normal G6PD enzyme activity and 50 females with moderate (40-70%) G6PD enzyme activity) was based on the regulatory requirement to obtain an appropriate total safety database in subjects treated with TQ/CQ at the selected dose, given that subjects are randomized to TQ/CQ: PQ/CQ on a 2:1 ratio.

2.4. Statistical Hypotheses

There will be no hypotheses tested in this study.

3. PLANNED ANALYSES

3.1. Interim Analyses

No formal interim analyses are planned for this study.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

- All subjects have completed (or withdrawn) from the study.
- All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
- All criteria for unblinding the randomisation codes have been met.
- Randomisation codes have been distributed according to RandAll NG procedures.
- An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Safety	• All randomized subjects who received at least one dose of blinded study medication. • Subjects will be analysed according to the treatment a subject actually received.	• Primary population for all safety analyses and data presentations
Microbiologic-Intent-To-Treat (mITT)	• All randomized subjects who receive at least one dose of blinded study medication and have microscopically-confimed vivax parasitemia at Baseline. • Subjects will be analysed according to the treatment a subject was randomized to.	• Primary population for all efficacy analyses
Per-Protocol (PP)	• All subjects in the mITT population for whom there were no major protocol violations.	• Sensitivity/ supporting analyses of efficacy data only
Ophthalmic Safety	• All subjects in the safety population who have results from any eye assessments.	• Analyses of ophthalmic endpoints

NOTES :

- Please refer to Appendix 14: List of Data Displays which details the population to be used for each displays being generated.
- PK and PK/PD data are being handled outside of this RAP so PK and PK/PD populations are not included in this table.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/ exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

- Important deviations which result in exclusion from the analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to the unblinding of the GSK study and statistical team and freezing of the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
    - This dataset will be the basis for the summaries and listings of protocol deviations.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/ exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Appendix
Section 13.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
Section 13.2	Appendix 2: Time and Events
Section 13.3	Appendix 3: Assessment Windows
Section 13.4	Appendix 4: Treatment States & Phases
Section 13.5	Appendix 5: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 13.6	Appendix 6: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Pharmacokinetic • Healthcare Resource Use • Pharmacogenetic
Section 13.7	Appendix 7: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data

Section	Appendix
Section 13.8	Appendix 8: Values of Potential Clinical Importance
Section 13.9	Appendix 9: Multicentre Studies
Section 13.10	Appendix 10: Examination of Covariates and Subgroups
Section 13.11	Appendix 11: Multiple Comparisons and Multiplicity
Section 13.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the safety population, unless otherwise specified.

Section 6 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 14: List of Data Displays.

Categorical variables will be summarised by the number and percentage of subjects, and the continuous parameters will be summarised by n, mean, median, sample standard deviation, minimum and maximum unless otherwise specified. See Section 13.5.3 for further details.

All data will be listed as presented in Appendix 14: List of Data Displays.

6.2. Study Populations and Subject Disposition

A table will be produced detailing the number of subjects eligible for each of the analysis populations by treatment group (Table 1.1). The table will also show the total number of subjects screened.

The number and percentage of subjects who were randomized or entered into the trial, but deviated from the inclusion or exclusion criteria will be summarized by treatment group (Table 1.2).

A table summarising study conclusion records will be produced showing the reasons for withdrawal for any subjects not completing the study as planned (Table 1.3). For subjects who discontinue investigational product, the reasons for discontinuation will be presented in a separate table (Table 1.4). The definition of study completion is given in Section 13.7.1.

The number of subjects recruited per centre and per country will be summarised by treatment group (Table 1.5).

The reasons for screen failure will also be summarised (Table 1.6)

6.3. Protocol Deviations

The number and percentage of subjects who had deviations defined as part of the protocol deviation management plan for the study (see Section 13.1) will be summarized by treatment group (Table 1.7)

6.4. Demographic and Baseline Characteristics

Subjects' demography data (age, sex, ethnicity, weight, height, body mass index (BMI), respiratory rate, G6PD enzyme activity and G6PD enzyme activity as a percentage of the site's median) will be summarised for the safety population (Table 1.8).

Summaries of race and racial combinations (Table 1.9) and race and racial combination details (Table 1.10) will be produced.

Malaria signs and symptoms (Table 1.14), splenomegaly status at baseline (Table 1.19) and previous episodes of malaria (Table 1.20) will be summarised by treatment group.

The eCRF captured the System Organ Class of current and past medical conditions, as well as preferred terms for current and past medical conditions of particular interest. Therefore, 4 summaries will be produced:

- Summary of Current Medical Conditions by Body System (Table 1.15)
- Summary of Past Medical Conditions by Body System (Table 1.16)
- Summary of Current Specific Medical Conditions (Table 1.17)
- Summary of Past Specific Medical Conditions (Table 1.18)

In addition to the G6PD enzyme activity test, which was used to assess whether subjects were eligible to enter the study, a point of care test may also have been administered, which classified subjects as G6PD normal or G6PD deficient (Table 1.22). The results of the point of care test will be summarised (n, %) versus the enzyme activity test for all subjects screened in the study, where G6PD enzyme activity is classified as <40% of median, 40% to <70% of median, and >=70% of median. This display will not be presented by treatment group.

Baseline efficacy data (e.g., asexual parasite counts and parasite gametocyte counts) will not be summarised and listed separately but will be included in efficacy summaries by assessment.

6.5. Prior and Concomitant Medications

Prior and concurrent medications will be tabulated (Table 1.11 and Table 1.12). Percentages will be calculated out of the number of subjects in the safety population. See Section 13.6.2 for definitions of prior and concomitant medications.

Paracetamol usage will be summarised separately (Table 1.13).

6.6. Exposure and Treatment Compliance

Compliance (defined in Section 13.6.2) will be summarised split by in clinic and outpatient dosing (Table 1.21). For in clinic compliance, the number of compliant doses of CQ and whether subjects were compliant with TQ/TQ placebo and each dose of in clinic PQ/PQ placebo will be summarised (n, %). For outpatient compliance, the number of doses taken will be summarised classified into 11 or fewer doses, 12 or more doses. Compliance determined using Day 8, Day 15, Day 8 or Day 15, Day 8 and Day 15 carboxyPQ PK samples will also be summarised in the table. A summary of subjects meeting the pill count and PK compliance criteria, and also the number of subjects meeting the pill count or PK compliance criteria will additionally be provided in the table.

7. PRIMARY STATISTICAL ANALYSES

7.1. Safety Analyses

7.1.1. Overview of Planned Safety Analyses

The primary safety analyses will be based on safety population, unless otherwise specified.

Full details of data displays are presented in Appendix 14: List of Data Displays.

7.1.2. Planned Safety Statistical Analyses

Primary Statistical Analyses

Endpoint(s)

- Occurrence of clinically relevant haemolysis in all subjects. See Section 13.6.3 for derivation of clinically relevant haemolysis.

Model Specification

- No formal statistical analyses will be performed as the incidence of clinically relevant haemolysis is expected to be low.
- 95% confidence intervals for the proportion of subjects ($\hat{p}$) with clinically relevant haemolysis in each treatment group (i,j) will be based in the Wilson score:

$$\left(\hat{p}_i + z^2_{\alpha/2}/2n_i \pm z_{\alpha/2}\sqrt{\left(\hat{p}_i(1-\hat{p}_i) + z^2_{\alpha/2}/4n_i\right)/n_i}\right) / 1 + z^2_{\alpha/2}/n_i$$

  This can be obtained in SAS using the BINOMIAL option in PROC FREQ.
- The Newcombe method based on the Wilson score will be used to calculate the 95% confidence interval for the difference in proportion $(\hat{p}_i - \hat{p}_j)$ (Newcombe, 1998):

$$lower\ limit = (\hat{p}_i - \hat{p}_j) - \sqrt{(\hat{p}_i - L_i)^2 + (U_j - \hat{p}_j)^2}$$

$$upper\ limit = (\hat{p}_i - \hat{p}_j) + \sqrt{(U_i - \hat{p}_i)^2 + (\hat{p}_j - L_j)^2}$$

  where U and L represent the upper and lower limit respectively of the corresponding

Primary Statistical Analyses
proportion. This can be obtained in SAS using the RISKDIFF option with (CL=(NEWCOMBE)) in PROC FREQ.
Results Presentation
• Table 3.1, Figure 3.1: The proportion of subjects with clinically relevant haemolysis in each treatment group will be presented together with a confidence interval based on the Wilson score • The difference between treatment groups in the proportion of subjects with clinically relevant haemolysis in each treatment group will be presented together with a confidence interval based on the Newcombe method (tables only) • Due to the low number of G6PD deficient females expected, they will be included in the primary analysis but their data will be listed separately.

Sensitivity and Supportive Statistical Analyses
• To assess the impact of missing data, a sensitivity analysis will be performed using imputed data where data is missing, as described in Section 13.7.2.3 and the methodology detailed above (Table 3.2).

Further safety analyses are described in Section 8.2.

8. SECONDARY STATISTICAL ANALYSES

8.1. Efficacy Analyses

8.1.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on mITT population, unless otherwise specified.

Details of data displays are presented in Appendix 14: List of Data Displays.

8.1.2. Planned Efficacy Statistical Analyses

Secondary Statistical Analyses
Endpoint(s)
• Relapse-free efficacy six months post-dosing • Relapse-free efficacy four months post-dosing • See Section 13.6.4 for derivations including censoring.
Model Specification
• Estimates for the relapse-free efficacy rate and time to relapse will be determined for each treatment group using the Kaplan-Meier method. • Cox Proportional Hazards model with region and treatment as covariates will provide the hazard ratio • mITT population

Secondary Statistical Analyses
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation

• Summary of the proportion of subjects with relapse-free efficacy by treatment group as n (%), including the sub-reasons for why subjects are not considered relapse-free defined in Section 13.6.4 (Table 2.5 for 6 months, Table 2.7 for 4 months). Note only the sub-reasons that apply to the population being displayed will be included.
• Analysis tables (Table 2.9 for 6 months, Table 2.11 for 4 months) will show:
  • Number of subjects with an observed relapse and numbers of subjects censored (censored prior to 6/4 months, and censored relapse-free at 6/4 months)
  • Kaplan-Meier estimate and 95% confidence intervals of the relapse-free efficacy rate at 6/4 months for each treatment
  • Kaplan-Meier quartile estimates and 95% confidence intervals of time to relapse
  • Hazard ratio of TQ+CQ vs PQ+CQ over the first 6/4 months from Cox Proportional Hazards model
• 95% CI Kaplan-Meier survival curves will also be produced for 6 months (Figure 2.1).

Sensitivity and Supportive Statistical Analyses
1. Per Protocol population – Relapse free efficacy at 6 months and 4 months

• Summary of the proportion of subjects with relapse-free efficacy by treatment group as n (%), including the sub-reasons for why subjects are not considered relapse-free defined in Section 13.6.4 (Table 2.6 for 6 months, Table 2.8 for 4 months). Note only the sub-reasons that apply to the population being displayed will be included.
• Analysis tables (Table 2.10 for 6 months, Table 2.12 for 4 months) will show:
  • Number of subjects with an observed relapse and numbers of subjects censored (censored prior to 6/4 months, and censored relapse-free at 6 months)
  • Kaplan-Meier estimate and 95% confidence intervals of the relapse-free efficacy rate at 6/4 months for each treatment
  • Kaplan-Meier quartile estimates and 95% confidence intervals of time to relapse
  • Hazard ratio of TQ+CQ vs PQ+CQ over the first 6/4 months from Cox Proportional Hazards model
• 95% CI Kaplan-Meier survival curves will also be produced for 6 months (Figure 2.2).

2. Logistic Regression Model – 6 months and 4 months
• 6 months: Table 2.13, 4 months: Table 2.14 • Logistic regression model with region and treatment as covariates. • Response variable = relapse free (confirmed at 6 (or 4) months) vs relapse (confirmed relapse at or prior to 6 (or 4) months). Subjects who are censored prior to 6 (or 4) months will be excluded from the analysis. • mITT only • Present the number and percentage of subjects considered relapse free, the adjusted odds ratio of TQ+CQ vs PQ+CQ and 95% CI for the odds ratio
3. Missing=Failure analysis - 6 months and 4 months
• See Section 13.6.4 for derivation of missing=failure dataset • Logistic regression with region and treatment as covariates

Sensitivity and Supportive Statistical Analyses

• mITT only
• Presentation of results (6 months: Table 2.15, 4 months: Table 2.16):
  • Number and percentage of subjects considered relapse free
  • Adjusted odds ratio of TQ+CQ vs PQ+CQ and 95% CI

4. Missing on or after Day 29 = Failure analysis – 6 months

• See Section 13.6.4 for derivation of missing=failure dataset
• Logistic regression with region and treatment as covariates
• mITT only
• Presentation of results (Table 2.17):
  • Number and percentage of subjects considered relapse free
  • Adjusted odds ratio of TQ+CQ vs PQ+CQ and 95% CI

5. By genetic classification - 6 months and 4 months

• Repeat primary analysis censoring subjects with homologous infections (6 months: Table 2.18, 4 months: Table 2.20); and censoring subjects with heterologous infections (6 months: Table 2.19, 4 months: Table 2.21) present:
  • Number of subjects with an observed relapse and numbers of subjects censored
  • Kaplan-Meier estimate and 95% confidence intervals of the relapse-free efficacy rate for each treatment
  • Kaplan-Meier estimate and 95% confidence intervals of the relapse-free efficacy rate at 6/4 months for each treatment
  • Kaplan-Meier quartile estimates and 95% confidence intervals of time to relapse
  • Kaplan-Meier survival curves (6 months only: Figure 2.3, Figure 2.4)

6. Covariate and Interaction Testing
• The significance of region and the treatment*region interaction will be tested in the Cox Proportional Hazards model. The primary model will be fitted with region and treatment as covariates, and another model will be fitted with the additional treatment*region interaction. • The significance of the chloroquine supply date category (as described in Section 13.10.1) and the treatment*chloroquine supply date category will also be fitted on top of the core model. The covariate will be fitted first on top of the core model, and then the treatment*covariate interaction will be fitted additionally. • mITT only • The degrees of freedom, Wald chi-square and p-values will be presented (Table 2.22) • If the treatment*region interaction is significant at the 10% level, analyses split by region will be performed.
7. By Chloroquine Supply Date Category
• Repeat primary analysis by chloroquine supply date category (as described in Section 13.10.1) (6 months: Table 2.23, 4 months: Table 2.24), regardless of whether the interaction with treatment tested in Table 2.20 is significant or not.

Secondary Statistical Analyses
Endpoint(s)
• Time to relapse • Time to parasite clearance • Time to fever clearance

Secondary Statistical Analyses
• Time to gametocyte clearance • See Section 13.6.4 for derivations including censoring.
Model Specification
• mITT population • Estimates for time to endpoint will be determined for each treatment group using the Kaplan-Meier method. • Cox Proportional Hazards model with region and treatment as covariates
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation

• Time to relapse: this is covered in Table 2.9
• Time to clearance endpoints: Table 2.25 to Table 2.27:
  • Number of subjects with the endpoint and number censored
  • Estimates for time to the endpoint: 1st quartile, median, 3rd quartile and associated 95% confidence intervals
  • Hazard ratio (TQ+CQ vs PQ+CQ) and 95% confidence interval

Secondary Statistical Analyses
Endpoint(s)
• Recrudescence - see Section 13.6.4 for derivations including censoring
Model Specification
• No statistical model will be constructed; descriptive statistics only • 95% Wilson confidence intervals for the rate of recrudescence in each treatment group and treatment difference in the rate • mITT population
Model Results Presentation
• Summary table showing the number of subjects with recrudescence or censored, rate of recrudescence and 95% CI for each treatment group, plus treatment difference and 95% CI (Table 2.29).

Secondary Statistical Analyses
Endpoint(s)
• Early failures • See Section 13.6.4 for derivation
Model Specification
• No statistical model will be constructed; descriptive statistics only • mITT population
Model Results Presentation

• Summary table (n and %) showing the proportion of subjects in each treatment group (Table 2.30):
  • Considered early failures
  • Early failures who fail to demonstrate initial clearance

Secondary Statistical Analyses
• Early failures who demonstrate initial clearance • Early failures who demonstrate initial clearance with genetically homolgous infections • Early failures who demonstrate initial clearance with genetically heterologous infections • Early failures who demonstrate initial clearance with missing parasite genetics • Listing of subjects considered early failures, together with their CQ and desethylCQ concentrations from the PK draw closest to the study day of recrudescence, and whether the infection is determined genetically homologous or heterologous (Listing 29).

Secondary Statistical Analyses
Endpoint(s)
• Genetic classification by PCR of relapse infections occurring on or after Study Day 33 • See Section 13.6.4 for derivation of a relapse
Model Specification
• No statistical model will be constructed; descriptive statistics only • mITT population
Model Results Presentation
• Summary table (n and %) (Table 2.31) showing the proportion of subjects in each treatment group with *P. vivax* relapse infections classified as genetically heterologous or homologous • n will be the number of subjects with a relapse occurring on or after Study Day 33 • Bar chart of the percentage of subjects on each treatment arm with genetically heterologous or homologous infections, with 95% Wilson confidence intervals (Figure 2.5)

Secondary Statistical Analyses
Endpoint(s)
• Effect of CYP2D6 metabolism on relapse-free efficacy six months post-dosing within the treatment arms
Model Specification
• mITT population • Logistic regression model adjusting for region and derived CYP2D6 metabolizer class within treatment arm (models fitted separately for each treatment arm) • One-sided test at the 5% significance level (given published data indicating reduced CYP2D6 metabolism decreases PQ efficacy) • Table 2.33: Poor Metaboliser (PM) and Intermediate Metaboliser (IM) vs Extensive Metaboliser (EM) and Ultra Metaboliser (UM) combined (PM vs EM+UM, IM vs EM+UM) • Table 2.34: Intermediate Metaboliser vs Extensive Metaboliser (IM vs EM) (Rationale:the number of PMs and the number of UMs are expected to be small)
Model Results Presentation
• Number and percentage of subjects relapse free in each metaboliser class within each treatment arm • Adjusted odds ratio, 90% CI and p-value

Secondary Statistical Analyses
Endpoint(s)
• Effect of qualitative CYP2D6 Activity Score (AS) on relapse-free efficacy six months post-dosing within the treatment arms
Model Specification
• mITT population • Logistic regression model adjusting for region and qualitative CYP2D6 AS within treatment arm (models fitted separately for each treatment arm)
Model Results Presentation
• Table 2.35: degrees of freedom, wald chi-square and p-value of the type III effect of AS in the model

Additional Efficacy Summaries

• *P. vivax* asexual parasite counts (Table 2.1), mITT population:
  • Summary statistics (n, median, Q1, Q3, min and max) at each timepoint
• Other malarial asexual parasite counts (Table 2.2), *P. vivax* gametocyte counts (Table 2.3), other malaria gametocyte counts (Table 2.4), mITT population:
  • Summary statistics (n, median, Q1, Q3, min and max) at each timepoint
• Summary of subjects with *P. vivax* gametocyte emergence post baseline (n, %) (Table 2.28) Summary of subjects with *P. falciparum* asexual parasite emergence post baseline (n, %) (Table 2.32)

Efficacy Listings
• Efficacy data will be listed as presented in Appendix 14: List of Data Displays

8.2. Safety Analyses

The safety analyses will be based on the Safety population, unless otherwise specified.

Details of data displays are presented in Appendix 14: List of Data Displays.

8.2.1. Overview of Planned Adverse Events Analyses

Counting of AEs will be based on the number of subjects – not the number of AEs. For example, if a subject reports the same AE on three occasions within the relevant time interval, that AE will only be counted once. If a subject experiences the same AE (i.e. same preferred term) more than once, they are counted only once under the count for the preferred term. If a subject experiences more than one AE in a particular SOC, they will only be included once in the count for the SOC, but will appear in the count for each appropriate preferred term within the SOC. Therefore, the sum of the numbers of subjects with each preferred term event within a SOC may exceed the total number of subjects with at least one event. For the summary of AEs by maximum intensity, subjects who experience the same event several times with different intensity will only be counted once with the maximum intensity.

Only treatment emergent AEs (TEAEs) will be presented as all subjects receive study medication on Study Day 1. TEAEs are defined as AEs with an onset date and time on or after that of the start of first dose of study medication (including CQ)

The occurrence of *P. vivax* malaria and any associated signs and symptoms are recorded as Disease Related Events (DREs) and will not be included in the AE data displays, but will be listed separately.

Adverse Events will be summarized by treatment group and as specified below and in Appendix 14: List of Data Displays and presented in order of descending frequency. Table 2 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 14: List of Data Displays.

Table 2 Overview of Planned Adverse Event Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
All AEs			Y[1]
All Treatment Emergent AEs by SOC	Y		
All Treatment Emergent AEs by PT	Y		
Drug-related TEAE by PT	Y		
TEAEs by maximum intensity	Y		
Common (>=5% in any treatment group) TEAEs by PT	Y	Y[2]	
Common (>=5% in any treatment group) Non-serious TEAEs by SOC and PT – number of subjects and occurrences	Y		
TEAEs by month of onset	Y		
Subject numbers for individual AEs			Y
Relationship between AE SOCs, PTs and verbatim text			Y
Serious and Other Significant AEs			
Fatal TEAEs by PT	Y		Y
Serious TEAEs[3]	Y		Y
Drug related serious TEAEs by PT	Y		
Drug related fatal serious TEAEs by PT	Y		
TEAEs leading to withdrawal from the study	Y		Y
TEAEs leading to discontinuation from study treatment	Y		
AEs that are considered to be haematologically-related (i.e. clinically relevant drops in Hb or Hct or other complications)	Y		
Grade 3 and Grade 4 AEs by PT	Y		
Disease Related Events			Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, SOC = System Organ Class, PT = Preferred Term.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- Treatment emergent AEs (SAEs) are defined as AEs (SAEs) with an onset date and time on or after that of the start of first dose of study medication (including CQ).
- AEs which have missing onset dates and any with an onset date equal to that of medication, but where onset time is unknown, will be considered to be treatment emergent.
- For each preferred term counting will be done by subject and not event.
- AEs related to drug will be selected based on where the 'Relationship to Investigational Product' flag on the eCRF has been marked 'Yes'.
- See Section 13.6.3 for additional information on the derivations and definitions of AEs
- Additional information on any deaths will be provided by Global Clinical Safety and Pharmacovigilance (GCSP) as part of the SAE reconciliation process.
- Events will be sorted based on Total incidence unless otherwise noted in Section 13.14.6
- [1] Treatment Emergent AEs will be flagged
- [2] Plot of common AEs and relative risk will be generated.
- [3] By SOC, by overall frequency and by SOC – number of subjects and occurrences

8.2.1.1. Pregnancies

Any pregnancies occurring will be discussed in the Clinical Study Report.

8.2.1.2. Patient Profiles of Cardiovascular Events and Deaths

Additional information collected on cardiovascular events and deaths will be reported in Patient Profiles for inclusion in the CSR. One profile per subject with an event will be produced using IDSL patient profile display standards.

8.2.2. Overview of Planned Clinical Laboratory Analyses

Table 3 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 14: List of Data Displays.

Table 3 Overview of Planned Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Chemistry						
Chemistry Data by Treatment and Time	Y	Y[1]				
Chemistry Changes from Baseline				Y	Y	
Chemistry Laboratory Abnormalities[2]	Y	Y	Y			
Haematology						
Haematology Data by Treatment, Time and Sex	Y	Y				
Haematology Changes from Baseline by Treatment, Time and Sex				Y	Y	
Haematology Laboratory Abnormalities[2]	Y	Y	Y			
Haemoglobin Categories[4] of Change from Baseline by Treatment and Time				Y		
Haemoglobin Categories[4] of Change from Baseline by Treatment, Time and Sex				Y		
Maximum Fall in Haemoglobin Over First 29 Days[4]					Y	
Mean Change in Haemoglobin Over First 29 Days[4]				Y	Y	
Urinalysis						
Urine Concentration			Y			
Urinalysis Dipstick Results	Y		Y			
Hepatobiliary (Liver)						
Liver Monitoring/Stopping Event Reporting	Y		Y			
Liver Biopsy Details	Y		Y			
Liver Imaging Details	Y		Y			
Medical Conditions for Subjects with Liver Stopping Events			Y			

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
LFT Abnormalities		Y				
Maximum LFTs		Y				
LFT Changes from Baseline		Y				

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1] Boxplots by treatment, time and gender for total bilirubin and indirect bilirubin
- [2] Abnormalities refer to values outside of the clinical concern range (F3) as defined in Section 13.8.1.
- [3] G6PD enzyme activity only
- [4] Categories defined as <=20 g/L, >20 g/L to <=30 g/L, > 30 g/L
- [5] See Section 8.2.2.1
- All scheduled visits should be included in the tables and figures.
- Data recorded at unscheduled assessments will not be included in tables and figures but will be listed.
- Change from baseline is defined in Section 13.5.2.

8.2.2.1. Haemoglobin Declines and Related Laboratory Parameters

For all subjects with a drop in haemoglobin >20 g/L, G6PD enzyme activity will be plotted against maximum drop in haemoglobin up to and including the Day 29 visit, with separate pages for each treatment group (Figure 3.35). Within the plot, different symbols will be used for the following categories:

- subjects who were genotyped and had a mutation classified as World Health Organization (WHO) class 1
- subjects who were genotyped and had a mutation classified as WHO class 2
- subjects who were genotyped and had a mutation classified as WHO class 3
- subjects who were genotyped and had a mutation of unknown significance
- subjects who were genotypically normal or had a mutation classified as a normal variant (WHO class 4)
- subjects who were not genotyped or did not have an evaluable genotyping result

A second plot will include only females with a drop in haemoglobin >20 g/L (Figure 3.36), with separate pages for each treatment group, and a third for G6PD deficient males only (Figure 3.37).

A further set of plots will be produced for each treatment group for all subjects with non-missing G6PD genotype results, with males and females plotted on separate pages. Mean change from baseline haemoglobin will be plotted for G6PD normals by visit, up to and including Day 60 (Figure 3.38). Error bars will be plotted at each time point. Mean change from baseline haemoglobin for G6PD deficients will also be plotted on the same

graph. It is anticipated that the number of G6PD deficients will be very low, so all change from baseline values will be plotted for all G6PD-deficient subjects, but no error bars will be produced.

A further plot by treatment group will display mean change from baseline haemoglobin for all male subjects where G6PD genotype is unknown (Figure 3.39). This plot will cover all visits up to and including Day 29. Error bars will be plotted at each time point.

If a subject has a >20g/L decline from baseline haemoglobin or is a female who was genotyped and found to be G6PD deficient, a haematological profile plot will be produced for the subject (Figure 3.41). This will display their haemoglobin, absolute reticulocyte, methaemoglobin and bilirubin results (total and indirect bilirubin on same plot) at each visit. The subject ID, treatment group, sex, age and G6PD status should be included as a header for each subject's plot.

A summary of haemoglobin declines of the first 29 days by treatment (Table 3.30) and by treatment and sex (Table 3.31) will also be produced.

A listing of all G6PD deficient subjects will be produced including their drop in haemoglobin, G6PD mutation, and their haemoglobin data over time (Listing 31).

Patient profile plots of G6PD for G6PD deficient females will be produced (Figure 3.43). Boxplots by visit and treatment group will also be produced for G6PD enzyme activity (Figure 3.29) and change from baseline in G6PD enzyme activity (Figure 3.30). G6PD will be presented in IU/gHB,

8.2.3. Overview of Planned Other Safety Analyses

Table 4 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 14: List of Data Displays.

Table 4 Overview of Planned Other Safety Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
ECG						
ECG findings	Y		Y			
ECG Values by Visit			Y	Y	Y[1]	
QTcF values by Category[2] and Visit	Y			Y		
Maximum Change from Baseline QTcF Up to 72 hours Post Randomised Treatment				Y		
Vital Signs						
Vital Signs by Time Point and Treatment Group	Y		Y	Y		
Mean Arterial Blood Pressure by Timepoint and Treatment Group		Y				

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Ophthalmic Assessments[3]						
Retinal Abnormalities	Y		Y	Y		
Keratopathy	Y		Y			
Slit Lamp Assessments	Y		Y	Y		
Humphrey Perimetry Assessments	Y		Y	Y		
Colour Perception Assesments	Y		Y			
Best Corrected Visual Acuity Test Scores	Y		Y			
Best Corrected Visual Acuity Classification	Y		Y	Y		
Blood Transfusions						
Blood Transfusion	Y					

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1] QTcF only
- [2] QTcF categories defined in Section 8.2.3.1; include maximum post baseline rows
- [3] Presentation of ophthalmic assessments described in Section 8.2.3.2
- Where triplicate assessments are performed (i.e. at baseline), the mean of the 3 assessments will first be derived and the summary statistics will be presented using the mean of the assessments.
- Temperature readings will be used in these summaries, regardless of the methodology of temperature assessment.

8.2.3.1. Electrocardiogram

QTcF categories for each post baseline timepoint (Table 3.39) are defined as:

- Absolute QTcF:
  - ≤450 msec
  - >450 to ≤480 msec
  - >480 to ≤500 msec
  - >500 msec

- Increase from baseline QTcF:
  - <60 msec
  - ≥60 and absolute QTcF≤480 msec
  - ≥60 and absolute QTcF>480 msec

8.2.3.2. Ophthalmic assessments

Ophthalmic assessments will all be summarised for the Ophthalmic Safety population.

Each type of eye assessment (keratopathy (Table 3.43), slit lamp (Table 3.44), Humphrey perimetry (Table 3.45), colour perception (Table 3.46), and best corrected visual acuity (Table 3.47, Table 3.48)) will be summarised separately by eye, visit and treatment group, including maximum changes from baseline to any visit.

Keratopathy will be summarised by presenting the number of subjects with keratopathy at baseline, and at each visit. For each visit, the proportion of subjects displaying keratopathy and grade of keratopathy in the each eye will be summarised. The number and percentage of subjects with a new keratopathy at any post-baseline visit will also be presented in the same table (Table 3.43).

For best corrected visual acuity, summary statistics for the logMAR score will be displayed for each visit (Table 3.47). A separate tabulation (Table 3.48) will classify changes in logMAR score from baseline as no change (<0.12), possible change (≥0.12 to <0.3)), or definite change (≥0.3) (see Section 13.6.3) for each visit and the maximum change from baseline.

For the colour perception data, the number of Ishihara plates missed will be summarised by visit, and maximum change from baseline, for each eye (Table 3.46).

For retinal data, hyperpigmentation (Table 3.49), hypopigmentation (Table 3.50), appearance of retinal vessel (Table 3.51), optic nerve pallor (Table 3.52), confounding abnormalities (Table 3.53) and retinal changes from baseline (Table 3.54) will be summarised. The number and percentage of subjects with each response (definite, absent, questionable, cannot read, not applicable) will be summarised by visit, eye and treatment group. For retinal changes from baseline, the categories will be no change, questionable change, definite change and cannot grade. The number and percentage of subjects with a definite result at any post-baseline visit, where it was absent or questionable at baseline, will also be included in each table.

9. PHARMACOKINETIC ANALYSES

PK and Population PK analyses will be the responsibility of Clinical Pharmacology Modelling and Simulation within GSK and will be detailed in a separate document.

9.1. Pharmacokinetic / Pharmacodynamic Analyses

If data permit, exploratory PK/PD analyses for TQ data may be undertaken to examine any relationship between PK parameters (e.g. systemic exposure) and/or clinical outcome (relapse-free efficacy) or safety parameters (e.g. change in MetHb). Similarly, exploratory PK/PD analyses for chloroquine and/or desethylchloroquine data will be undertaken only if safety or efficacy results indicate that these data are needed to understand the PK/PD relationships for TQ. Any exposure-response analyses based on emerging data will be described in detail in the study report. A separate analysis plan will describe the details for the population PK/PD analyses.

10. PHARMACOGENETIC ANALYSES

A summary of the number (and percentage) of subjects who gave Pharmacogenetics consent and the status of the genotype samples and data will be produced for all randomised subjects (Table 5.1) Genetic consent will be further detailed in Table 5.2 (reasons consent not obtained, consent withdrawn, sample destruction) for all randomised subjects. A summary of allele frequency by treatment (Table 5.3) and by treatment and region will also be produced for the Safety population (Table 5.4).

10.1. CYP2D6 Metabolism Status

The effect of CYP2D6 metaboliser class on relapse-free efficacy will be analysed as described in Section 8.1.2

11. OTHER STATISTICAL ANALYSES

11.1. Health Outcomes Analyses

Descriptive summaries of the cost of illness questionnaire will be produced for the Safety population.

The aim of these analyses is to determine the cost of an episode of *P. vivax* malaria and an event of haemolysis (regardless of treatment received in this study).

The costs spent on treatment, transport, medication and tests, together with a total cost, will be summarised according to the place at which the subject went to for care (drug shop, trial clinic, other clinic, hospital (inpatient/outpatient), traditional healer, other). Table 6.1 will present the costs associated with the initial episode of malaria, split by country and by visit (Randomisation, Day 15 (follow-up), overall). Table 6.2 will present the costs associated with a relapse episode of malaria, split by country and by visit. Table 6.3 will present the same information associated with a haemolysis event.

The medications purchased will be summarised by cost and according to whether they were associated with a clinic/healer or hospital. Again these will be split by country and visit for the initial episode of malaria (Table 6.4), a relapse episode of malaria (Table 6.5) and haemolysis events (Table 6.6).

A summary of the time lost due to an episode of malaria will be summarised in days according to the subject's occupation. Again these will be split by country and visit for the initial episode of malaria (Table 6.7), a relapse episode of malaria (Table 6.8) and haemolysis events (Table 6.9).

A summary of what subjects did to treat the illness before attending the trial clinic will be summarised by country and visit for the initial episode of malaria (Table 6.10), a relapse episode of malaria (Table 6.11) and haemolysis events (Table 6.12).

Costs will be presented in the original currency and also in United States dollars (USD) to allow costs to be compared across countries. See Section 13.6.5 for conversion to US dollars.

12. REFERENCES

DPWG: Dutch Pharmacogenetics Working Group. Available at https://www.pharmgkb.org/page/dpwg.

Gaedigk A, Simon SD, Pearce RE, Bradford LD, Kennedy MJ, Leeder JS. The CYP2D6 Activity Score: Translating Genotype Information into a Qualitative Measure of Phenotype. *Clin Pharmacol Ther.* 2008; 83:234-242.

GlaxoSmithKline Document Number 2012N152563_01. A Randomized, Double-Blind, Double Dummy, Comparative, Multicenter Study to Assess the Incidence of Hemolysis, Safety, and Efficacy of Tafenoquine (SB-252263, WR238605) versus Primaquine in the Treatment of Subjects with Plasmodium vivax Malaria. Amendment Number 5. Effective Date 15-JUL-2015

GUI_137354, Information for Authors: Reporting and Analysis Plan (RAP), Global

http://www.xe.com/currencytables/?from=USD&date=2015-02-15 (accessed on 23JUL2016)

Nair, I & Patel, B. Attain 100% Confidence in Your 95% Confidence Interval. *Proceedings for the PharmaSUG Conference 2014. (*2014) Available at: http://www.pharmasug.org/proceedings/2014/IB/PharmaSUG-2014-IB05.pdf

Newcombe, RG. Two-Sided Confidence Intervals for the Single Proportion: Comparison of Seven Methods. *Statistics in Medicine* 1998: **17**, 857-872

SOP_54838, Development, Review & Approval of Reporting & Analysis Plan (RAP), Global

Supportive Templates (for RAP), IMMS Example: Reporting and Analysis Plan (RAP) Template_Core Safety Reporting Standards

13. APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 13.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 13.2	Appendix 2: Time and Events
Section 13.3	Appendix 3: Assessment Windows
Section 13.4	Appendix 4: Treatment States & Phases
Section 13.5	Appendix 5: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 13.6	Appendix 6: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Pharmacokinetic • Healthcare Resource Use • Pharmacogenetic
Section 13.7	Appendix 7: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 13.8	Appendix 8: Values of Potential Clinical Importance
Section 13.9	Appendix 9: Multicentre Studies
Section 13.10	Appendix 10: Examination of Covariates and Subgroups
Section 13.11	Appendix 11: Multiple Comparisons and Multiplicity
Section 13.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 13.13	Appendix 13: Abbreviations & Trade Marks
Section 13.14	Appendix 14: List of Data Displays

13.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

13.1.1. Protocol deviations

Major protocol violations could impact the ability to assess efficacy and our primary endpoints for our study. A subject meeting any of the following criteria will be excluded from the Per Protocol population:

Number	Exclusion Description
1	Subject does not have a parasitology assessment within window for any of the Day 2, Day 3, Day 29, Day 60, Day 90, Day 120, Day 150 or Day 180 visits
2	Subject does not demonstrate initial parasite clearance but does not receive rescue medication
3	When in the clinic on Day 1 to 3, subject vomited a dose of study medication and either vomited the redose, or a redose was not given
4	PQ/PQ placebo pill count suggests that the subject failed to take two or more scheduled doses when away from the clinic
5	Violation of any of the following entry criteria: • Subject had a mixed malaria infection at baseline • Subject had an asexual *P. vixax* parasite count $\leq$100 or $\geq$100000 • Subject had a severe malaria infection • Subject had severe vomiting or diarrhoea • Subject had taken anti-malarials within the previous 30 days
6	The subject has taken/received: • anti-malarials (e.g., artemisinin-based combination therapies, mefloquine, primaquine, or any other 4- or 8-aminoquinoline) within 30 days prior to study entry. • treatment with any investigational drug within 30 days of study entry, or within 5 half-lives, whichever is longer. • a concomitant medication with an anti-malarial activity between Day 1 and the Day 180 visit, and remained parasite negative throughout the study. A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified accordingly

NOTES:

- A listing will be produced for the PP population showing
  1. individual subject numbers for each protocol violation
  2. the number and percentage of subjects for each violation
  3. the total number of subjects with one or more violation will be tabulated, by type of violation.

13.2. Appendix 2: Time & Events

13.2.1. Protocol Defined Time & Events

Protocol Activity	Visit Day															
	Screening/Treatment Period[a]							Follow-Up Period							Relapse Visit[b]	Withdrawal Visit[c]
	Day 1[d]	Day 2	Day 3	Day 5	day 8	Day 11	Day 15	Day 22	Day 29	Day 60	Day 90	Day 120	Day 150	Day 180	Relapse	Withdrawal
Window				+1d	-/+1d	-/+1d	-/+2d	-/+3d	-/+3d	-/+7d	-/+7d	-/+10d	-/+10d	-14/+21d		
Informed Consent Process	X															
Demographic Information	X															
Initial History Only [e]	X															
Physician Assess. Malaria Signs & Symptoms	X															
Inclusion/Exclusion Criteria	X															
Efficacy Assessments																
Parasitological Assessment (blood smear)	X[f]	X[f]	X[f]		X		X	X	X	X	X	X	X	X	X	X
Plasmodium PCR Genotyping	X														X	
Plasmodium whole genome sequencing	X														X	
Safety Assessments																
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs [g]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X

Protocol Activity	Visit Day															
	Screening/Treatment Period[a]							Follow-Up Period							Relapse Visit[b]	Withdrawal Visit[c]
	Day 1[d]	Day 2	Day 3	Day 5	day 8	Day 11	Day 15	Day 22	Day 29	Day 60	Day 90	Day 120	Day 150	Day 180	Relapse	Withdrawal
Window				+1d	-/+1d	-/+1d	-/+2d	-/+3d	-/+3d	-/+7d	-/+7d	-/+10d	-/+10d	-14/+21d		
Physical Examination	X	X	X		X		X	X	X	X	X	X	X	X	X	X
ECG w/ Interpret. & Report [h]	X	X							X						X	X
Adverse Events Assessment [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
G6PD (phenotyping) [k]	X									X		X				
G6PD and CYP2D6 (genotyping)		X														
Ophthalmological Exam (qualified sites only)	X								X		X			X[l]		X
Laboratory Assessments																
Hematology [m]	X		X[n]	X	X	X	X	X	X	X	X	X			X	X
Clinical Chemistry [o]	X		X[n]	X	X	X	X	X	X	X	X	X			X	X
Methemoglobin	X	X	X	X	X	X	X	X	X	X		X			X	X
Urinalysis [p]	X		X	X	X	X	X	X	X	X	X	X			X	X
Blood Draw for PGx		X[q]														
Pregnancy Test [r]	X						X		X	X				X	X	X
Health Outcomes																
Health Outcomes Assessments [s]	X						X	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]

Protocol Activity	Visit Day															
	Screening/Treatment Period[a]							Follow-Up Period							Relapse Visit[b]	Withdrawal Visit[c]
	Day 1[d]	Day 2	Day 3	Day 5	day 8	Day 11	Day 15	Day 22	Day 29	Day 60	Day 90	Day 120	Day 150	Day 180	Relapse	Withdrawal
Window				+1d	-/+1d	-/+1d	-/+2d	-/+3d	-/+3d	-/+7d	-/+7d	-/+10d	-/+10d	-14/+21d		
Pharmacokinetic Assessments																
PK/PD Sampling [u]		X	X		X		X		X	X					X	
Investigational Product																
Dispense Open Label Chloroquine	X	X	X													
Dispense Blinded Study Medication	X[v]	X[v]														
Treatment Compliance Int. - Invest.	X	X	X	X	X	X	X									
IVRS Registration	X															

a All subjects must remain hospitalized for Days 1 through 3.
b Subjects who relapse will continue to be monitored for safety and efficacy at all scheduled visits through day 180. Relapse is defined by a positive blood smear with or without vivax symptoms.
c If subjects withdraw from blinded study medication, all scheduled follow-up visits should be performed to conduct safety assessments up to and including Day 180.
d Visit Day 1 includes all screening procedures and the first day of treatment with study medication.
e Includes medical, disease and therapy histories.
f Blood smears are to be taken twice a day, 6-12 hours apart for the first 3 days, or until 2 consecutive negative thick blood smears are obtained.
g Vital signs include height and weight (screening only), blood pressure, temperature, heart rate and respiratory rate. Vital signs are to be performed twice a day on Days 1 through 3, at least 4 hours apart, and immediately prior to PK measurements.
h ECGs are to be performed at screening (in triplicate), 12 hours after the first dose of blinded study medication, and on Day 29.
i Adverse events are recorded from the time of the first dose of study medication.
j Serious adverse events are recorded from the time of consent in order to fulfil international regulatory requirements.
k G6PD phenotyping to be performed by both quantitative spectrophotometric analysis and rapid point of care test.
l Only if Day 90 ophthalmological exam shows abnormalities.
m Hematology includes hemoglobin, hematocrit, red blood cell/white blood cell/platelet counts, mean cell volume, white blood cell differential and reticulocyte count.

n Hematology and clinical chemistry on Day 3 must be reviewed prior to discharge from the hospital.
o Clinical Chemistry includes CPK, BUN, serum creatinine, total and indirect bilirubin and liver clinical chemistry.
p Mid-stream urine will be analyzed for protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen and leukocyte esterase by dipstick method.
q The pharmacogenetics sample must be collected at the earliest opportunity after randomization and during the in-clinic treatment visit (Days 1-3).
r Serum or urine pregnancy test that is routinely used at site with a test sensitivity for hCG level ≤ 25 mIU/mL. FSH serum test only for post-menopausal females with less than 6 months spontaneous amenorrhea.
s Refer to Section 6.5 of the protocol for details on health outcome data collection.
t Health outcomes assessments will only be collected at these visits from subjects with confirmed parasitemia or from subjects with clinically relevant hemolysis.
u Day 2 and Day 3 PK samples must be taken 6-12 hours and 24-48 hours post TQ dose.
v Treatment with blinded study medication will begin on either Day 1 or Day 2.

13.3. Appendix 3: Assessment Windows

13.3.1. Definitions of Assessment Windows for All Analyses

Visit	Analysis Window	
	Beginning Timepoint	Ending Timepoint
Day 1	Study Day 1	Study Day 1
Day 2	Study Day 2	Study Day2
Day 3	Study Day 3	Study Day 4
12 hours post randomised treatment[1]	11.5 hours post first dose of randomised treatment (Study Days 1-4)	12.5 hours post first dose of randomised treatment (Study Days 1-4)
Day 5	Study Day 5	Study Day 6
Day 8	Study Day 7	Study Day 9
Day 11	Study Day 10	Study Day 12
Day 15	Study Day 13	Study Day 17
Day 22	Study Day 19	Study Day 25
Day 29	Study Day 26	Study Day 32
Day 60	Study Day 53	Study Day 67
Day 90	Study Day 83	Study Day 97
Day 120	Study Day 110	Study Day 130
Day 150	Study Day 140	Study Day 160
Day 180	Study Day 166	Study Day 201

[1]For ECG parameters only

For all data summarised by visit, the nominal visit description will be used. Unscheduled and withdrawal visit data will be slotted into a scheduled visit window, if no competing visit exists within the window. If there are multiple assessments within the same window which are not unscheduled visits, the earliest result will be used in the summaries.

Note that the 12 hours post dose window is used only for the ECG parameters. If there are multiple measurements within the acceptable window, the assessment closest to the nominal visit description will be used in the summaries. If triplicate readings were taken, the mean of the triplicates will be used in the summaries.

13.4. Appendix 4: Treatment States and Phases

13.4.1. Treatment Phases

Treatment phases are not required for this study.

13.4.2. Treatment States

Adverse events will be classified according to time of occurrence relative to the start of the study treatment. No other treatment states are required for this study.

13.4.2.1. Treatment States for Adverse Event Data

Treatment State	Definition
Onset Time Since 1st Dose (Days)	If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on eCRF or value is missing.
Onset in Month 1	AE Start Date ≤ Study Day 29
Onset in Months 2 or 3	Study Day 30 ≤ AE Start Date < Study Day 91
Onset after Month 3	AE Start Date ≥ Study Day 91

NOTES:

- If the study treatment stop date is missing then the AE will be considered to be On-Treatment.

13.5. Appendix 5: Data Display Standards & Handling Conventions

13.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Tafenoquine 300 mg	TQ+CQ	1
B	Primaquine 15 mg	PQ+CQ	2

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

13.5.2. Baseline Definition & Derivations

13.5.2.1. Baseline Definitions

For all endpoints (expect as noted in the additional definitions below) the baseline value will be the latest pre-treatment assessment where treatment is their first dose of study medication (CQ/PQ/TQ/Placebo).

Asexual parasite and gametocyte counts

If there are multiple pre-treatment assessments, a subject will be considered to have a positive (non-zero) baseline count if *any* of the assessments are positive. They will only be considered to have a zero baseline count if all of the pre-treatment assessments are zero.

Pharmacogenetics

The PGx blood draw must be performed at the earliest opportunity after randomisation and during in-clinic treatment (Days 1-3). This will be considered baseline.

Ophthalmic assessments

The last assessment performed on the day of randomisation or earlier will be considered baseline.

13.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 13.5.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

13.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Area	: /arenv/arprod/sb252263/taf116564/final
QC Spreadsheet	: \\UK1DSNTV003\SB252263-TAFENOQUINE\Vivax Trt\TAF116564
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.13 & AdaM IG Version 1.0 • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated (see Section 4). • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DPs) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DPs, including: o Proportions and their Confidence Intervals will be presented to 3 decimal places. o Rates and their 95% Confidence Intervals will be presented to 1 decimal place
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses : • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: • Planned and actual time relative to study drug dosing will be shown in listings (Refer to

Reporting Standards	
IDSL Statistical Principle 5.05.1). • Unscheduled or unplanned readings will be presented within the subject's listings. • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables unless they slot into a missing planned visit (see Section 13.3.1) in which case they will be reported as the planned visit. • Unscheduled visits will not be included in figures unless they slot into a missing visit (see Section 13.3.1) in which case they will be reported as the planned visit. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

13.6. Appendix 6: Derived and Transformed Data

13.6.1. General

Multiple Measurements at One Time Point

- If there are multiple assessments within the same window which are not unscheduled visits, the earliest result will be used in the summaries. All values will be listed. For ECGs, if there are multiple assessments at the same visit, the mean will be derived and used in any derivation of summary statistics but if listed, all data will be presented.
- Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.

Study Day

- Calculated as the number of days from the date of the Study Day 1 (first dose of study medication including CQ):
  - Ref Date = Missing → Study Day = Missing
  - Ref Date < Date of Study Day 1 → Study Day = Ref Date – Date of Study Day 1
  - Ref Data ≥ Date of Study Day 1 → Study Day = Ref Date – (Date of Study Day 1) + 1
- Study Day 180 refers to a time point exactly 179 days after Study Day 1 (when the first dose of study medication including CQ was taken), whereas the 'Day 180 visit' refers to the nominal Day 180 assessments which did not necessarily occur on Study Day 180.

13.6.2. Study Population

Demographics

Age

- Only the year of birth is collected in the eCRF and the day and month are imputed as '30th June'.
- GSK standard IDSL algorithms are used to calculate age at baseline.
- Birth date will be presented in listings as 'YYYY'.
- Age on the date of first dose will be calculated in years.

Prior and Concomitant Medications

- Medications will be coded using the latest version of GSK Drug.
- Prior medications = medications taken up to 30 days before the date and time of the first dose of study medication.
- Any medications with stop dates earlier than 30 days will not be reported in tables and listings.
- Concomitant medications = medications with start date and time on or after the start date and time of the first dose of study medication (Study Day 1).
- See Section 13.7.2 for the handling of missing and partial dates.

Treatment Compliance and Exposure

- For the first three days of the study, all study medication will be administered in the presence of the Investigator or study nurse, and ingestion confirmed.
- On any day of in clinic dosing, a subject will be classified as compliant with daily administered dose if they do not vomit the initial dose or if they are successfully re-dosed.
- A subject is considered to be compliant in clinic if they retain all study medication given to them on all three days of dosing.
- Subjects will also take PQ or PQ placebo on Study Days 4 to 15, where administration is not directly observed (with the exception of G6PD-deficient subjects, who will receive directly-observed therapy on all 15 days).
- A patient will be considered to be compliant as an outpatient if their final pill count data shows they took at least 12 doses of PQ or PQ placebo.
- Compliance will also be determined using the Day 8 and Day 15 PK samples i.e. a quantifiable amount of carboxyPQ from samples taken at the Day 8 and Day 15 visits. No assessment windows will be applied.
- Subjects who were randomized but did not report a treatment start date will be categorised as having zero doses.
- Treatment stop dates are not recorded so duration of exposure will not be calculated.

G6PD enzyme activity as a percentage of site median

- Each site has a median G6PD enzyme value for healthy G6PD-normal subjects, determined from G6PD-normal males in study TAF115226:

Region	Country	Site	Investigator	Centre ID	G6PD median value (IU/g Hb)
South America	Brazil	Manaus	De Lacerda	PPD	7.92
	Peru	Iquitos	Llanos		9.01
	Colombia	Monteria	Velez		8.32
	Colombia	Cali	Villegas		7.17
Asia	Thailand	Bangkok	Krudsood		7.40
	Thailand	Umphang	Namaik-Larp		8.16
	Thailand	SMRU Shoklo Malaria Research Unit	Nosten		7.79
	Vietnam	Ho Chi Minh City	Tran		8.38

- Enzyme activity as percentage of site median = (absolute enzyme activity / site median) x 100%

13.6.3. Safety

Clinically Relevant Haemolysis
• Clinically relevant haemolysis is defined as: a decrease in haemoglobin of ≥30% or >30 g/L (>3 g/dL) from baseline; or, an overall drop in haemoglobin below 60 g/L (6.0 g/dL) at any visit after the first dose of study medication. • If a subject has any missing post-baseline haemoglobin data up to Study Day 17, the primary endpoint will be set to missing. • A subject will be classified as not having haemolysis at any visit if they do not meet the above haemoglobin criteria and no visits are missing up to Study Day X. • See Section 13.7.2.3 for further handling of missing data.

ECG Parameters
RR Interval
• ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value so no derivation is required.
Corrected QT Intervals
• QTcF will be derived at the site and entered into the eCRF.

Adverse Events
• All AEs reported up to and including the Day 180 visit following enrolment of a subject into the study will be documented. • These will be recorded and coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). All terms applied will be reviewed by a GSK physician prior to unblinding. If any malaria related coded terms are considered to have lost useful information in the coding step (e.g., if a verbatim term of '*Plasmodium vivax* malaria' is mapped to 'malaria'), he/she will recommend a study-specific code, which will be documented. The process will be completed prior to study unblinding. • Treatment emergent AEs are defined as AEs with an onset date and time on or after that of the start of first dose of study medication (including CQ). • AEs with entirely missing or unknown start dates will be assumed to be treatment emergent for reporting. AEs where the start date is equal to that of study medication, but where the start time is unknown will also be assumed to be treatment emergent. AEs with missing end dates are not anticipated to affect reporting. • If the grade/intensity is missing for an AE, it will be considered severe/Grade 3 if an AE, or Grade 4 if an SAE and the subject is alive, or Grade 5 if an SAE and the subject dies (i.e. the highest intensity possible) for the summary of AEs by maximum intensity. • See Section 13.7.2 for more information on missing and partial dates. • Common AEs are those occurring in ≥5% of subjects in any treatment group. • The occurrence of malaria and any associated signs and symptoms are recorded as Disease Related Events (DREs) and will not be classified as AEs. • The GSK clinical team will review terms that qualify as haematologically related.

Laboratory Parameters

- If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' is present, the number of decimal places of x will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  - Example 1: 2 Decimal Places = '< x' becomes x – 0.01
  - Example 2: 1 Decimal Place = '> x' becomes x + 0.1
  - Example 3: 0 Decimal Places = '< x' becomes x – 1

Absolute differentials and reticulocytes

- If sites provide white blood cell (WBC) differential (i.e., eosinophil, neutrophil, lymphocyte, monocyte and basophil) results as a percentage of total WBCs, these values will be converted to an absolute result (expressed in 10^9/L , equivalent to GI/L) for reporting purposes using the following formula:

  *Absolute differential (*10^9/L*) = 0.01x (percentage differential) x (WBC in 10^9/L).*
- If reticulocytes are reported as a proportion of total red blood cells (RBCs), these values will also be converted to an absolute result (expressed in 10^12/L, equivalent to TI/L) using the following formula:

  Absolute reticulocytes (10^12/L) = (reticulocytes as a proportion) x (RBC in 10^12/L).

Estimated Glomerular Filtration Rate (eGFR)

- eGFR will be defined using the abbreviated Modification of Diet in Renal Disease formula, when creatinine is in standard unites of µmol/L:

  $eGFR\ (ML/SEC/1.73M2) = 32788 \times (Creatinine)^{-1.154} \times (Age)^{-0.203} \times (0.742\ if\ female) \times (1.210\ if\ Black) \times 0.0167$
- A subject with a race of Black or African American or who has a mixed race including Black or African American will be considered Black for the purpose of the eGFR calculation.

Best Corrected Visual Acuity

- Best corrected visual acuity is assessed individually for each eye. In the eCRF, scores will be recorded as a ratio, for example 6/6, 6/7.5, or 6/9.5. These values will be used to derive a logMAR score for the statistical analysis, where logMAR = -1x $\log_{10}$ (ratio score). Thus, a ratio score of 6/9.5 corresponds to a logMAR score of 0.20.
- logMAR changes from baseline are classified as:
  - no change: <0.12
  - possible change: ≥0.12 to <0.3
  - definite change: ≥0.3

Vital Signs – Mean Arterial Blood Pressure
• To be calculated (to 1 decimal place) where systolic and diastolic blood pressure are both present at the same timepoint: $$mean\ arterial\ blood\ pressure = \frac{(systolic\ blood\ pressure + 2(diastolic\ blood\ pressure)}{3}$$

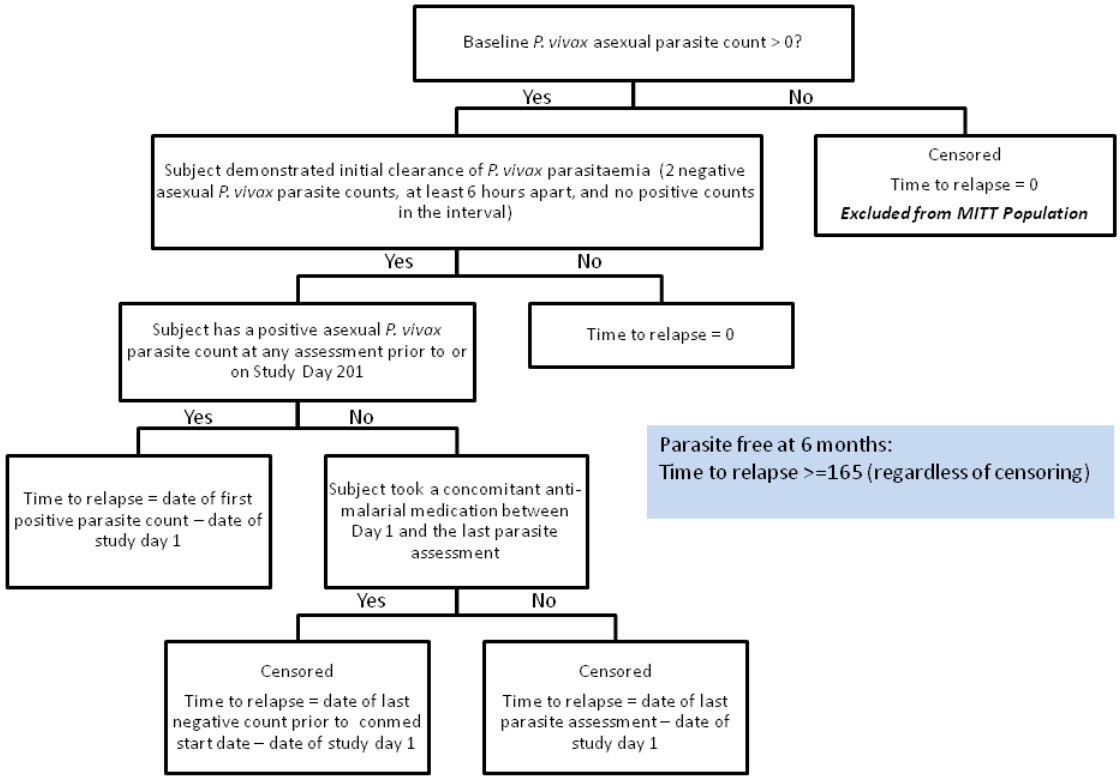
13.6.4. Efficacy

Relapse free efficacy and Time to Relapse
Six months

• A subject will be considered to have demonstrated relapse-free efficacy at 6 months for the purposes of the analysis if **all** of the following are true (also described in the flowchart below):
  • Subject had a non-zero *P. vivax* asexual parasite count at baseline. Subjects with no asexual *P. vivax* parasites at this time point will be censored with time to relapse = 0 days.
  • Subject demonstrated initial clearance of *P. vivax* parasitaemia. This is defined as two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval. Subjects who do not meet this criteria will be classified as relapses, with time to relapse = 0 days.
  • Subject has no positive asexual *P. vivax* parasite count at any assessment prior to or on Study Day 201 following initial parasite clearance. Subjects who do have a positive count will be classified as relapses, with time to relapse = (date of first positive count) – (date of Study Day 1) days.
  • Subject did not take a concomitant medication with anti-malarial activity at any point between Study Day 1 and their last parasite assessment. A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified accordingly. 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 last negative parasite assessment prior to concomitant medication start) – (date of Study Day 1). If a subject has not had a negative assessment prior to the concomitant medication start date, they will be censored at 0.
  • Subject is parasite-free at 6 months. This is defined as a negative asexual *P. vivax* parasite count at the first parasite assessment performed on or after Study Day 166.
• Subjects who do not have a positive asexual *P. vivax* parasite count following initial clearance but where the final parasite count occurred before Study Day 166 will not have been classified by the preceding rules. These subjects will be considered to be censored, with time to relapse censored at (Date of final parasite assessment) – (date of Study Day 1).
• If a subject has a relapse outcome and a censored outcome, they will be considered to be a relapse, even if the time point of the relapse is later than the time point of censoring. For example, a subject who took a medication with anti-malarial activity at Study Day 32, but remained parasite-free after initial clearance until Study Day 68 will be treated as a relapse at Study Day 68.

Relapse free efficacy and Time to Relapse

Flow chart of algorithm:



Four months

- A subject will be considered to have demonstrated relapse-free efficacy at 4 months for the purposes of the analysis if **all** of the following are true (also described in the flowchart below)::
  - Subject had a non-zero *P. vivax* asexual parasite count at baseline. Subjects with no asexual *P. vivax* parasites at this time point will be censored with time to relapse = 0 days.
  - Subject demonstrated initial clearance of *P. vivax* parasitaemia. This is defined as two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval. Subjects who do not meet this criteria will be classified as relapses, with time to relapse = 0 days.
  - Subject has no positive asexual *P. vivax* parasite count at any assessment prior to or on Study Day 130 following initial parasite clearance. Subjects who do have a positive count will be classified as relapses, with time to relapse = (date of first positive count) – (date of Study Day 1) days.
  - Subject did not take a concomitant medication with anti-malarial activity at any point between Study Day 1 and their first parasite assessment after Study Day 109 (up to and including Study Day 130). A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified accordingly. 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 last negative parasite assessment prior to concomitant medication start) – (date of Study Day 1). If a

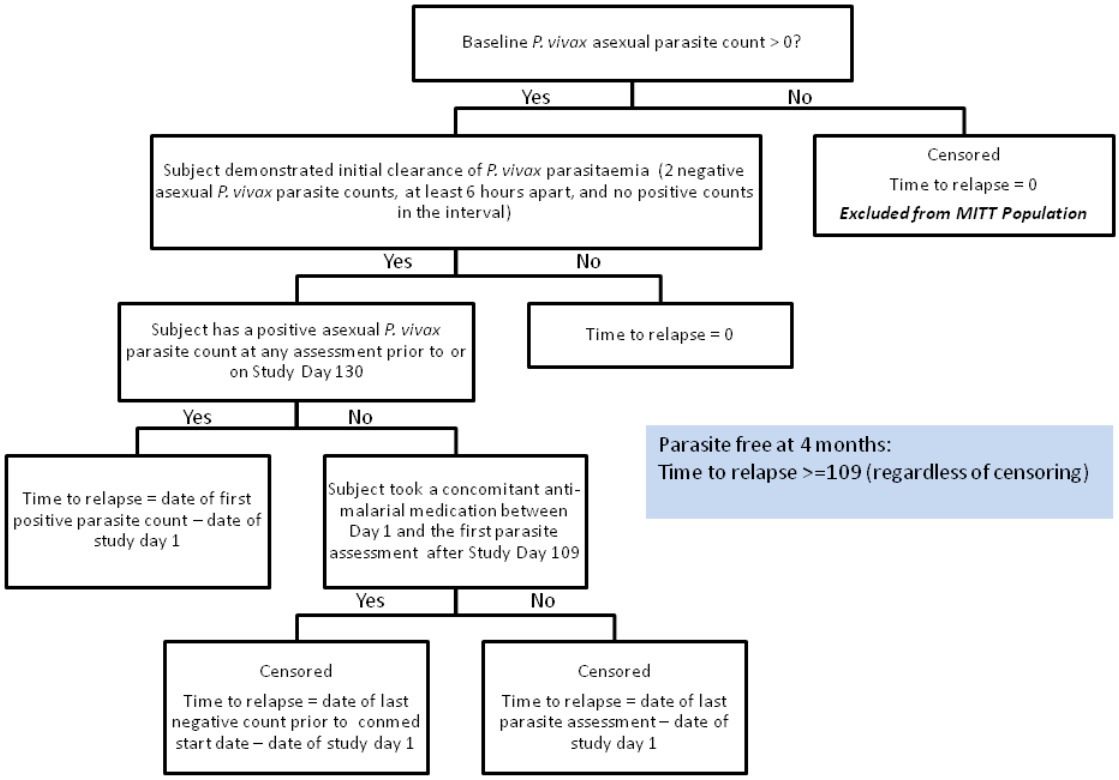
Relapse free efficacy and Time to Relapse

subject has not had a negative assessment prior to the concomitant medication start date, they will be censored at 0.

- Subject is parasite-free at 4 months. This is defined as a negative asexual *P. vivax* parasite count at the first parasite assessment performed after Study Day 109 (up to and including Study Day 130).

- Subjects who do not have a positive asexual *P. vivax* parasite count following initial clearance but where the final parasite count occurred on or before Study Day 109 will not have been classified by the preceding rules. These subjects will be considered to be censored, with time to relapse censored at (Date of final parasite assessment) – (date of Study Day 1).
- If a subject has a relapse outcome and a censored outcome, they will be considered to be a relapse, even if the time point of the relapse is later than the time point of censoring. For example, a subject who took a medication with anti-malarial activity at Study Day 32, but remained parasite-free after initial clearance until Study Day 68 will be treated as a relapse at Study Day 68.

Flow chart of algorithm:



Relapse free efficacy at 6 months missing=failure definition

- In addition to those with a positive asexual *P. vivax* parasite count at any assessment prior to or on Study Day 201, the following subjects will also be defined to have relapsed:
  - Subject did not demonstrate initial clearance of *P. vivax* parasitaemia (i.e. did not have

Relapse free efficacy and Time to Relapse
two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval) o Subject took a concomitant medication with anti-malarial activity at any point between Study Day 1 and their last parasite assessment. A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified accordingly. o Subject does not have a parasite assessment between Study Day 166 and 201. • Subjects with a zero *P. vivax* asexual parasite count at baseline will be excluded from the analysis.
Relapse free efficacy at 6 months missing on or after Day 29=failure definition
• In addition to those with a positive asexual *P. vivax* parasite count at any assessment prior to or on Study Day 201, the following subjects will also be defined to have relapsed: • Subject did not demonstrate initial clearance of *P. vivax* parasitaemia (i.e. did not have two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval) • Subject took a concomitant medication with anti-malarial activity at any point between Study Day 1 and their last parasite assessment. A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified accordingly. • Subject with a missing parasite assessment on or after the Day 29 assessment • Subjects with a zero *P. vivax* asexual parasite count at baseline will be excluded from the analysis.
Relapse free efficacy at 4 months missing=failure definition
• In addition to those with a positive asexual *P. vivax* parasite count at any assessment prior to or on Study Day 130, the following subjects will also be defined to have relapsed: o Subject did not demonstrate initial clearance of *P. vivax* parasitaemia (i.e. did not have two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval) o Subject took a concomitant medication with anti-malarial activity at any point between Study Day 1 and their last parasite assessment. A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified accordingly. o Subject does not have a parasite assessment between Study Day 110 and 130. • Subjects with a zero *P. vivax* asexual parasite count at baseline will be excluded from the analysis.
Genetic classification of relapse (heterologous/homologous)
• Relapse-free efficacy at 6 and 4 months will be assessed separately according to whether the re-infection is homologous or heterologous to the original infection. The definition is as detailed above but heterologous infections will be censored at the time at which they occur for the endpoint looking at homologous infections only; and homologous infections will be censored at

Relapse free efficacy and Time to Relapse
the time at which they occur for the endpoint looking at heterologous infections only. If the parasite genetics are missing, the subject will be censored at the time of event.

Incidence of recrudescence
Recrudescence

• A subject will be considered to have had a recrudescence if both of the following are true:
  ◦ Subject had a positive *P. vivax* asexual parasite count at baseline and demonstrates clearance (i.e. did not have two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval)
  ◦ Subject has a positive *genetica*lly homologous asexual *P. vivax* parasite count, after their zero count in days 1 to 5, but on or be*fore Stu*dy Day 32.
• The following subjects will have a censored time to recrudescence of 0 days:
  ◦ Subject had no asexual *P. vivax* parasites at baseline.
  ◦ Subject had *a posit*ive *P. vivax* asexual parasite count at baseline but had no subsequent zero asexual parasite count within Study Days 1-5.
• If a subject does not meet the definition of recrudescence, but took a concomitant medication with anti-malarial activity between Study Day 1 and Study Day 32, they will be censored, with time to recrudescence censored at (date of last negative parasite assessment prior to concomitant medication start) – (date of Study Day 1). If a subject has not had a negative assessment prior to the concomitant medication start date, they will be censored at 0.
• All other subjects will be censored with time to recrudescence censored at their last parasite assessment on or before Study Day 32, with time to recrudescence = (Date of final parasite assessment) – (date of Study Day 1).

Clearance time
Parasite (PCT)
• Defined as: time needed to clear asexual parasite from the blood i.e. parasite numbers falling below the limit of detection in the thick blood smear and remaining undetectable ≥6 hours later. • If a subject has a non-zero asexual *P. vivax* parasite count at baseline, and prior to Study Day 8 has two negative counts with at least 6 hours between the counts and no positive parasite counts within this time period, parasite clearance time will be defined as the time elapsed between the first dose of study medication (including CQ) and the first of these negative counts (measured in hours). • Subjects with a negative parasite count at baseline will be censored with a parasite clearance time of 0 hours. All other subjects will be censored at the time of the last non-missing assessment prior to Study Day 8.
Fever (FCT)
• Defined as: time from first dose of treatment to the time when body temperature falls to normal within Study Days 1-4 and remains normal for at least 48 hours up to the Day 8 visit. • Any subject who does not have a temperature in excess of 37.4^0C at any point prior to the first dose of study medication (including CQ) on Study Day 1 will be censored with a fever clearance time of 0 hours. Subjects will also be censored at time 0 if the method of temperature measurement is not consistent throughout Study Days 1 to 4 (i.e., method is not consistently oral, tympanic, or axillary).

Clearance time
• Fever clearance is considered to have been achieved once an initial temperature of >37.4^{0}C is reduced to a value ≤37.4^{0}C, in the absence of value >37.4^{0}C in the following 48 hours up to the Day 8 visit. • Subjects who do not demonstrate this endpoint prior to or on the final assessment of Study Day 4 will be censored at that time point. • As temperature is only collected twice a day whilst subjects are in the hospital, they may not have assessments for the 48 hours following an initial temperature if this occurs after they have been discharged. Clearance will be defined based on observed data only.
Gametocyte (GCT)
• Defined as: time from first dose until the first slide that was gametocyte negative and remained so at the next slide reading. • Any subject with negative *P. vivax* gametocytes at baseline will be censored with a time to gametocyte clearance of 0 days. • For all other subjects, gametocyte clearance will be considered to have been achieved once a negative gametocyte value has been seen, unless the next gametocyte count is positive. Time to clearance will then be defined as (time to first negative value) – (time of first dose of study medication including CQ). • Subjects who fail to reach this endpoint will be censored at the visit of their final gametocyte assessment.

Gametocyte emergence
• Gametocyte emergence is defined as the presence of *P. vivax* gametocytes at a post-baseline visit, where the subject did not have gametocytes at baseline.

Early Failure

• An early failure is defined as a subject who either:
  • Did not demonstrate initial clearance of *P. vivax* parasitaemia (i.e. did not have two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval), OR
  • Demonstrates initial clearance and has a subsequent non-zero asexual *P. vivax* parasite count on or before Study Day 32.

13.6.5. Healthcare Resource Use

Currency Conversion

- To convert local currencies into a comparable combinable unit, all currencies will be converted into US Dollars (USD), at the exchange rate obtained from xe.com reported for 15 February 2015 (accessed on 23JUL2016). This date was chosen as a midpoint in the study.

Currency	USD per unit
Brazilian Real	0.3528270266
Peruvian Sol	0.3272251315

Currency Conversion			
	Colombian Peso	0.0004193751	
	Thai Baht	0.0306701426	
	Vietnamese Dong	0.0000468165	

13.6.6. Exploratory G6PD and CYP-2D6 Genotype Analyses

G6PD Mutations

Emory Genetics Laboratory will provide a description of the G6PD mutation (such as Vanua Lava (c.383T>C, p.L128P- exon 5) het). In addition, the WHO classification of G6PD enzyme deficiency will be provided for each mutation observed

CYP2D6 Activity and Metabolizer Phenotype

- Quest Nichols laboratory will provide CYP2D6 *alleles which will be used to derive metabolizer class (PM, IM, EM, UM)
- Each of the two CYP2D6 *alleles, comprising the genotype, will be assigned a value relative to its activity compared to the *1 reference allele:
  - Value of 0 for null activity alleles: *3, *4, *4xN, *5, *6, *7, *8, *11, *12,*13, *15, *16, *19, *20, *21, *38, *40, *42, *56B
  - Value of 0.5 for reduced activity alleles: *9, *10, *17, *29, *41
  - Value of 1 for fully functional alleles: *1, *2, *33, *35
  - Value of 2 for fully functional alleles carrying gene duplications: *1xN, *2xN, *33xN, *35xN
  - For all *alleles that are not captured above, the activity score will be determined prior to unblinding the data.
- Alleles denoting gene duplications, represented by 'xN', will receive double the non-duplicated value. For example *1xN will receive a value of 2 whereas *1 receives a value of 1.
- The CYP2D6 Activity Score (AS) [Gaedigk, 2008] is then calculated as the sum of activity values from the two alleles comprising the genotype. For example, a subject with 2 null alleles will have an AS of 0; one null and one reduced activity allele will have a score of 0.5; or one null allele and one fully functional allele will have an AS of 1.
- The CYP2D6 phenotype will be classified based on the AS and follows the Dutch Pharmacogenomics Working Group [DPWG] classification scheme.
  - Poor metabolizer (PM) if AS = 0
  - Intermediate metabolizer (IM) if AS = 0.5 or 1
  - Extensive metabolizer (EM) if AS is 1.5 or 2
  - Ultrametabolizer (UM) if AS ≥2.5

13.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

13.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion is defined as a subject that does not withdraw from the study and attends the Day 180 visit. • Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

13.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument : o These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects with outlying results may be excluded in additional *ad hoc* summaries and/or statistical analyses. These will be documented along with the reason for exclusion in the clinical study report, but the primary conclusions will remain based on the full population sets.

13.7.2.1. Handling of Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• It is not possible to record partial dates in the eCRF for AEs. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • AEs with entirely missing or unknown start dates will be assumed to be treatment emergent for reporting. • AEs with missing end dates are not anticipated to affect reporting.
Concomitant medications	• Where the start or stop date of a concomitant medication record is entirely unknown and is totally missing at the time of reporting, the eCRF flags 'Taken prior to study?' and 'Ongoing medication?' will be used in order to derive whether it is prior or concurrent. • If these flags are also missing, then it will be assumed that it is concurrent.

Element	Reporting Detail
	• In the event that use of the same medication is recorded at more than one visit (and if this has not been collapsed to one record), the eCRF flags will be cross-checked for both records.

13.7.2.2. Handling of Partial Dates

Element	Reporting Detail

Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
	• The recorded partial date will be displayed in listings.

Adverse Events	• It is not possible to record partial dates in the eCRF for AEs.
Date of birth	• Where a subject's date and month of birth is not known, the investigator has been asked to enter them as 30th June, and where month is known but date is unknown, the investigator has been asked to enter the 15th. • Thus all subjects should have an actual or an assumed date of birth entered on the eCRF. • In the event that any partial dates do occur for date of birth, age should be calculated using 30th June for an unknown date and month, and 15th for an unknown date only. • Only the year will be displayed in listings.

13.7.2.3. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Incidence of Haemolysis	• For the primary analysis only observed data will be used. • A sensitivity analysis will be performed where missing haemolysis data before Study Day 17 will be imputed as 'haemolysis=YES'.
Relapse-free efficacy and time to event endpoints	• For all analyses of the mITT population, subjects will not be excluded from any statistical analyses. • From the Day 29 assessment onwards, subjects who have not relapsed but fail to have an evaluable parasite smear within the visit window for every scheduled visit will be excluded from the PP population. • See Section 13.6.4 for further details on how missing assessments will be censored.
Derived variables	• For derived variables, details of how any missing eCRF data will be handled are provided in Section 13.6.

13.8. Appendix 8: Values of Potential Clinical Importance

13.8.1. Laboratory Values

Element	Reporting Detail
F1 flag	• Denotes a value that falls outside the normal range. • Used by the laboratory and provided directly by the site for inclusion on the database.
F2 flag	• Denotes a value that has increased or decreased from baseline by more than a specified amount. • Defined below

F3 flag	• Denotes a value that falls outside an extended normal range.
	• This range is independent of direction of change or other values.
	• F3 range is calculated as:
	  • Absolute: pre-specified limits.
	  • Proportional: upper and lower limits are defined by multiplying the normal range limits by different factors
	• Defined below

General	• If a subject has both 'high' and 'low' values flagged for a parameter during the study, they will be reported once under each category.

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Haemoglobin	G/L	F2	Max(baseline – >30 g/L, ≥30% decline from baseline)	
Platelets	10^9/L	F3	50	
Leukocytes	10^9/L	F3	2	
Neutrophils, segmented	10^9/L	F3	1	
Eosinophils	10^9/L	F3		1.5
Lymphocytes	10^9/L	F3	0.5	4
Methaemoglobin	%	F3		10
Reticulocytes	10^12/L	F3		1xULN

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Creatine kinase [a]	IU/L	F3		5x ULN
Creatinine[a]	μmol/L	F2		3x baseline
		F3		3x ULN
Urea [b]	mmol/L	F3		11.067
Estimated glomerular filtration rate[a]	ml/sec/ 1.73m^2	F3	0.4843	
Alanine aminotransferase	IU/L	F3		3x ULN
Aspartate aminotransferase	IU/L	F3		3x ULN
Total bilirubin	μmol/L	F3		1.5x ULN
Indirect bilirubin	μmol/L	F3		1.5x ULN
Alkaline phosphatase	IU/L	F3		2.5xULN

a. CTC AE criteria
b. FDA industry toxicity grading scale for healthy volunteer adults and adolescents in preventative vaccine trials

13.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	**Upper**
Absolute			
Absolute QTc Interval	msec		> 480
Change from Baseline			
Increase from Baseline QTc	msec		> 60

Note: both criteria (absolute and change from baseline) must be met to be of clinical concern.

13.9. Appendix 9: Multicenter Studies

13.9.1. Methods for Handling Centres

- In this multicentre global study, enrolment will be presented by investigative site and country.
- Regions are defined geographically for inclusion as covariates as:

Region	Countries
South America	Brazil, Peru, Colombia
Asia	Thailand, Vietnam

Centers will be pooled for assessing the primary assessment of incidence of clinically relevant hemolysis.

13.10. Appendix 10: Examination of Covariates, Subgroups & Other Strata

13.10.1. Handling of Covariates, Subgroups & Other Strata

Region is defined as in Section 13.9.1. Section 8.1.2 details how the impact of region will be assessed.

The chloroquine supply date category is defined as whether subjects received chloroquine before or on/after 31st August 2015. Section 8.1.2 details how the impact of this will be assessed.

13.11. Appendix 11: Multiple Comparisons & Multiplicity

13.11.1. Handling of Multiple Comparisons & Multiplicity

No multiple comparisons will be performed in this study and so no adjustments for multiplicity are required.

13.12. Appendix 12: Model Checking and Diagnostics for Statistical Analyses

13.12.1. Statistical Analysis Assumptions

If models are not deemed appropriate following the checks described below, alternative appropriate methods (e.g. Fisher's exact test) will be additionally performed.

13.12.1.1. Cox proportional hazards model

The proportional hazards assumption should be assessed including a check of the Kaplan-Meier curves. The shape of the curves should be similar for the 2 treatment groups with the separation between the curves remaining proportional across time. A complementary log-log plot may also be used to check the proportional hazards assumption.

13.12.1.2. Logistic Regression

Model checking may include goodness of fit tests and residual plots (Pearson and deviance residuals to detect outliers and/or influential points).

13.13. Appendix 13 – Abbreviations & Trade Marks

13.13.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
A&R	Analysis and Reporting
AS	Activity Score
BMI	Body Mass Index
Bun	Blood Urea Nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CQ	Chloroquine
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DRE	Disease-Related Event
DP	Decimal Places
DPWG	Dutch Pharmacogenomics Working Group
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
eGFR	Estimated Glomerular Filtration Rate
FCT	Fever Clearance Time
G	Gram
G6PD	Glucose-6-phosphate dehydrogenase
GCSP	Global Safety and Pharmacovigilance
GCT	Gametocyte Clearance Time
GSK	GlaxoSmithKline
Hb	Haemoglobin
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IVRS	Interactive Voice Recognition System
ITT	Intent-To-Treat
GUI	Guidance
kg	Kilogram
L	Litre
LFT	Liver Function Tests
mITT	Microbiologic Intent To Treat
m	Metre

Abbreviation	Description
MedDRA	Medical Dictionary for Regulatory Activities
MetHb	Methaemoglobinemia
MPV	Major Protocol Deviation
mg	Milligram
msec	Millisecond
PCI	Potential Clinical Importance
PCR	Polymerase Chain Reaction
PCT	Parasite Clearance Time
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
P. falciparum	*Plasmodium falciparum*
PGx	Pharmacogenetics
PK	Pharmacokinetic
PP	Per Protocol
PQ	Primaquine
P. vivax	*Plasmodium vivax*
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RBC	Red Blood Cell
RUCAM	Roussel Uclaf Causality Assessment Method
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	Standard Operation Procedure
SPM	Study Procedures Manual
TA	Therapeutic Area
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures & Listings
TQ	Tafenoquine
ULN	Upper Limit of Normal
USD	United States Dollars
V/F	Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organisation

13.13.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

13.14. Appendix 14: List of Data Displays

13.14.1. Data Display Numbering

Section	Tables	Figures
Study Population	1.1 to 1.22	None
Efficacy	2.1 to 2.32	2.1 to 2.4
Safety	3.1 to 3.56	3.1 to 3.48
Pharmacogenetics	5.1 to 5.4	None
Health Outcomes	6.1 to 6.12	None
Section	**Listings**	
ICH Listings	1 to 19	
Other Listings	20-38	

13.14.2. Deliverable

Delivery	Description
SAC	Final Statistical Analysis Complete
Headline	Headline Results

13.14.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Populations Analysed					
1.1.	All Subjects Screened	SA1	Summary of Analysis Populations	IDSL	Headline
Subject Disposition					
1.2.	Safety	IE1	Summary of Inclusion/Exclusion Criteria Deviations		SAC
1.3.	Safety	ES1	Summary of Subject Disposition	ICH E3, GSK CTR, FDAAA, EudraCT	SAC
1.4.	Safety	SA3	Summary of Discontinuation of Study Medication		SAC
1.5.	Safety	SA2	Summary of Study Recruitment – Number of Subjects by Country and Centre	EudraCT	Headline
1.6.	All Subjects Screened	ES6	Summary of Reasons for Screen Failure	Journal Requirements Add footnote: 'G6PD normal females screened after randomisation was closed to normal females had reason recorded as Investigator Discretion.'	SAC
Protocol Deviations					
1.7.	Safety	DV1B	Summary of Important Protocol Deviations	ICH E3	SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Demographic and Baseline Characteristics					
1.8.	Safety	DM1	Summary of Demographic Characteristics	ICH E3, GSK CTR, FDAAA, EudraCT Include age, sex, ethnicity, weight, height, BMI, respiratory rate, G6PD enzyme activity, G6PD enzyme activity (as % of site median). Height, Weight, BMI, and respiratory rate are collected in DMDATA. VITALS where VISITNUM=10 and PTMNUM=20. G6PD enzyme activity is collected in DMDATA.LAB where VISITNUM=10 and LBTESTCD='G6PD_BLC'. All other parameters are collected on DMDATA.DEMO	Headline
1.9.	Safety	DM5	Summary of Race and Racial Combinations	ICH E3, GSK CTR, FDA, FDAAA, EudraCT	SAC
1.10.	Safety	DM6	Summary of Race and Racial Combinations Details	ICH E3, FDA	SAC
Prior and Concomitant Medications and Conditions					
1.11.	Safety	CM1	Summary of Prior Medications	Add footnote 'Only medications taken prior to the start date and time of first dose of study medication, and within 30 days of Study Day 1 are included.' ICH E3	SAC
1.12.	Safety	CM1	Summary of Concomitant Medications	ICH E3	Headline
1.13.	Safety	CM1	Summary of Paracetamol Usage		SAC
1.14.	Safety	SA4	Summary of Malarial Signs and Symptoms		SAC
1.15.	Safety	MH1	Summary of Current Medical Conditions by Body System	ICH E3	SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.16.	Safety	MH1	Summary of Past Medical Conditions by Body System	ICH E3	SAC
1.17.	Safety	MH4	Summary of Current Specific Medical Conditions		SAC
1.18.	Safety	MH4	Summary of Past Specific Medical Conditions		SAC
1.19.	Safety	SA5	Summary of Splenomegaly at Baseline		SAC
1.20.	Safety	SA6	Summary of Previous Episodes of Malaria		SAC
Exposure and Treatment Compliance					
1.21.	Safety	SA7	Summary of Study Medication Compliance and Exposure	ICH E3	Headline – excluding PQ PK data SAC – including PQ PK data
Diagnostic					
1.22.	All subjects screened	SA8	Comparison of G6PD point of care test versus G6PD enzyme activity test		SAC

13.14.4. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Parasite counts					
2.1.	mITT	SA9	Summary of *P.vivax* Asexual Parasites at all Timepoints (count per ml)		SAC
2.2.	mITT	SA10	Summary of Other Malarial Asexual Parasites at all Timepoints (count per ml)	Page by parasite	SAC
2.3.	mITT	SA10	Summary of *P.vivax* Gametocytes at all Timepoints (count per ml)		SAC
2.4.	mITT	SA10	Summary of Other Malarial Gametocytes at all Timepoints (count per ml)	Page by gametocyte	SAC
Relapse-free efficacy					
2.5.	mITT	SA11	Summary of Relapse-Free Efficacy at 6 Months		SAC
2.6.	PP	SA12	Summary of Relapse-Free Efficacy at 6 Months		SAC
2.7.	mITT	SA13	Summary of Relapse-Free Efficacy at 4 Months		SAC
2.8.	PP	SA14	Summary of Relapse-Free Efficacy at 4 Months		SAC
2.9.	mITT	TTE6	Survival Analysis of Relapse-Free Efficacy over 6 Months		Headline
2.10.	PP	TTE6	Survival Analysis of Relapse-Free Efficacy over 6 Months		Headline
2.11.	mITT	TTE6	Survival Analysis of Relapse-Free Efficacy over 4 Months		Headline
2.12.	PP	TTE6	Survival Analysis of Relapse-Free Efficacy over 4 Months		Headline
2.13.	mITT	SA15	Analysis of Relapse-Free Efficacy at 6 Months (Logistic Regression) (Subjects Censored Prior to 6 Months Excluded)		Headline
2.14.	mITT	SA15	Analysis of Relapse-Free Efficacy at 4 Months (Logistic Regression) (Subjects Censored Prior to 4 Months Excluded)		Headline

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.15.	mITT	SA15	Analysis of Relapse-Free Efficacy at 6 Months (Logistic Regression) (Missing=Failure Analysis)	Add footnotes: "Subjects who do not demonstrate initial clearance, take a concomitant medication with anti-malarial activity or have a missing Day 180 assessment are counted as relapses." "Subjects with a zero *P. vivax* asexual parasite count at baseline are excluded from the analysis."	Headline
2.16.	mITT	SA15	Analysis of Relapse-Free Efficacy at 4 Months (Logistic Regression) (Missing=Failure Analysis)	Add footnotes: "Subjects who do not demonstrate initial clearance, take a concomitant medication with anti-malarial activity or do not have an assessment between Study Day 110 and 130 are counted as relapses." "Subjects with a zero *P. vivax* asexual parasite count at baseline are excluded from the analysis."	Headline
2.17.	mITT	SA15	Analysis of Relapse-Free Efficacy at 6 Months (Logistic Regression) (Missing on or after Study Day 29=Failure Analysis)	Add footnotes: "Subjects who do not demonstrate initial clearance, take a concomitant medication with anti-malarial activity or have a missing assessment on or after Study Day 29 are counted as relapses." "Subjects with a zero *P. vivax* asexual parasite count at baseline are excluded from the analysis."	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.18.	mITT	TTE6	Survival Analysis of Relapse-Free Efficacy over 6 Months – Homologous Relapses Censored	Add footnote: Homologous relapses and relapses with missing parasite genetics are censored at the point at which they occur. X subjects have missing parasite genetics.	SAC
2.19.	mITT	TTE6	Survival Analysis of Relapse-Free Efficacy over 6 Months – Heterologous Relapses Censored	Add footnote: Heterologous relapses and relapses with missing parasite genetics are censored at the point at which they occur. X subjects have missing parasite genetics.	SAC
2.20.	mITT	TTE6	Survival Analysis of Relapse-Free Efficacy over 4 Months – Homologous Relapses Censored	Add footnote: Homologous relapses and relapses with missing parasite genetics are censored at the point at which they occur. X subjects have missing parasite genetics.	SAC
2.21.	mITT	TTE6	Survival Analysis of Relapse-Free Efficacy over 4 Months – Heterologous Relapses Censored	Add footnote: Heterologous relapses and relapses with missing parasite genetics are censored at the point at which they occur. X subjects have missing parasite genetics.	SAC
2.22.	mITT	SA37	Summary of Covariate and Treatment*Covariate Interaction Significance For Cox Proportional Hazards Model of Relapse-Free Efficacy over 6 Months		SAC
2.23.	mITT	TTE6	Survival Analysis of Relapse-Free Efficacy over 6 Months - by Chloroquine Supply Date Category		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.24.	mITT	TTE6	Survival Analysis of Relapse-Free Efficacy over 4 Months - by Chloroquine Supply Date Category		SAC
Time to Event endpoints					
2.25.	mITT	TTE3	Analysis of Parasite Clearance Time	Give time in hours	SAC
2.26.	mITT	TTE3	Analysis of Fever Clearance Time	Give time in hours	SAC
2.27.	mITT	TTE3	Analysis of Gametocyte Clearance Time	Give time in days	SAC
Other efficacy endpoints					
2.28.	mITT	SA23	Summary of *P. vivax* Gametocyte Emergence		SAC
2.29.	mITT	TTE7	Analysis of Recrudescence (Blood Stage Failure) Rates		SAC
2.30.	mITT	SA24a	Summary of Early Failures		SAC
2.31.	mITT	SA24b	Summary of Genetic Classification by PCR of Relapse Infections Occurring on or After Study Day 33		SAC
2.32.	mITT	SA25	Summary of *P. falciparum* Asexual Parasite Emergence	Change display to a listing if 5 or fewer subjects in total	SAC
CYP2D6					
2.33.	mITT	SA45	Analysis of Subjects with Relapse-Free Efficacy at 6 Months by CYP2D6 Metaboliser Class – Logistic Regression – PM and IM vs EM+UM		SAC
2.34.	mITT	SA45	Analysis of Subjects with Relapse-Free Efficacy at 6 Months by CYP2D6 Metaboliser Class – Logistic Regression – IM vs EM		SAC
2.35.	mITT	SA37	Effect of CYP2D6 Activity Score (AS) on Relapse-Free Efficacy at 6 Months – Logistic Regression		SAC

13.14.5. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Relapse-free efficacy					
2.1.	mITT	SF4	Kaplan-Meier Survival Curves for Relapse-Free Efficacy over 6 Months		Headline
2.2.	PP	SF4	Kaplan-Meier Survival Curves for Relapse-Free Efficacy over 6 Months		SAC
2.3.	mITT	SF4	Kaplan-Meier Survival Curves for Relapse-Free Efficacy over 6 Months – Homologous Relapses Censored	Add footnote: Homologous relapses and relapses with missing parasite genetics are censored at the point at which they occur. X subjects have missing parasite genetics.	SAC
2.4.	mITT	SF4	Kaplan-Meier Survival Curves for Relapse-Free Efficacy over 6 Months – Heterologous Relapses Censored	Add footnote: Heterologous relapses and relapses with missing parasite genetics are censored at the point at which they occur. X subjects have missing parasite genetics.	SAC
2.5.	mITT	SF5	Frequency (95% Confidence Interval) of Genetically Homologous and Genetically Heterologous Infections Occurring on or After Study Day 33		SAC

13.14.6. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Incidence of haemolysis					
3.1.	Safety	SA40	Analysis of Incidence of Haemolysis		Headline
3.2.	Safety	SA40	Analysis of Incidence of Haemolysis (Missing data sensitivity analysis)	Exclude 'Missing' row. Add footnote to say 'Missed visits up to Study Day 17 have been imputed as Yes'	Headline
Adverse Events (AEs)					
3.3.	Safety	AE1	Summary of All Treatment Emergent Adverse Events by Treatment by System Organ Class	ICH E3 Add footnote: 'Events are ordered based on Total incidence'	SAC
3.4.	Safety	AE3	Summary of Common Treatment Emergent Adverse Events (>=5% in Any Treatment Group) by Preferred Term	ICH E3, GSK CTR Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	Headline
3.5.	Safety	AE15	Summary of Common (>=5% in Any Treatment Group) Non-serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC
3.6.	Safety	AE3	Summary of All Drug-Related Treatment Emergent Adverse Events by Treatment by Preferred Term	GSK CTR Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	Headline
3.7.	Safety	AE5	Summary of Treatment Emergent Adverse Events by Maximum Intensity	Add footnote: 'Events are ordered based on Total incidence'	SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.8.	Safety	AE3	Summary of All Treatment Emergent Adverse Events by Treatment by Preferred Term	Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	SAC
3.9.	Safety	AE3	Summary of Treatment Emergent Adverse Events with Onset On or Prior to Study Day 29	Add footnote: 'Events are ordered based on Total incidence'	Headline
3.10.	Safety	AE3	Summary of Treatment Emergent Adverse Events with Onset Date in Month 2 or 3	Add footnote: 'Events are ordered based on Total incidence'	SAC
3.11.	Safety	AE3	Summary of Treatment Emergent Adverse Events with Onset On After Month 3	Add footnote: 'Events are ordered based on Total incidence'	SAC
Serious and Other Significant Adverse Events					
3.12.	Safety	AE3	Summary of Fatal Serious Treatment Emergent Adverse Events	GSK CTR Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	SAC
3.13.	Safety	AE1	Summary of Serious Treatment Emergent Adverse Events by System Organ Class	GSK CTR, IDSL Add footnote: 'Events are ordered based on Total incidence'	SAC
3.14.	Safety	AE3	Summary of Serious Treatment Emergent Adverse Events by Preferred Term	GSK CTR Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	Headline

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.15.	Safety	AE3	Summary of Drug-Related Treatment Emergent Serious Adverse Events by Preferred Term	GSK CTR Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	SAC
3.16.	Safety	AE3	Summary of Drug-Related Fatal Serious Treatment Emergent Adverse Events by Preferred Term	GSK CTR Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	SAC
3.17.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAA, EudraCT	SAC
3.18.	Safety	AE3	Summary of Treatment Emergent Adverse Events Leading to Withdrawal from the Study	IDSL Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	Headline
3.19.	Safety	AE3	Summary of Treatment Emergent Adverse Events Leading to Discontinuation of Study Treatment	IDSL Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	Headline
3.20.	Safety	AE1	Summary of Treatment Emergent Adverse Events Considered to be Haematologically-Related	Add footnote: 'Events are ordered based on Total incidence'	Headline
3.21.	Safety	AE3	Summary of Grade 3 and Grade 4 Treatment-Emergent Adverse Events by Preferred Term	Include Grade 3 and Grade 4 events only. Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Laboratory: Chemistry					
3.22.	Safety	SA35	Summary of Clinical Chemistry Data by Treatment and Time	Remove sex column	Headline
3.23.	Safety	SA36	Summary of Change from Baseline in Clinical Chemistry Data by Treatment and Time	ICH E3 Remove sex column	Headline
3.24.	Safety	LB2	Summary of Clinical Chemistry Laboratory Data Outside the Reference Range (F3)		SAC
Laboratory: Haematology					
3.25.	Safety	SA35	Summary of Haematology Data by Treatment, Time and Sex		Headline
3.26.	Safety	SA36	Summary of Change from Baseline in Haematology Data by Treatment, Time and Sex	ICH E3	Headline
3.27.	Safety	LB2	Summary of Haematology Laboratory Data Outside the Reference Range (F3)		SAC
3.28.	Safety	SA26	Summary of Categories of Change from Baseline Haemoglobin (G/L)) Data by Treatment and Time		SAC
3.29.	Safety	SA26	Summary of Categories of Change from Baseline Haemoglobin (G/L)) Data by Treatment, Time and Sex	Add sex column	Headline
3.30.	Safety	SA41	Summary of Haemoglobin Declines over First 29 Days		SAC
3.31.	Safety	SA41	Summary of Haemoglobin Declines over First 29 Days by Sex	Add sex column	SAC
Laboratory: Urinalysis					
3.32.	Safety	UR1	Summary of Urinalysis Dipstick Results	IDSL	SAC
Hepatobiliary (Liver)					
3.33.	Safety	LIVER1	Summary of Liver Events Assessment	IDSL	SAC
3.34.	Safety	LIVER2	Summary of Time on Treatment Before Liver Event		SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.35.	Safety	LIVER3	Summary of Liver Biopsy Details		SAC
3.36.	Safety	LIVER4	Summary of Liver Imaging Details		SAC
ECG					
3.37.	Safety	EG1	Summary of ECG Findings	IDSL	SAC
3.38.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL At baseline, 12 hours post-first dose of randomised study medication, Day 29	SAC
3.39.	Safety	SA27	Summary of QTcF Values by Category and Visit	At baseline, 12 hours post-first dose of randomised study medication, Day 29	Headline
3.40.	Safety	CP_EG12	Summary of Maximum Change from Baseline QTcF up to 72 hours Post Randomised Treatment		Headline
Vital signs					
3.41.	Safety	VS1	Summary of Absolute Values in Vital Signs by Visit	ICHE3 Include Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Blood Pressure, Heart Rate, Respiratory Rate and Temperature	SAC
3.42.	Safety	VS1	Summary of Change From Baseline in Vital Signs by Visit	ICHE3 Include Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Blood Pressure, Heart Rate, Respiratory Rate and Temperature	SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Ophthalmic Assessments					
3.43.	Ophthalmic Safety	SA29	Summary of Keratopathy	If no keratopathy is reported, display should be blank with 'No subjects reported keratopathy displayed'	SAC
3.44.	Ophthalmic Safety	SA30	Summary of Slit Lamp Assessments		SAC
3.45.	Ophthalmic Safety	SA30	Summary of Humphrey Perimetry Assessments		SAC
3.46.	Ophthalmic Safety	SA32	Summary of Colour Perception Assessments		SAC
3.47.	Ophthalmic Safety	SA33	Summary of Best Corrected Visual Acuity Test Scores		SAC
3.48.	Ophthalmic Safety	SA34	Summary of Best Corrected Visual Acuity Classification		SAC
3.49.	Ophthalmic Safety	SA28	Summary of Hyperpigmentation		SAC
3.50.	Ophthalmic Safety	SA28	Summary of Hypopigmentation		SAC
3.51.	Ophthalmic Safety	SA28	Summary of Appearance of Retinal Vessel		SAC
3.52.	Ophthalmic Safety	SA28	Summary of Optic Nerve Pallor		SAC
3.53.	Ophthalmic Safety	SA28	Summary of Confounding Abnormalities		SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.54.	Ophthalmic Safety	SA28	Summary of Retinal Changes from Baseline	Exclude baseline rows. Categories will be 'no change', 'questionable change', 'definite change', 'cannot grade'	SAC
Blood Transfusions					
3.55.	Safety	SA38	Summary of Blood Transfusions		SAC

13.14.7. Safety Figures

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Incidence of haemolysis					
3.1.	Safety	SF3	Incidence of Haemolysis by Treatment Group		SAC
Adverse Events					
3.2.	Safety	AE10	Plot for Common Adverse Events (>=5% in Any Treatment Group) by Overall Frequency	IDSL	SAC
Clinical laboratory endpoints					
3.3.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Eosinophils		SAC
3.4.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Haemoglobin		SAC
3.5.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Haematocrit		SAC
3.6.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Lymphocytes		SAC
3.7.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Mean Corpuscle Volume		SAC
3.8.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Methaemoglobin (%)		SAC
3.9.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Segmented Neutrophils		SAC
3.10.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Platelet Count		SAC

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.11.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Erythrocytes		SAC
3.12.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Reticulocytes		SAC
3.13.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Leukocytes		SAC
3.14.	Safety	LB9	Boxplot of Haemoglobin by Visit and Treatment Group – Males		SAC
3.15.	Safety	LB9	Boxplot of Haemoglobin by Visit and Treatment Group – Females		SAC
3.16.	Safety	LB9	Boxplot of Change from Baseline in Haemoglobin by Visit and Treatment Group		SAC
3.17.	Safety	LB9	Boxplot of Methaemoglobin by Visit and Treatment Group – Males		SAC
3.18.	Safety	LB9	Boxplot of Methaemoglobin by Visit and Treatment Group – Females		SAC
3.19.	Safety	LB9	Boxplot of Reticulocytes by Visit and Treatment Group – Males		SAC
3.20.	Safety	LB9	Boxplot of Reticulocytes by Visit and Treatment Group – Females		SAC
3.21.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Indirect Bilirubin		SAC
3.22.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Total Bilirubin		SAC
3.23.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Creatine Kinase		SAC

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.24.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Urea		SAC
3.25.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Creatinine		SAC
3.26.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Alkaline Phosphatase		SAC
3.27.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Alanine Amino Transferase		SAC
3.28.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Aspartate Amino Transferase		SAC
3.29.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group - G6PD enzyme activity		SAC
3.30.	Safety	LB9	Boxplot of Change from Baseline in Clinical Chemistry Parameters by Visit and Treatment Group - G6PD enzyme activity		SAC
3.31.	Safety	LB9	Boxplot of Total Bilirubin by Visit and Treatment Group – Males		SAC
3.32.	Safety	LB9	Boxplot of Total Bilirubin by Visit and Treatment Group – Females		SAC
3.33.	Safety	LB9	Boxplot of Indirect Bilirubin by Visit and Treatment Group – Males		SAC
3.34.	Safety	LB9	Boxplot of Indirect Bilirubin by Visit and Treatment Group – Females		SAC
3.35.	Safety	SF1	Maximum Fall in Haemoglobin over First 29 Days by Enzyme Activity and Treatment Group	Subjects with decline of >20g/L in haemoglobin only	SAC

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.36.	Safety	SF1	Maximum Fall in Haemoglobin over First 29 Days by Enzyme Activity and Treatment Group - Females	Subjects with decline of >20g/L in haemoglobin only	SAC
3.37.	Safety	SF1	Maximum Fall in Haemoglobin over First 29 Days by Enzyme Activity and Treatment Group – G6PD Deficient Males	Subjects with decline of >20g/L in haemoglobin only	SAC
3.38.	Safety	SF2	Mean Change from Baseline in Haemoglobin by Treatment Group, Visit and G6PD status (Subjects with Known G6PD Genotype)		SAC
3.39.	Safety	SF2	Mean Change from Baseline in Haemoglobin by Treatment Group and Visit (Male Subjects with Unknown G6PD Genotype)		SAC
3.40.	Safety	LB11	LFT Profile Plots	Only for subjects with >3 ULN in ALT or AST. Add footnote to this effect. The subject ID, treatment group, sex, age and race should be included as a header for each subject's plot.	SAC
3.41.	Safety	LB11	Haematology Profile Plots	Only for subjects with a >20g/L decline from baseline haemoglobin or is a female who was genotyped and found to be G6PD deficient Add footnote to this effect. The subject ID, treatment group, sex, age and G6PD status should be included as a header for each subject's plot.	SAC

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.42.	Safety	LB11	Clinical Chemistry Profile Plots	Only for subjects with >3 ULN in ALT or ASTor change from baseline in urea or creatinine > 50% Add footnote to this effect. The subject ID, treatment group, sex, age and race should be included as a header for each subject's plot.	SAC
3.43.	Safety	LB11	G6PD Enzyme Activity Profile Plots	Only for G6PD deficient females	SAC
3.44.	Safety	LB10	Distribution of Maximum LFTs by Treatment Group		SAC
3.45.	Safety	LB7	LFT Shift from Baseline to Maximum Value		SAC
3.46.	Safety	LB8	Matrix Display of Maximum LFT Values		SAC
ECG					
3.47.	Safety	LB9	Boxplot of Changes in QTcF by Visit and Treatment Group		SAC
Vital Signs					
3.48.	Safety	LB9	Boxplot of Mean Arterial Blood Pressure by Visit and Treatment Group		SAC

13.14.8. PharmacogeneticTables

Pharmacogenetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PGx General Summaries					
5.1.	All Randomised	GN1	Summary of Subject Accountability for PGx	Categories to use under Genotype sample status: • Collected and evaluable • Collected but consent withdrawn • Collected but not evaluable • Not collected Change 'Genotype data status' to 'Genetic data status' and include: • G6PD • CYP2D6	SAC
5.2.	All Randomised	GN2	Summary of Genetic Consent Not Obtained/Withdrawn		SAC
5.3.	Safety	GN5	Summary of Allele Frequency by Treatment		SAC
5.4.	Safety	GN5	Summary of Allele Frequency by Treatment and Region		SAC

13.14.9. Health Outcomes Tables

Health Outcomes: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Cost of Illness Survey					
6.1	Safety	COI1	Summary of Costs Associated with the Initial Episode of *P. vivax* Malaria - By Country and Visit		SAC
6.2	Safety	COI1	Summary of Costs Associated with a Relapse Episode of P. *vivax* Malaria - By Country and Visit		SAC
6.3	Safety	COI1	Summary of Costs Associated with a Haemolysis Event - By Country and Visit		SAC
6.4	Safety	COI2	Summary of Medication Costs Associated with the Initial Episode of *P. vivax* Malaria - By Country and Visit		SAC
6.5	Safety	COI2	Summary of Medication Costs Associated with a Relapse Episode of *P. vivax* Malaria - By Country and Visit		SAC
6.6	Safety	COI2	Summary of Medication Costs Associated with a Haemolysis Event - By Country and Visit		SAC
6.7	Safety	COI3	Summary of Time Lost Due to the Initial Episode of *P. vivax* Malaria - By Country and Visit		SAC
6.8	Safety	COI3	Summary of Time Lost Due to a Relapse Episode of *P. vivax* Malaria - By Country and Visit		SAC
6.9	Safety	COI3	Summary of Time Lost Due to a Haemolysis Event - By Country and Visit		SAC
6.10	Safety	COI4	Summary of Actions Associated with the Initial Episode of *P. vivax* Malaria - By Country and Visit		SAC
6.11	Safety	COI4	Summary of Actions Associated a Relapse Episode of *P. vivax* Malaria - By Country and Visit		SAC

Health Outcomes: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
6.12	Safety	COI4	Summary of Actions Associated with a Haemolysis Event - By Country and Visit		SAC

13.14.10. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population - Subject Disposition					
1.	Safety	BL1	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	SAC
2.	Safety	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
Study Population - Protocol Deviations					
3.	Safety	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
4.	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Study Population - Populations Analysed					
5.	Safety	SA3a	Listing of Subjects Excluded from Any Population	ICH E3	SAC
Study Population - Demographic and Baseline Characteristics					
6.	Safety	DM2	Listing of Demographic Characteristics	ICH E3	SAC
7.	Safety	DM9	Listing of Race and Racial Combinations	ICH E3	SAC
Study Population - Exposure					
8.	Safety	LA7a	Listing of Exposure Data	ICH E3	SAC
Safety - Adverse Events					
9.	Safety	AE8	Listing of All Adverse Events	ICH E3 Include flag for treatment emergent	SAC
10.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
Safety - Serious and Other Significant Adverse Events					
11.	Safety	AE8	Listing of Fatal Adverse Events	ICH E3 Include reasons for considering AE to be serious	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
12.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3 Include reasons for considering AE to be serious	SAC
13.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal From Study	ICH E3	SAC
14.	Safety	AE8	Listing of Disease Related Events	ICH E3	SAC
Safety - All Laboratory endpoints					
15.	Safety	LB5	Listing of Laboratory Data with Abnormalities of Potential Clinical Importance	ICH E3	SAC
16.	Safety	LB5	Listing of Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance	ICH E3	SAC
17.	Safety	UR2a	Listing of Urinalysis Data	ICH E3 All subjects	SAC
Safety - Hepatobiliary (Liver)					
18.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Criteria	IDSL	SAC
Safety - Vital Signs					
19.	Safety	VS4	Listing of Vital Signs	Include mean arterial BP	SAC

13.14.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population - Subject Disposition					
20.	All Subjects Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
21.	Safety	TA1	Listing of Planned and Actual Treatments	IDSL	SAC
Study Population - Demographic and Baseline Characteristics					
22.	Safety	LA1	Listing of Malaria Signs and Symptoms at Baseline		SAC
23.	Safety	MH2	Listing of Past and Current Medical Conditions		SAC
Study Population - Concomitant Medication					
24.	Safety	CM2	Listing of Prior and Concomitant Medications	Include concomitant medications and prior medications taken within 30 days of first dose of study medication	SAC
Study Population - Compliance					
25.	Safety	LA7b	Listing of Compliance Data		SAC
Efficacy					
26.	mITT	LA4	Listing of Results of Efficacy Endpoints		SAC
27.	mITT	LA5	Listing of Malarial Parasite Counts		SAC
28.	mITT	LA6	Listing of Time to Fever Clearance Data		SAC
29.	mITT	LA10	Listing of Choloroquine and Desethylchloroquine Concentrations for Subjects who are Early Failures		SAC
Safety - Adverse Events					
30.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms and Verbatim Text	IDSL	SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Safety - All Laboratory endpoints					
31.	Safety	LA8	Listing of Haemoglobin Drops for G6PD Deficient Subjects		
Safety - Hepatobiliary (Liver)					
32.	Safety	LIVER5	Listing of Liver Event Results and Time of Event Relative to Treatment		SAC
33.	Safety	LIVER6	Listing of Liver Event Information for RUCAM Score		SAC
34.	Safety	LIVER8	Listing of Liver Imaging Details		SAC
35.	Safety	LIVER7	Listing of Liver Biopsy Details		SAC
Safety - ECG					
36.	Safety	EG3	Listing of ECG Values		SAC
37.	Safety	EG5	Listing of ECG Findings		SAC
Safety - Ophthalmic Assessments					
38.	Ophthalmic Safety	LA2	Listing of Ophthalmic Assessments		SAC
39.	Ophthalmic Safety	LA3	Listing of Retinal Examination		SAC
Health Outcomes – Cost of Illness Survey					
40.	Safety	LA9	Listing of Cost of Illness Survey		SAC

Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for TAF116564: A Randomized, Double-Blind, Double Dummy, Comparative, Multicenter Study to Assess the Incidence of Haemolysis, Safety, and Efficacy of Tafenoquine (SB-252263, WR238605) versus Primaquine in the Treatment of Subjects with *Plasmodium vivax* Malaria.
Compound Number	:	SB-252263
Effective Date	:	05-AUG-2016

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol TAF116564.
- This RAP is intended to describe the planned safety, efficacy, tolerability, pharmacokinetic and pharmacogenetic analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

Author's Name and Functional Area:

PPD Statistician, Clinical Statistics	19-APR-2016
PPD Principal Statistician, Clinical Statistics	03-AUG-2016

Approved via e-mail by:

PPD Director, Clinical Statistics	05-AUG-2016

TABLE OF CONTENTS

PAGE

1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the RAP
Purpose	• The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol TAF116564. This document will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverables.
Protocol	• This RAP is based on the original protocol amendment 5 (15-JUL-2015) of study TAF116564 [GSK Document No.: 2012N152563_01] and eCRF Version 3.0.
Primary Objective	• To investigate the occurrence of clinically relevant haemolysis in adult subjects with *P. vivax*.
Primary Endpoint	• Occurrence of clinically relevant haemolysis in all subjects; defined as, a decrease in haemoglobin of ≥30% or >30 g/L (>3 g/dL) from baseline; or, an overall drop in haemoglobin below 60 g/L (6.0 g/dL).
Study Design	• Study TAF116564 is a prospective, double-blind, double-dummy, multicenter, comparative study. • The duration of the study is 180 days, including screening and randomization to treatment (Day 1), three in-hospital days (Days 1-3), four out-patient visits while on treatment with study medication (Days 5, 8, 11 and 15) and seven follow-up visits (Days 22, 29, 60, 90, 120, 150 and 180). • A total of 300 subjects will be randomized 2:1 to receive TQ/CQ or the active comparator PQ/CQ.
Planned Analyses	• No interim analysis is planned. • All decisions regarding final analysis, as defined in this RAP document, will be made prior to Database Freeze (unblinding) of the study data.
Analysis Populations	• Safety Population: all randomized subjects who received at least one dose of blinded study medication. 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. • Microbiologic Intent to Treat (mITT) Population: all randomized subjects who receive at least one dose of blinded study medication and have microscopically-confirmed vivax parasitemia. 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 mITT population for whom there were no major protocol violations. This population will be used for sensitivity/supporting analyses of efficacy data only. • Ophthalmic Safety Population: all subjects in the safety population who have results from any eye assessments. • Pharmacogenetic (PGx) Population: all subjects in the safety population who

Overview	Key Elements of the RAP
	gave consent and had an evaluable sample collected.
Hypothesis	• There will be no hypotheses tested in this study.
Primary Analyses	• The proportion of subjects with clinically relevant haemolysis in each treatment group will be presented together with a confidence interval based on the Wilson score. • The difference between treatment groups in the proportion of subjects with clinically relevant haemolysis in each treatment group will be presented together with a confidence interval based on the Newcombe method
Secondary Analyses	• All survival efficacy endpoints, e.g. time to relapse, relapse as a success/failure will be analysed by Cox proportional hazards and Kaplan Meier methodology. Binary endpoints, e.g. relapse/no relapse at 6 months, will be analysed by logistic regression. • Other secondary efficacy endpoints will be summarised descriptively by treatment group. • Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. • Pharmacokinetic analyses will be detailed in a separate document. • Pharmacogenetic data will be summarised and an exact logistic regression model will be used to assess the effect of derived CYP2D6 metabolizer class within treatment arm on relapse efficacy six months post-dosing. • Healthcare resource use of *P. vivax* relapses and haemolysis events will be summarised descriptively.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There are changes or deviations to the originally planned statistical analysis specified in the protocol amendment 5 (Dated: 15-JUL-2015). In the protocol, the primary objectives are:

1. To investigate the occurrence of clinically relevant haemolysis in adult subjects with *P. vivax*.
2. The incidence of haemolysis in the subgroup of female patients with moderate (40-70%) G6PD activity is of particular interest.

Due to difficulties in recruitment of G6PD deficient subjects, this subgroup of subjects will be limited in number and therefore the incidence in this subgroup will not be estimated. Therefore the only primary objective is the treatment difference of the occurrence of clinically relevant haemolysis in adult subjects with *P. vivax*.

Any subjects who are G6PD deficient will be included in the main analyses unless described otherwise.

The protocol defined subject study completion as: the subject meets all inclusion/ exclusion criteria, is considered compliant with all study medication, completes the 3 day hospital stay, and attends the Day 180 visit; however a more appropriate definition of "a subject that does not withdraw from the study and attends the Day 180 visit" will be used.

The protocol specified that data will be allocated to visit windows using actual visit dates rather than nominal visit numbers, however to remain consistent with study TAF112582, nominal visit will be used. Further details are given in Section 13.3.

Duration of exposure will not be calculated as specified in the protocol as date of last dose of active study medication – date of first dose of study medication + 1, because the date of last dose is not collected. Compliance and exposure will be presented as described in Section 6.6.

Adverse events that are considered to be gastrointestinal-related will not be reported separately as earlier studies have shown these not to be Adverse Events of special interest.

The protocol stated that Fisher's Exact analyses will be performed for the missing=failure analysis of relapse-free efficacy (see Section 8.1.2), but as the number of subjects relapse-free is expected to be large enough, logistic regression will be performed to allow the inclusion of important covariates.

Time to event endpoints will be analysed using Cox proportional hazards methodology, in addition to the Kaplan-Meier methodology described in the protocol.

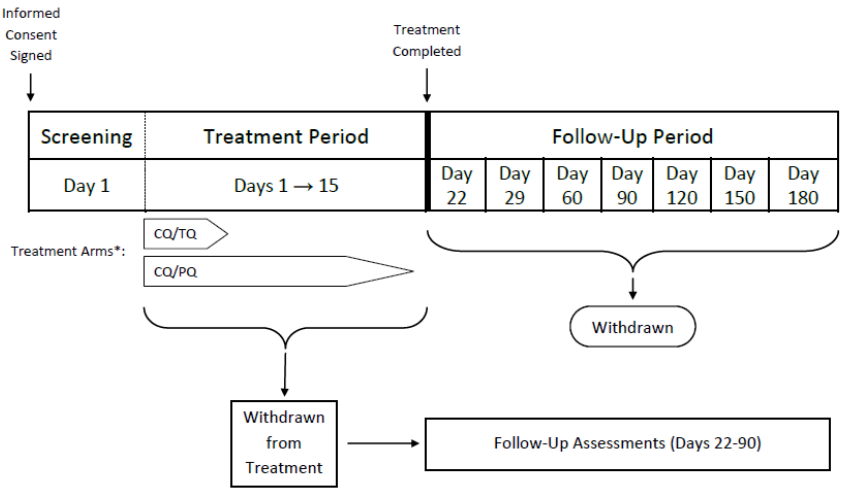
The effect of CYP2D6 metabolism on relapse efficacy within treatment arm and ophthalmic assessments as safety endpoints were not explicitly specified in the protocol as objectives and endpoints. They have been added to the list in Section 2.2.

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To investigate the occurrence of clinically relevant haemolysis in adult subjects with *P. vivax*.	• Occurrence of clinically relevant haemolysis in all subjects; defined as, a decrease in haemoglobin of ≥30% or >30 g/L (>3 g/dL) from baseline; or, an overall drop in haemoglobin below 60 g/L (6.0 g/dL).
Secondary Objectives	**Second Endpoints**
• To compare the clinical and parasitological efficacy, safety and tolerability of tafenoquine to primaquine as a radical cure for adult subjects with *P. vivax* malaria when co-administered with chloroquine.	• Relapse-free efficacy six months post-dosing • Relapse-free efficacy four months post-dosing • Time to relapse • Parasite clearance time • Fever clearance time • Gametocyte clearance time

Objectives	Endpoints
	• Recrudescence, defined as any *P. vivax* parasitemia occurring on or before Day 32 (i.e. blood stage treatment failure). • Incidence of genetically homologous and genetically heterologous *P. vivax* infections (determined by PCR) • Safety evaluation of data from clinical laboratory tests, urinalysis, spontaneous/elicited adverse event reporting, ECGs and vital signs in all subjects who received at least one dose of study medication. • Incidence of *P. falciparum* malaria • Ophthalmic assessments
• To characterize the socioeconomic impact of *P. vivax* relapse.	• Characterization of healthcare resource use and socio-economic impact of *P. vivax* relapses and adverse events caused by treatment to prevent *P. vivax* relapses, especially haemolytic anemia.
• To evaluate the pharmacokinetics of tafenoquine in the treatment of 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)
• To characterize the pharmacokinetic/ pharmacodynamic relationship in this study population.	• PK and selected PD endpoints (e.g. relapse-free efficacy, change in methaemoglobin) if appropriate
• To evaluate the effect of CYP2D6 metabolism on relapse efficacy within treatment arm	• Relapse-free efficacy six months post-dosing

2.3. Study Design

Overview of Study Design and Key Features	
 CQ/TQ = Chloroquine 600mg OD Days 1 & 2; 300mg OD Day 3 / Tafenoquine 300mg single dose Day 2 CQ/PQ = Chloroquine 600mg OD Days 1 & 2; 300mg OD Day 3 / Primaquine 15mg OD Days 2-15	
Design Features	• Study TAF116564 is a prospective, double-blind, double-dummy, multicenter, comparative study. • The duration of the study is 180 days, including screening and randomization to treatment (Day 1), three in-hospital days (Days 1-3), four out-patient visits while on treatment with study medication (Days 5, 8, 11 and 15) and seven follow-up visits (Days 22, 29, 60, 90, 120, 150 and 180). • Subjects will be screened and randomized to treatment on Day 1. Subjects must have a blood smear that is positive for *P. vivax* at entry. Subjects will remain in the hospital for the first 3 days of the study, or until two consecutive thick blood smears are negative for *P. vivax*, to monitor study medication compliance and infection status. Subjects will continue on treatment for the first 15 days of the study and will be monitored up to day 32 for recrudescence. Subjects will continue to be monitored up to 180 days post randomization for evidence of relapsing infection. • All subjects will receive open label CQ (Chloroquine) for the first 3 days of the study to treat the blood stage of the infection. Beginning on Day 1 or Day 2, subjects will receive TQ (Tafenoquine) or the active comparator, PQ (Primaquine), and the

Overview of Study Design and Key Features	
	corresponding placebo for treatment of the liver stage of infection. • At the Day 1 visit subjects will be screened for G6PD deficiency by a quantitative assay and the result will be determined as a percentage of the predetermined median enzyme activity of the site. Female subjects must have a minimum G6PD assay value of 40% to be enrolled, and male subjects must have a minimum G6PD assay value of 70% to be enrolled. • Parasitological assessments will be carried out at each visit in the follow up period. • Other assessments include healthcare resource use and socio-economic data, ophthalmic assessments (selected investigator centres only), vital signs, ECGs, laboratory assessments and blood samples for pharmacokinetic and pharmacodynamic analyses.
Dosing	• All subjects will receive CQ on Study Days 1 to 3, followed by TQ or PQ and matching placebo beginning on Study Day 1 or 2. Tafenoquine, or matching placebo, will be given as a single, 300mg dose. Subjects will receive PQ (15mg once daily) or matching placebo for 14 days.
Treatment Assignment	• A total of 300 subjects (250 with normal G6PD enzyme activity and 50 females with moderate (40-70%) G6PD enzyme activity) were to be randomized 2:1 to receive TQ or the active comparator PQ. • GSK RANDALL NG will be used to generate randomisation schedules. • Treatment allocation will occur by centralised randomisation using GSK RAMOS, accessed by sites via an Interactive Voice Recognition System (IVRS)
Interim Analysis	• No formal interim analyses are planned for this study.
Sample Size	• A sample size of 300 (250 with normal G6PD enzyme activity and 50 females with moderate (40-70%) G6PD enzyme activity) was based on the regulatory requirement to obtain an appropriate total safety database in subjects treated with TQ/CQ at the selected dose, given that subjects are randomized to TQ/CQ: PQ/CQ on a 2:1 ratio.

2.4. Statistical Hypotheses

There will be no hypotheses tested in this study.

3. PLANNED ANALYSES

3.1. Interim Analyses

No formal interim analyses are planned for this study.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

- All subjects have completed (or withdrawn) from the study.
- All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
- All criteria for unblinding the randomisation codes have been met.
- Randomisation codes have been distributed according to RandAll NG procedures.
- An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Safety	• All randomized subjects who received at least one dose of blinded study medication. • Subjects will be analysed according to the treatment a subject actually received.	• Primary population for all safety analyses and data presentations
Microbiologic-Intent-To-Treat (mITT)	• All randomized subjects who receive at least one dose of blinded study medication and have microscopically-confimed vivax parasitemia at Baseline. • Subjects will be analysed according to the treatment a subject was randomized to.	• Primary population for all efficacy analyses
Per-Protocol (PP)	• All subjects in the mITT population for whom there were no major protocol violations.	• Sensitivity/ supporting analyses of efficacy data only
Ophthalmic Safety	• All subjects in the safety population who have results from any eye assessments.	• Analyses of ophthalmic endpoints
Pharmacogenetic (PGx)	• All subjects in the safety population who gave consent and had an evaluable sample collected.	• Analyses of pharmacogenetic data

NOTES :

- Please refer to Appendix 14: List of Data Displays which details the population to be used for each displays being generated.
- PK and PK/PD data are being handled outside of this RAP so PK and PK/PD populations are not included in this table.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/ exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- Important deviations which result in exclusion from the analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to the unblinding of the GSK study and statistical team and freezing of the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
    - This dataset will be the basis for the summaries and listings of protocol deviations.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/ exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Appendix
Section 13.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
Section 13.2	Appendix 2: Time and Events
Section 13.3	Appendix 3: Assessment Windows
Section 13.4	Appendix 4: Treatment States & Phases
Section 13.5	Appendix 5: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 13.6	Appendix 6: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Pharmacokinetic

Section	Appendix
	• Healthcare Resource Use • Pharmacogenetic
Section 13.7	Appendix 7: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 13.8	Appendix 8: Values of Potential Clinical Importance
Section 13.9	Appendix 9: Multicentre Studies
Section 13.10	Appendix 10: Examination of Covariates and Subgroups
Section 13.11	Appendix 11: Multiple Comparisons and Multiplicity
Section 13.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the safety population, unless otherwise specified.

Section 6 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 14: List of Data Displays.

Categorical variables will be summarised by the number and percentage of subjects, and the continuous parameters will be summarised by n, mean, median, sample standard deviation, minimum and maximum unless otherwise specified. See Section 13.5.3 for further details.

All data will be listed as presented in Appendix 14: List of Data Displays.

6.2. Study Populations and Subject Disposition

A table will be produced detailing the number of subjects eligible for each of the analysis populations by treatment group (Table 1.1). The table will also show the total number of subjects screened.

The number and percentage of subjects who were randomized or entered into the trial, but deviated from the inclusion or exclusion criteria will be summarized by treatment group (Table 1.2).

A table summarising study conclusion records will be produced showing the reasons for withdrawal for any subjects not completing the study as planned (Table 1.3). For subjects who discontinue investigational product, the reasons for discontinuation will be presented in a separate table (Table 1.4). The definition of study completion is given in Section 13.7.1.

The number of subjects recruited per centre and per country will be summarised by treatment group (Table 1.5).

The reasons for screen failure will also be summarised (Table 1.6)

6.3. Protocol Deviations

The number and percentage of subjects who had deviations defined as part of the protocol deviation management plan for the study (see Section 13.1) will be summarized by treatment group (Table 1.7)

6.4. Demographic and Baseline Characteristics

Subjects' demography data (age, sex, ethnicity, weight, height, body mass index (BMI), respiratory rate, G6PD enzyme activity and G6PD enzyme activity as a percentage of the site's median) will be summarised for the safety population (Table 1.8).

Summaries of race and racial combinations (Table 1.9) and race and racial combination details (Table 1.10) will be produced.

Malaria signs and symptoms (Table 1.14), splenomegaly status at baseline (Table 1.19) and previous episodes of malaria (Table 1.20) will be summarised by treatment group.

The eCRF captured the System Organ Class of current and past medical conditions, as well as preferred terms for current and past medical conditions of particular interest. Therefore, 4 summaries will be produced:

- Summary of Current Medical Conditions by Body System (Table 1.15)
- Summary of Past Medical Conditions by Body System (Table 1.16)
- Summary of Current Specific Medical Conditions (Table 1.17)
- Summary of Past Specific Medical Conditions (Table 1.18)

In addition to the G6PD enzyme activity test, which was used to assess whether subjects were eligible to enter the study, a point of care test may also have been administered, which classified subjects as G6PD normal or G6PD deficient (Table 1.22). The results of the point of care test will be summarised (n, %) versus the enzyme activity test for all subjects screened in the study, where G6PD enzyme activity is classified as <40% of median, 40% to 70% of median, and >70% of median. This display will not be presented by treatment group.

Baseline efficacy data (e.g., asexual parasite counts and parasite gametocyte counts) will not be summarised and listed separately but will be included in efficacy summaries by assessment.

6.5. Prior and Concomitant Medications

Prior and concurrent medications will be tabulated (Tables 1.11 and Table 1.12). Percentages will be calculated out of the number of subjects in the safety population. See Section 13.6.2 for definitions of prior and concomitant medications.

Paracetamol usage will be summarised separately (Table 1.13).

6.6. Exposure and Treatment Compliance

Compliance (defined in Section 13.6.2) will be summarised split by in clinic and outpatient dosing (Table 1.21). For in clinic compliance, the number of compliant doses of CQ and whether subjects were compliant with TQ/TQ placebo and each dose of in clinic PQ/PQ placebo will be summarised (n, %). For outpatient compliance, the number of doses taken will be summarised classified into 11 or fewer doses, 12 or more doses. Compliance determined using Day 8, Day 15, Day 8 or Day 15, Day 8 and Day 15 carboxyPQ PK samples will also be summarised in the table. A summary of subjects meeting the pill count and PK compliance criteria, and also the number of subjects meeting the pill count or PK compliance criteria will additionally be provided in the table.

7. PRIMARY STATISTICAL ANALYSES

7.1. Safety Analyses

7.1.1. Overview of Planned Safety Analyses

The primary safety analyses will be based on safety population, unless otherwise specified.

Full details of data displays are presented in Appendix 14: List of Data Displays.

7.1.2. Planned Safety Statistical Analyses

Primary Statistical Analyses
Endpoint(s)
• Occurrence of clinically relevant haemolysis in all subjects. See Section 13.6.3 for derivation of clinically relevant haemolysis.
Model Specification
• No formal statistical analyses will be performed as the incidence of clinically relevant haemolysis is expected to be low. • 95% confidence intervals for the proportion of subjects ($\hat{p}$) with clinically relevant haemolysis in each treatment group (*i,j*) will be based in the Wilson score: $\left(\hat{p}_i + z^2_{\alpha/2}/2n_i \pm z_{\alpha/2}\sqrt{(\hat{p}_i(1-\hat{p}_i) + z^2_{\alpha/2}/4n_i)/n_i}\right) / 1 + z^2_{\alpha/2}/n_i$ This can be obtained in SAS using the BINOMIAL option in PROC FREQ. • The Newcombe method based on the Wilson score will be used to calculate the 95% confidence interval for the difference in proportion $(\hat{p}_i - \hat{p}_j)$ (Newcombe, 1998): $lower\ limit = (\hat{p}_i - \hat{p}_j) - \sqrt{(\hat{p}_i - L_i)^2 + (U_j - \hat{p}_j)^2}$ $upper\ limit = (\hat{p}_i - \hat{p}_j) + \sqrt{(U_j - \hat{p}_i)^2 + (\hat{p}_j - L_j)^2}$ where *U* and *L* represent the upper and lower limit respectively of the corresponding

Primary Statistical Analyses
proportion. This can be obtained in SAS using the RISKDIFF option with (CL=(NEWCOMBE)) in PROC FREQ.
Results Presentation
• Table 3.1, Figure 3.1: The proportion of subjects with clinically relevant haemolysis in each treatment group will be presented together with a confidence interval based on the Wilson score • The difference between treatment groups in the proportion of subjects with clinically relevant haemolysis in each treatment group will be presented together with a confidence interval based on the Newcombe method (tables only) • Due to the low number of G6PD deficient females expected, they will be included in the primary analysis but their data will be listed separately.

Sensitivity and Supportive Statistical Analyses
• To assess the impact of missing data, a sensitivity analysis will be performed using imputed data where data is missing, as described in Section 13.7.2.3 and the methodology detailed above (Table 3.2).

Further safety analyses are described in Section 8.2 8.2.

8. SECONDARY STATISTICAL ANALYSES

8.1. Efficacy Analyses

8.1.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on mITT population, unless otherwise specified.

Details of data displays are presented in Appendix 14: List of Data Displays.

8.1.2. Planned Efficacy Statistical Analyses

Secondary Statistical Analyses
Endpoint(s)
• Relapse-free efficacy six months post-dosing • Relapse-free efficacy four months post-dosing • See Section 13.6.4 for derivations including censoring.
Model Specification
• Cox Proportional Hazards model with region and treatment as covariates for the time to relapse (during the first 6 months and first 4 months separately) • mITT population
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.

Secondary Statistical Analyses
Model Results Presentation

• Summary of the proportion of subjects with relapse-free efficacy by treatment group as n (%), including the sub-reasons for why subjects are not considered relapse-free defined in Section 13.6.4 (Table 2.5 for 6 months, Table 2.7 for 4 months). Note only the sub-reasons that apply to the population being displayed will be included.
• Analysis tables (Table 2.9 for 6 months, Table 2.11 for 4 months) will show:
  • Number of subjects with an observed relapse and numbers of subjects censored (censored prior to 6/4 months, and censored relapse-free at 6/4 months)
  • Point estimates and 95% confidence intervals of the relapse-free efficacy rate for each treatment
• Hazard ratio of TQ+CQ vs PQ+CQ over the first 6/4 months and 95% CI Kaplan-Meier survival curves will also be produced for 6 months (Figure 2.1).

Sensitivity and Supportive Statistical Analyses
1. Per Protocol population – Relapse free efficacy at 6 months and 4 months

• Summary of the proportion of subjects with relapse-free efficacy by treatment group as n (%), including the sub-reasons for why subjects are not considered relapse-free defined in Section 13.6.4 (Table 2.6 for 6 months, Table 2.8 for 4 months). Note only the sub-reasons that apply to the population being displayed will be included.
• Analysis tables (Table 2.10 for 6 months, Table 2.12 for 4 months) will show:
  • Number of subjects with an observed relapse and numbers of subjects censored (censored prior to 6/4 months, and censored relapse-free at 6 months)
  • Point estimates and 95% confidence intervals of the relapse-free efficacy rate for each treatment
• Hazard ratio of TQ+CQ vs PQ+CQ over the first 6/4 months and 95% CI Kaplan-Meier survival curves will also be produced for 6 months (Figure 2.2).

2. Logistic Regression Model – 6 months and 4 months
• 6 months: Table 2.13, 4 months: Table 2.14 • Logistic regression model with region and treatment as covariates. • Response variable = relapse free (confirmed at 6 (or 4) months) vs relapse (confirmed relapse at or prior to 6 (or 4) months). Subjects who are censored prior to 6 (or 4) months will be excluded from the analysis. • mITT only • Present the number and percentage of subjects considered relapse free, the adjusted odds ratio of TQ+CQ vs PQ+CQ and 95% CI for the odds ratio
3. Missing=Failure analysis - 6 months and 4 months

• See Section 13.6.4 for derivation of missing=failure dataset
• Logistic regression with region and treatment as covariates
• mITT only
• Presentation of results (6 months: Table 2.15, 4 months: Table 2.16):
  • Number and percentage of subjects considered relapse free
  • Adjusted odds ratio of TQ+CQ vs PQ+CQ and 95% CI

4. Missing on or after Day 29 = Failure analysis – 6 months
• See Section 13.6.4 for derivation of missing=failure dataset

Sensitivity and Supportive Statistical Analyses

• Logistic regression with region and treatment as covariates
• mITT only
• Presentation of results (Table 2.17):
  • Number and percentage of subjects considered relapse free
  • Adjusted odds ratio of TQ+CQ vs PQ+CQ and 95% CI

5. By genetic classification - 6 months and 4 months

• Repeat primary analysis by genetic classification (heterologous/homologous) (6 months: Table 2.18, 4 months: Table 2.19), present:
  • Number of subjects with an observed relapse and numbers of subjects censored
  • Point estimates and 95% confidence intervals of the relapse-free efficacy rate for each treatment and for the differences in relapse-free efficacy between TQ and PQ.
  • Hazard ratio of TQ+CQ vs PQ+CQ and 95% CI
  • Kaplan-Meier survival curves (6 months only: Figure 2.3)

6. Covariate and Interaction Testing
• The significance of region and the treatment*region interaction will be tested in the Cox Proportional Hazards model. The primary model will be fitted with region and treatment as covariates, and another model will be fitted with the additional treatment*region interaction. • mITT only • The maximum likelihood estimates, standard errors, Wald chi-square and p-values will be presented (Table 2.20) • If the interaction is significant at the 10% level, analyses split by region will be performed.

Secondary Statistical Analyses
Endpoint(s)
• Time to relapse • Time to parasite clearance • Time to fever clearance • Time to gametocyte clearance • See Section 13.6.4 for derivations including censoring.
Model Specification
• mITT population • Estimates for time to endpoint will be determined for each treatment group using the Kaplan-Meier method. • Cox Proportional Hazards model with region and treatment as covariates for time to parasite, fever and gametocyte clearance
Model Checking & Diagnostics
• Refer to Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation

• Table 2.21 to Table 2.24:
  • Number of subjects with the endpoint and number censored
  • Estimates for time to the endpoint: 1st quartile, median, 3rd quartile and associated 95% confidence intervals
  • For time to parasite, fever and gametocyte clearance:

Secondary Statistical Analyses
• Hazard ratio (TQ+CQ vs PQ+CQ) and 95% confidence interval

Secondary Statistical Analyses
Endpoint(s)
• Recrudescence - see Section 13.6.4 for derivations including censoring
Model Specification
• No statistical model will be constructed; descriptive statistics only • 95% Wilson confidence intervals for the rate of recrudescence in each treatment group and treatment difference in the rate • mITT population
Model Results Presentation
• Summary table showing the number of subjects with recrudescence or censored, rate of recrudescence and 95% CI for each treatment group, plus treatment difference and 95% CI (Table 2.26).

Secondary Statistical Analyses
Endpoint(s)
• Early failures • See Section 13.6.4 for derivation
Model Specification
• No statistical model will be constructed; descriptive statistics only • mITT population
Model Results Presentation

• Summary table (n and %) showing the proportion of subjects in each treatment group (Table 2.27):
  • Considered early failures
  • Early failures who fail to demonstrate initial clearance
  • Early failures who demonstrate initial clearance
  • Early failures who demonstrate initial clearance with genetically homolgous infections
  • Early failures who demonstrate initial clearance with genetically heterologous infections

Secondary Statistical Analyses
Endpoint(s)
• Genetic classification by PCR of relapse infections occurring on or after Study Day 33 • See Section 13.6.4 for derivation of a relapse
Model Specification
• No statistical model will be constructed; descriptive statistics only • mITT population

Secondary Statistical Analyses
Model Results Presentation
• Summary table (n and %) (Table 2.28) showing the proportion of subjects in each treatment group with *P. vivax* relapse infections classified as genetically heterologous or homologous • n will be the number of subjects with a relapse occurring on or after Study Day 33 • Bar chart of the percentage of subjects on each treatment arm with genetically heterologous or homologous infections, with 95% Wilson confidence intervals (Figure 2.4)

Secondary Statistical Analyses
Endpoint(s)
• Effect of CYP2D6 metabolism on relapse-free efficacy six months post-dosing within the treatment arms
Model Specification
• Pharmacogenetics population • Logistic regression model adjusting for region and derived CYP2D6 metabolizer class within treatment arm (models fitted separately for each treatment arm) • One-sided test at the 5% significance level (given published data indicating reduced CYP2D6 metabolism decreases PQ efficacy) • Table 2.30: Poor Metaboliser (PM) and Intermediate Metaboliser (IM) vs Extensive Metaboliser (EM) and Ultra Metaboliser (UM) combined (PM vs EM+UM, IM vs EM+UM) • Table 2.31: Intermediate Metaboliser vs Extensive Metaboliser (IM vs EM) (Rationale:the number of PMs and the number of UMs are expected to be small)
Model Results Presentation
• Number and percentage of subjects relapse free in each metaboliser class within each treatment arm • Adjusted odds ratio, 90% CI and p-value

Secondary Statistical Analyses
Endpoint(s)
• Effect of qualitative CYP2D6 Activity Score (AS) on relapse-free efficacy six months post-dosing within the treatment arms
Model Specification
• Pharmacogenetics population • Logistic regression model adjusting for region and qualitative CYP2D6 AS within treatment arm (models fitted separately for each treatment arm)
Model Results Presentation
• Table 2.32: Maximum likelihood estimate, standard error, wald chi-square and p-value of AS

Additional Efficacy Summaries
• *P. vivax* asexual parasite counts (Table 2.1), mITT population: • Summary statistics (n, median, Q1, Q3, min and max) at each timepoint • Other malarial asexual parasite counts (Table 2.2), *P. vivax* gametocyte counts (Table 2.3), other malaria gametocyte counts (Table 2.4), mITT population:

- Summary statistics (n, median, Q1, Q3, min and max) at each timepoint
- Summary of subjects with *P. vivax* gametocyte emergence post baseline (n, %) (Table 2.25)
- Summary of subjects with *P. falciparum* asexual parasite emergence post baseline (n, %) (Table 2.29)

Efficacy Listings
• Efficacy data will be listed as presented in Appendix 14: List of Data Displays

8.2. Safety Analyses

The safety analyses will be based on the Safety population, unless otherwise specified.

Details of data displays are presented in Appendix 14: List of Data Displays.

8.2.1. Overview of Planned Adverse Events Analyses

Counting of AEs will be based on the number of subjects – not the number of AEs. For example, if a subject reports the same AE on three occasions within the relevant time interval, that AE will only be counted once. If a subject experiences the same AE (i.e. same preferred term) more than once, they are counted only once under the count for the preferred term. If a subject experiences more than one AE in a particular SOC, they will only be included once in the count for the SOC, but will appear in the count for each appropriate preferred term within the SOC. Therefore, the sum of the numbers of subjects with each preferred term event within a SOC may exceed the total number of subjects with at least one event. For the summary of AEs by maximum intensity, subjects who experience the same event several times with different intensity will only be counted once with the maximum intensity.

Only treatment emergent AEs (TEAEs) will be presented as all subjects receive study medication on Study Day 1. TEAEs are defined as AEs with an onset date and time on or after that of the start of first dose of study medication (including CQ)

The occurrence of *P. vivax* malaria and any associated signs and symptoms are recorded as Disease Related Events (DREs) and will not be included in the AE data displays, but will be listed separately.

Adverse Events will be summarized by treatment group and as specified below and in Appendix 14: List of Data Displays and presented in order of descending frequency. Table 2 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 14: List of Data Displays.

Table 2 Overview of Planned Adverse Event Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
All AEs			Y[1]
All Treatment Emergent AEs by SOC	Y		
All Treatment Emergent AEs by PT	Y		
Drug-related TEAE by PT	Y		
TEAEs by maximum intensity	Y		
Common (>=5% in any treatment group) TEAEs by PT	Y	Y[2]	
Common (>=5% in any treatment group) Non-serious TEAEs by SOC and PT – number of subjects and occurrences	Y		
TEAEs by month of onset	Y		
Subject numbers for individual AEs			Y
Relationship between AE SOCs, PTs and verbatim text			Y
Serious and Other Significant AEs			
Fatal TEAEs by PT	Y		Y
Serious TEAEs[3]	Y		Y
Drug related serious TEAEs by PT	Y		
Drug related fatal serious TEAEs by PT	Y		
TEAEs leading to withdrawal from the study	Y		Y
TEAEs leading to discontinuation from study treatment	Y		
AEs that are considered to be haematologically-related (i.e. clinically relevant drops in Hb or Hct or other complications)	Y		
Grade 3 and Grade 4 AEs by PT	Y		
Disease Related Events			Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, SOC = System Organ Class, PT = Preferred Term.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- Treatment emergent AEs (SAEs) are defined as AEs (SAEs) with an onset date and time on or after that of the start of first dose of study medication (including CQ).
- AEs which have missing onset dates and any with an onset date equal to that of medication, but where onset time is unknown, will be considered to be treatment emergent.
- For each preferred term counting will be done by subject and not event.
- AEs related to drug will be selected based on where the 'Relationship to Investigational Product' flag on the eCRF has been marked 'Yes'.
- See Section 13.6.3 for additional information on the derivations and definitions of AEs
- Additional information on any deaths will be provided by Global Clinical Safety and Pharmacovigilance (GCSP) as part of the SAE reconciliation process.
- Events will be sorted based on Total incidence unless otherwise noted in Section 13.14.6
- [1] Treatment Emergent AEs will be flagged
- [2] Plot of common AEs and relative risk will be generated.
- [3] By SOC, by overall frequency and by SOC – number of subjects and occurrences

8.2.1.1. Pregnancies

Any pregnancies occurring will be discussed in the Clinical Study Report.

8.2.1.2. Patient Profiles of Cardiovascular Events and Deaths

Additional information collected on cardiovascular events and deaths will be reported in Patient Profiles for inclusion in the CSR. One profile per subject with an event will be produced using IDSL patient profile display standards.

8.2.2. Overview of Planned Clinical Laboratory Analyses

Table 3 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 14: List of Data Displays.

Table 3 Overview of Planned Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Chemistry						
Chemistry Data by Treatment and Time	Y	Y[1]				
Chemistry Changes from Baseline				Y	Y	
Chemistry Laboratory Abnormalities[2]	Y	Y	Y			
Haematology						
Haematology Data by Treatment, Time and Sex	Y	Y				
Haematology Changes from Baseline by Treatment, Time and Sex				Y	Y	
Haematology Laboratory Abnormalities[2]	Y	Y	Y			
Haemoglobin Categories[4] of Change from Baseline by Treatment and Time				Y		
Haemoglobin Categories[4] of Change from Baseline by Treatment, Time and Sex				Y		
Maximum Fall in Haemoglobin Over First 29 Days[4]					Y	
Mean Change in Haemoglobin Over First 29 Days[4]				Y	Y	
Urinalysis						
Urine Concentration			Y	Y		
Urinalysis Dipstick Results	Y		Y			
Hepatobiliary (Liver)						
Liver Monitoring/Stopping Event Reporting	Y		Y			
Liver Biopsy Details	Y					
Liver Imaging Details	Y		Y			
Medical Conditions for Subjects with Liver Stopping Events			Y			

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
LFT Abnormalities		Y				
Maximum LFTs		Y				
LFT Changes from Baseline		Y				

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1] Boxplots by treatment, time and gender for total bilirubin and indirect bilirubin
- [2] Abnormalities refer to values outside of the clinical concern range (F3) as defined in Section 13.8.1.
- [3] G6PD enzyme activity only
- [4] Categories defined as <=20 g/L, >20 g/L to <=30 g/L, > 30 g/L [5] See Section 8.2.2.1
- All scheduled visits should be included in the tables and figures.
- Data recorded at unscheduled assessments will not be included in tables and figures but will be listed.
- Change from baseline is defined in Section 13.5.2.

8.2.2.1. Haemoglobin Declines and Related Laboratory Parameters

For all subjects with a drop in haemoglobin >20 g/L, G6PD enzyme activity will be plotted against maximum drop in haemoglobin up to and including the Day 29 visit, with separate pages for each treatment group (Figure 3.35). Within the plot, different symbols will be used for the following categories:

- subjects who were genotyped and had a mutation classified as World Health Organization (WHO) class 1
- subjects who were genotyped and had a mutation classified as WHO class 2
- subjects who were genotyped and had a mutation classified as WHO class 3
- subjects who were genotyped and had a mutation of unknown significance
- subjects who were genotypically normal or had a mutation classified as a normal variant (WHO class 4)
- subjects who were not genotyped or did not have an evaluable genotyping result

A second plot will include only females with a drop in haemoglobin >20 g/L (Figure 3.36), with separate pages for each treatment group, and a third for G6PD deficient males only (Figure 3.37).

A further set of plots will be produced for each treatment group for all subjects with non-missing G6PD genotype results, with males and females plotted on separate pages. Mean change from baseline haemoglobin will be plotted for G6PD normals by visit, up to and including Day 60 (Figure 3.38). Error bars will be plotted at each time point. Mean change from baseline haemoglobin for G6PD deficients will also be plotted on the same graph. It is anticipated that the number of G6PD deficients will be very low, so all change

from baseline values will be plotted for all G6PD-deficient subjects, but no error bars will be produced.

A further plot by treatment group will display mean change from baseline haemoglobin for all male subjects where G6PD genotype is unknown (Figure 3.39). This plot will cover all visits up to and including Day 29. Error bars will be plotted at each time point.

If a subject has a >20g/L decline from baseline haemoglobin or is a female who was genotyped and found to be G6PD deficient, a haematological profile plot will be produced for the subject (Figure 3.41). This will display their haemoglobin, absolute reticulocyte, methaemoglobin and bilirubin results (total and indirect bilirubin on same plot) at each visit. The subject ID, treatment group, sex, age and G6PD status should be included as a header for each subject's plot.

A summary of haemoglobin declines of the first 29 days by treatment (Table 3.29) and by treatment and sex (Table 3.30) will also be produced.

A listing of all G6PD deficient subjects will be produced including their drop in haemoglobin, G6PD mutation, and their haemoglobin data over time (Listing 30).

Patient profile plots of G6PD for G6PD deficient females will be produced (Figure 3.43). Boxplots by visit and treatment group will also be produced for G6PD enzyme activity (Figure 3.29) and change from baseline in G6PD enzyme activity (Figure 3.30). G6PD will be presented in IU/gHB,

8.2.3. Overview of Planned Other Safety Analyses

Table 4 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 14: List of Data Displays.

Table 4 Overview of Planned Other Safety Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
ECG						
ECG findings	Y		Y			
ECG Values by Visit			Y	Y	Y[1]	
QTcF values by Category[2] and Visit	Y			Y		
Maximum Change from Baseline QTcF Up to 72 hours Post Randomised Treatment				Y		
Vital Signs						
Vital Signs by Time Point and Treatment Group	Y		Y	Y		
Mean Arterial Blood Pressure by Timepoint and Treatment Group		Y				

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Ophthalmic Assessments[3]						
Retinal Abnormalities	Y		Y	Y		
Keratopathy	Y		Y			
Slit Lamp Assessments	Y		Y	Y		
Humphrey Perimetry Assessments	Y		Y	Y		
Colour Perception Assesments	Y		Y			
Best Corrected Visual Acuity Test Scores	Y		Y			
Best Corrected Visual Acuity Classification	Y		Y	Y		
Blood Transfusions						
Blood Transfusion	Y					

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1] QTcF only
- [2] QTcF categories defined in Section 8.2.3.1; include maximum post baseline rows
- [3] Presentation of ophthalmic assessments described in Section 8.2.3.2
- Where triplicate assessments are performed (i.e. at baseline), the mean of the 3 assessments will first be derived and the summary statistics will be presented using the mean of the assessments.
- Temperature readings will be used in these summaries, regardless of the methodology of temperature assessment.

8.2.3.1. Electrocardiogram

QTcF categories for each post baseline timepoint (Table 3.40) are defined as:

- Absolute QTcF:
  - ≤450 msec
  - >450 to ≤480 msec
  - >480 to ≤500 msec
  - >500 msec

- Increase from baseline QTcF:
  - <60 msec
  - ≥60 and absolute QTcF≤480 msec
  - ≥60 and absolute QTcF>480 msec

8.2.3.2. Ophthalmic assessments

Ophthalmic assessments will all be summarised for the Ophthalmic Safety population.

Each type of eye assessment (keratopathy (Table 3.44), slit lamp (Table 3.45), Humphrey perimetry (Table 3.46), colour perception (Table 3.47), and best corrected visual acuity (Tables 3.48, Table 3.49)) will be summarised separately by eye, visit and treatment group, including maximum changes from baseline to any visit.

Keratopathy will be summarised by presenting the number of subjects with keratopathy at baseline, and at each visit. For each visit, the proportion of subjects displaying keratopathy and grade of keratopathy in the each eye will be summarised. The number and percentage of subjects with a new keratopathy at any post-baseline visit will also be presented in the same table (Table 3.44).

For best corrected visual acuity, summary statistics for the logMAR score will be displayed for each visit (Table 3.48). A separate tabulation (Table 3.49) will classify changes in logMAR score from baseline as no change (<0.12), possible change (≥0.12 to <0.3)), or definite change (≥0.3) (see Section 13.6.3) for each visit and the maximum change from baseline.

For the colour perception data, the number of Ishihara plates missed will be summarised by visit, and maximum change from baseline, for each eye (Table 8.27).

For retinal data, hyperpigmentation (Table 3.50), hypopigmentation (Table 3.51), appearance of retinal vessel (Table 3.52), optic nerve pallor (Table 3.53), confounding abnormalities (Table 3.54) and retinal changes from baseline (Table 3.55) will be summarised. The number and percentage of subjects with each response (definite, absent, questionable, cannot read, not applicable) will be summarised by visit, eye and treatment group. For retinal changes from baseline, the categories will be no change, questionable change, definite change and cannot grade. The number and percentage of subjects with a definite result at any post-baseline visit, where it was absent or questionable at baseline, will also be included in each table.

9. PHARMACOKINETIC ANALYSES

PK and Population PK analyses will be the responsibility of Clinical Pharmacology Modelling and Simulation within GSK and will be detailed in a separate document.

9.1. Pharmacokinetic / Pharmacodynamic Analyses

If data permit, exploratory PK/PD analyses for TQ data may be undertaken to examine any relationship between PK parameters (e.g. systemic exposure) and/or clinical outcome (relapse-free efficacy) or safety parameters (e.g. change in MetHb). Similarly, exploratory PK/PD analyses for chloroquine and/or desethylchloroquine data will be undertaken only if safety or efficacy results indicate that these data are needed to understand the PK/PD relationships for TQ. Any exposure-response analyses based on emerging data will be described in detail in the study report. A separate analysis plan will describe the details for the population PK/PD analyses.

10. PHARMACOGENETIC ANALYSES

All pharmacogenetic analyses will be performed on the Pharmacogenetics population unless otherwise stated.

A summary of the number (and percentage) of subjects who gave Pharmacogenetics consent and the status of the genotype samples and data will be produced (Table 5.1) Genetic consent will be further detailed in Table 5.2 (reasons consent not obtained, consent withdrawn, sample destruction). A summary of allele frequency by treatment (Table 5.3) and by treatment and region will also be produced (Table 5.4).

10.1. CYP2D6 Metabolism Status

The effect of CYP2D6 metaboliser class on relapse-free efficacy will be analysed as described in Section 8.1.2

11. OTHER STATISTICAL ANALYSES

11.1. Health Outcomes Analyses

Descriptive summaries of the cost of illness questionnaire will be produced for the Safety population.

The aim of these analyses is to determine the cost of an episode of *P. vivax* malaria and an event of haemolysis (regardless of treatment received in this study).

The costs spent on treatment, transport, medication and tests, together with a total cost, will be summarised according to the place at which the subject went to for care (drug shop, trial clinic, other clinic, hospital (inpatient/outpatient), traditional healer, other). Table 6.1 will present the costs associated with the initial episode of malaria, split by country and by visit (Randomisation, Day 15 (follow-up), overall). Table 6.2 will present the costs associated with a relapse episode of malaria, split by country and by visit. Table 6.3 will present the same information associated with a haemolysis event.

The medications purchased will be summarised by cost and according to whether they were associated with a clinic/healer or hospital. Again these will be split by country and visit for the initial episode of malaria (Table 6.4), a relapse episode of malaria (Table 6.5) and haemolysis events (Table 6.6).

A summary of the time lost due to an episode of malaria will be summarised in days according to the subject's occupation. Again these will be split by country and visit for the initial episode of malaria (Table 6.7), a relapse episode of malaria (Table 6.8) and haemolysis events (Table 6.9).

A summary of what subjects did to treat the illness before attending the trial clinic will be summarised by country and visit for the initial episode of malaria (Table 6.10), a relapse episode of malaria (Table 6.11) and haemolysis events (Table 6.12).

Costs will be presented in the original currency and also in United States dollars (USD) to allow costs to be compared across countries. See Section 13.6.5 for conversion to US dollars.

12. REFERENCES

DPWG: Dutch Pharmacogenetics Working Group. Available at https://www.pharmgkb.org/page/dpwg.

Gaedigk A, Simon SD, Pearce RE, Bradford LD, Kennedy MJ, Leeder JS. The CYP2D6 Activity Score: Translating Genotype Information into a Qualitative Measure of Phenotype. *Clin Pharmacol Ther.* 2008; 83:234-242.

GlaxoSmithKline Document Number 2012N152563_01. A Randomized, Double-Blind, Double Dummy, Comparative, Multicenter Study to Assess the Incidence of Hemolysis, Safety, and Efficacy of Tafenoquine (SB-252263, WR238605) versus Primaquine in the Treatment of Subjects with Plasmodium vivax Malaria. Amendment Number 5. Effective Date 15-JUL-2015

GUI_137354, Information for Authors: Reporting and Analysis Plan (RAP), Global

http://www.xe.com/currencytables/?from=USD&date=2015-02-15 (accessed on 23JUL2016)

Nair, I & Patel, B. Attain 100% Confidence in Your 95% Confidence Interval. *Proceedings for the PharmaSUG Conference 2014. (*2014) Available at: http://www.pharmasug.org/proceedings/2014/IB/PharmaSUG-2014-IB05.pdf

Newcombe, RG. Two-Sided Confidence Intervals for the Single Proportion: Comparison of Seven Methods. *Statistics in Medicine* 1998: **17**, 857-872

SOP_54838, Development, Review & Approval of Reporting & Analysis Plan (RAP), Global

Supportive Templates (for RAP), IMMS Example: Reporting and Analysis Plan (RAP) Template_Core Safety Reporting Standards

13. APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 13.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 13.2	Appendix 2: Time and Events
Section 13.3	Appendix 3: Assessment Windows
Section 13.4	Appendix 4: Treatment States & Phases
Section 13.5	Appendix 5: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 13.6	Appendix 6: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Pharmacokinetic • Healthcare Resource Use • Pharmacogenetic
Section 13.7	Appendix 7: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 13.8	Appendix 8: Values of Potential Clinical Importance
Section 13.9	Appendix 9: Multicentre Studies
Section 13.10	Appendix 10: Examination of Covariates and Subgroups
Section 13.11	Appendix 11: Multiple Comparisons and Multiplicity
Section 13.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 13.13	Appendix 13: Abbreviations & Trade Marks
Section 13.14	Appendix 14: List of Data Displays

13.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

13.1.1. Protocol deviations

Major protocol violations could impact the ability to assess efficacy and our primary endpoints for our study. A subject meeting any of the following criteria will be excluded from the Per Protocol population:

Number	Exclusion Description
1	Subject does not have a parasitology assessment within window for any of the Day 2, Day 3, Day 29, Day 60, Day 90, Day 120, Day 150 or Day 180 visits
2	Subject does not demonstrate initial parasite clearance but does not receive rescue medication
3	When in the clinic on Day 1 to 3, subject vomited a dose of study medication and either vomited the redose, or a redose was not given
4	PQ/PQ placebo pill count suggests that the subject failed to take two or more scheduled doses when away from the clinic
5	Violation of any of the following entry criteria: • Subject had a mixed malaria infection at baseline • Subject had an asexual *P. vixax* parasite count $\leq$100 or $\geq$100000 • Subject had a severe malaria infection • Subject had severe vomiting or diarrhoea • Subject had taken anti-malarials within the previous 30 days
6	The subject has taken/received: • anti-malarials (e.g., artemisinin-based combination therapies, mefloquine, primaquine, or any other 4- or 8-aminoquinoline) within 30 days prior to study entry. • treatment with any investigational drug within 30 days of study entry, or within 5 half-lives, whichever is longer. • a concomitant medication with an anti-malarial activity between Day 1 and the Day 180 visit, and remained parasite negative throughout the study. A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified accordingly

NOTES:

- A listing will be produced for the PP population showing
  1. individual subject numbers for each protocol violation
  2. the number and percentage of subjects for each violation
  3. the total number of subjects with one or more violation will be tabulated, by type of violation.

13.2. Appendix 2: Time & Events

13.2.1. Protocol Defined Time & Events

Protocol Activity	Visit Day															
	Screening/Treatment Period[a]							Follow-Up Period							Relapse Visit[b]	Withdrawal Visit[c]
	Day 1[d]	Day 2	Day 3	Day 5	day 8	Day 11	Day 15	Day 22	Day 29	Day 60	Day 90	Day 120	Day 150	Day 180	Relapse	Withdrawal
Window				+1d	-/+1d	-/+1d	-/+2d	-/+3d	-/+3d	-/+7d	-/+7d	-/+10d	-/+10d	-14/+21d		
Informed Consent Process	X															
Demographic Information	X															
Initial History Only [e]	X															
Physician Assess. Malaria Signs & Symptoms	X															
Inclusion/Exclusion Criteria	X															
Efficacy Assessments																
Parasitological Assessment (blood smear)	X[f]	X[f]	X[f]		X		X	X	X	X	X	X	X	X	X	X
Plasmodium PCR Genotyping	X														X	
Plasmodium whole genome sequencing	X														X	
Safety Assessments																
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs [g]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X

Protocol Activity	Visit Day															
	Screening/Treatment Period[a]							Follow-Up Period							Relapse Visit[b]	Withdrawal Visit[c]
	Day 1[d]	Day 2	Day 3	Day 5	day 8	Day 11	Day 15	Day 22	Day 29	Day 60	Day 90	Day 120	Day 150	Day 180	Relapse	Withdrawal
Window				+1d	-/+1d	-/+1d	-/+2d	-/+3d	-/+3d	-/+7d	-/+7d	-/+10d	-/+10d	-14/+21d		
Physical Examination	X	X	X		X		X	X	X	X	X	X	X	X	X	X
ECG w/ Interpret. & Report [h]	X	X							X						X	X
Adverse Events Assessment [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
G6PD (phenotyping) [k]	X									X		X				
G6PD and CYP2D6 (genotyping)		X														
Ophthalmological Exam (qualified sites only)	X								X		X			X[l]		X
Laboratory Assessments																
Hematology [m]	X		X[n]	X	X	X	X	X	X	X	X	X			X	X
Clinical Chemistry [o]	X		X[n]	X	X	X	X	X	X	X	X	X			X	X
Methemoglobin	X	X	X	X	X	X	X	X	X	X		X			X	X
Urinalysis [p]	X		X	X	X	X	X	X	X	X	X	X			X	X
Blood Draw for PGx		X[q]														
Pregnancy Test [r]	X						X		X	X				X	X	X
Health Outcomes																
Health Outcomes Assessments [s]	X						X	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]

Protocol Activity	Visit Day															
	Screening/Treatment Period[a]							Follow-Up Period							Relapse Visit[b]	Withdrawal Visit[c]
	Day 1[d]	Day 2	Day 3	Day 5	day 8	Day 11	Day 15	Day 22	Day 29	Day 60	Day 90	Day 120	Day 150	Day 180	Relapse	Withdrawal
Window				+1d	-/+1d	-/+1d	-/+2d	-/+3d	-/+3d	-/+7d	-/+7d	-/+10d	-/+10d	-14/+21d		
Pharmacokinetic Assessments																
PK/PD Sampling [u]		X	X		X		X		X	X					X	
Investigational Product																
Dispense Open Label Chloroquine	X	X	X													
Dispense Blinded Study Medication	X[v]	X[v]														
Treatment Compliance Int. - Invest.	X	X	X	X	X	X	X									
IVRS Registration	X															

a All subjects must remain hospitalized for Days 1 through 3.
b Subjects who relapse will continue to be monitored for safety and efficacy at all scheduled visits through day 180. Relapse is defined by a positive blood smear with or without vivax symptoms.
c If subjects withdraw from blinded study medication, all scheduled follow-up visits should be performed to conduct safety assessments up to and including Day 180.
d Visit Day 1 includes all screening procedures and the first day of treatment with study medication.
e Includes medical, disease and therapy histories.
f Blood smears are to be taken twice a day, 6-12 hours apart for the first 3 days, or until 2 consecutive negative thick blood smears are obtained.
g Vital signs include height and weight (screening only), blood pressure, temperature, heart rate and respiratory rate. Vital signs are to be performed twice a day on Days 1 through 3, at least 4 hours apart, and immediately prior to PK measurements.
h ECGs are to be performed at screening (in triplicate), 12 hours after the first dose of blinded study medication, and on Day 29.
i Adverse events are recorded from the time of the first dose of study medication.
j Serious adverse events are recorded from the time of consent in order to fulfil international regulatory requirements.
k G6PD phenotyping to be performed by both quantitative spectrophotometric analysis and rapid point of care test.
l Only if Day 90 ophthalmological exam shows abnormalities.
m Hematology includes hemoglobin, hematocrit, red blood cell/white blood cell/platelet counts, mean cell volume, white blood cell differential and reticulocyte count.

n Hematology and clinical chemistry on Day 3 must be reviewed prior to discharge from the hospital.
o Clinical Chemistry includes CPK, BUN, serum creatinine, total and indirect bilirubin and liver clinical chemistry.
p Mid-stream urine will be analyzed for protein, glucose, ketones, bilirubin, blood, nitrites, urobilinogen and leukocyte esterase by dipstick method.
q The pharmacogenetics sample must be collected at the earliest opportunity after randomization and during the in-clinic treatment visit (Days 1-3).
r Serum or urine pregnancy test that is routinely used at site with a test sensitivity for hCG level ≤ 25 mIU/mL. FSH serum test only for post-menopausal females with less than 6 months spontaneous amenorrhea.
s Refer to Section 6.5 of the protocol for details on health outcome data collection.
t Health outcomes assessments will only be collected at these visits from subjects with confirmed parasitemia or from subjects with clinically relevant hemolysis.
u Day 2 and Day 3 PK samples must be taken 6-12 hours and 24-48 hours post TQ dose.
v Treatment with blinded study medication will begin on either Day 1 or Day 2.

13.3. Appendix 3: Assessment Windows

13.3.1. Definitions of Assessment Windows for All Analyses

Visit	Analysis Window	
	Beginning Timepoint	Ending Timepoint
Day 1	Study Day 1	Study Day 1
Day 2	Study Day 2	Study Day2
Day 3	Study Day 3	Study Day 4
12 hours post randomised treatment[1]	11.5 hours post first dose of randomised treatment (Study Days 1-4)	12.5 hours post first dose of randomised treatment (Study Days 1-4)
Day 5	Study Day 5	Study Day 6
Day 8	Study Day 7	Study Day 9
Day 11	Study Day 10	Study Day 12
Day 15	Study Day 13	Study Day 17
Day 22	Study Day 19	Study Day 25
Day 29	Study Day 26	Study Day 32
Day 60	Study Day 53	Study Day 67
Day 90	Study Day 83	Study Day 97
Day 120	Study Day 110	Study Day 130
Day 150	Study Day 140	Study Day 160
Day 180	Study Day 166	Study Day 201

[1]For ECG parameters only

For all data summarised by visit, the nominal visit description will be used. Unscheduled and withdrawal visit data will be slotted into a scheduled visit window, if no competing visit exists within the window. If there are multiple assessments within the same window which are not unscheduled visits, the earliest result will be used in the summaries.

Note that the 12 hours post dose window is used only for the ECG parameters. If there are multiple measurements within the acceptable window, the assessment closest to the nominal visit description will be used in the summaries. If triplicate readings were taken, the mean of the triplicates will be used in the summaries.

13.4. Appendix 4: Treatment States and Phases

13.4.1. Treatment Phases

Treatment phases are not required for this study.

13.4.2. Treatment States

Adverse events will be classified according to time of occurrence relative to the start of the study treatment. No other treatment states are required for this study.

13.4.2.1. Treatment States for Adverse Event Data

Treatment State	Definition
Onset Time Since 1st Dose (Days)	If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on eCRF or value is missing.
Onset in Month 1	AE Start Date ≤ Study Day 29
Onset in Months 2 or 3	Study Day 30 ≤ AE Start Date < Study Day 91
Onset after Month 3	AE Start Date ≥ Study Day 91

NOTES:

- If the study treatment stop date is missing then the AE will be considered to be On-Treatment.

13.5. Appendix 5: Data Display Standards & Handling Conventions

13.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Tafenoquine 300 mg	TQ+CQ	1
B	Primaquine 15 mg	PQ+CQ	2

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

13.5.2. Baseline Definition & Derivations

13.5.2.1. Baseline Definitions

For all endpoints (expect as noted in the additional definitions below) the baseline value will be the latest pre-treatment assessment where treatment is their first dose of study medication (CQ/PQ/TQ/Placebo).

Asexual parasite and gametocyte counts

If there are multiple pre-treatment assessments, a subject will be considered to have a positive (non-zero) baseline count if *any* of the assessments are positive. They will only be considered to have a zero baseline count if all of the pre-treatment assessments are zero.

Pharmacogenetics

The PGx blood draw must be performed at the earliest opportunity after randomisation and during in-clinic treatment (Days 1-3). This will be considered baseline.

Ophthalmic assessments

The last assessment performed on the day of randomisation or earlier will be considered baseline.

13.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 13.5.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.

- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

13.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Area	: /arenv/arprod/sb252263/taf116564/final
QC Spreadsheet	: \\UK1DSNTV003\SB252263-TAFENOQUINE\Vivax Trt\TAF116564
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.13 & AdaM IG Version 1.0 • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated (see Section 4). • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DPs) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DPs, including: o Proportions and their Confidence Intervals will be presented to 3 decimal places. o Rates and their 95% Confidence Intervals will be presented to 1 decimal place
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses : • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.

Reporting Standards	

• The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.
  • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables unless they slot into a missing planned visit (see Section 13.3.1) in which case they will be reported as the planned visit. • Unscheduled visits will not be included in figures unless they slot into a missing visit (see Section 13.3.1) in which case they will be reported as the planned visit. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

13.6. Appendix 6: Derived and Transformed Data

13.6.1. General

Multiple Measurements at One Time Point
• If there are multiple assessments within the same window which are not unscheduled visits, the earliest result will be used in the summaries. All values will be listed. For ECGs, if there are multiple assessments at the same visit, the mean will be derived and used in any derivation of summary statistics but if listed, all data will be presented. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from the date of the Study Day 1 (first dose of study medication including CQ):
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Date of Study Day 1 → Study Day = Ref Date – Date of Study Day 1
  • Ref Data ≥ Date of Study Day 1 → Study Day = Ref Date – (Date of Study Day 1) + 1
• Study Day 180 refers to a time point exactly 179 days after Study Day 1 (when the first dose of study medication including CQ was taken), whereas the 'Day 180 visit' refers to the nominal Day 180 assessments which did not necessarily occur on Study Day 180.

13.6.2. Study Population

Demographics
Age
• Only the year of birth is collected in the eCRF and the day and month are imputed as '30th June'. • GSK standard IDSL algorithms are used to calculate age at baseline. • Birth date will be presented in listings as 'YYYY'. • Age on the date of first dose will be calculated in years.

Prior and Concomitant Medications
• Medications will be coded using the latest version of GSK Drug. • Prior medications = medications taken up to 30 days before the date and time of the first dose of study medication. • Any medications with stop dates earlier than 30 days will not be reported in tables and listings. • Concomitant medications = medications with start date and time on or after the start date and time of the first dose of study medication (Study Day 1). • See Section 13.7.2 for the handling of missing and partial dates.

Treatment Compliance and Exposure

- For the first three days of the study, all study medication will be administered in the presence of the Investigator or study nurse, and ingestion confirmed.
- On any day of in clinic dosing, a subject will be classified as compliant with daily administered dose if they do not vomit the initial dose or if they are successfully re-dosed.
- A subject is considered to be compliant in clinic if they retain all study medication given to them on all three days of dosing.
- Subjects will also take PQ or PQ placebo on Study Days 4 to 15, where administration is not directly observed (with the exception of G6PD-deficient subjects, who will receive directly-observed therapy on all 15 days).
- A patient will be considered to be compliant as an outpatient if their final pill count data shows they took at least 12 doses of PQ or PQ placebo.
- Compliance will also be determined using the Day 8 and Day 15 PK samples i.e. a quantifiable amount of carboxyPQ from samples taken at the Day 8 and Day 15 visits. No assessment windows will be applied.
- Subjects who were randomized but did not report a treatment start date will be categorised as having zero doses.
- Treatment stop dates are not recorded so duration of exposure will not be calculated.

G6PD enzyme activity as a percentage of site median

- Each site has a median G6PD enzyme value for healthy G6PD-normal subjects, determined from G6PD-normal males in study TAF115226:

Region	Country	Site	Investigator	Centre ID	G6PD median value (IU/g Hb)
South America	Brazil	Manaus	De Lacerda	PPD	7.92
	Peru	Iquitos	Llanos		9.01
	Colombia	Monteria	Vilegas		8.32
	Colombia	Cali	Velez		7.17
Asia	Thailand	Bangkok	Krudsood		7.40
	Thailand	Umphang	Namaik-Larp		8.16
	Thailand	Shoklo Malaria Research Unit (SMRU)	Nosten		7.79
	Vietnam	Ho Chi Minh City	Tran		8.38

- Enzyme activity as percentage of site median = (absolute enzyme activity / site median) x 100%

13.6.3. Safety

Clinically Relevant Haemolysis

- Clinically relevant haemolysis is defined as: a decrease in haemoglobin of ≥30% or >30 g/L (>3

Clinically Relevant Haemolysis
g/dL) from baseline; or, an overall drop in haemoglobin below 60 g/L (6.0 g/dL) at any visit after the first dose of study medication. • If a subject has any missing post-baseline haemoglobin data up to Study Day 17, the primary endpoint will be set to missing. • A subject will be classified as not having haemolysis at any visit if they do not meet the above haemoglobin criteria and no visits are missing up to Study Day X. • See Section 13.7.2.3 for further handling of missing data.

ECG Parameters
RR Interval
• ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value so no derivation is required.
Corrected QT Intervals
• QTcF will be derived at the site and entered into the eCRF.

Adverse Events
• All AEs reported up to and including the Day 180 visit following enrolment of a subject into the study will be documented. • These will be recorded and coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). All terms applied will be reviewed by a GSK physician prior to unblinding. If any malaria related coded terms are considered to have lost useful information in the coding step (e.g., if a verbatim term of '*Plasmodium vivax* malaria' is mapped to 'malaria'), he/she will recommend a study-specific code, which will be documented. The process will be completed prior to study unblinding. • Treatment emergent AEs are defined as AEs with an onset date and time on or after that of the start of first dose of study medication (including CQ). • AEs with entirely missing or unknown start dates will be assumed to be treatment emergent for reporting. AEs where the start date is equal to that of study medication, but where the start time is unknown will also be assumed to be treatment emergent. AEs with missing end dates are not anticipated to affect reporting. • If the grade/intensity is missing for an AE, it will be considered severe/Grade 3 if an AE, or Grade 4 if an SAE and the subject is alive, or Grade 5 if an SAE and the subject dies (i.e. the highest intensity possible) for the summary of AEs by maximum intensity. • See Section 13.7.2 for more information on missing and partial dates. • Common AEs are those occurring in ≥5% of subjects in any treatment group. • The occurrence of malaria and any associated signs and symptoms are recorded as Disease Related Events (DREs) and will not be classified as AEs. • The GSK clinical team will review terms that qualify as haematologically related.

Absolute differentials and reticulocytes
• If sites provide white blood cell (WBC) differential (i.e., eosinophil, neutrophil, lymphocyte,

monocyte and basophil) results as a percentage of total WBCs, these values will be converted to an absolute result (expressed in 10^9/L , equivalent to GI/L) for reporting purposes using the following formula:

*Absolute differential (*10^9/L*) = 0.01x (percentage differential) x (WBC in 10^9/L).*

- If reticulocytes are reported as a proportion of total red blood cells (RBCs), these values will also be converted to an absolute result (expressed in 10^12/L, equivalent to TI/L) using the following formula:

Absolute reticulocytes (10^12/L) = (reticulocytes as a proportion) x (RBC in 10^12/L).

Estimated Glomerular Filtration Rate (eGFR)

- eGFR will be defined using the abbreviated Modification of Diet in Renal Disease formula, when creatinine is in standard unites of µmol/L:

$$eGFR\ (ML/SEC/1.73M2) = 32788 \times (Creatinine)^{-1.154} \times (Age)^{-0.203} \times (0.742\ \text{if female}) \times (1.210\ \text{if Black}) \times 0.0167$$

- A subject with a race of Black or African American or who has a mixed race including Black or African American will be considered Black for the purpose of the eGFR calculation.

Best Corrected Visual Acuity

- Best corrected visual acuity is assessed individually for each eye. In the eCRF, scores will be recorded as a ratio, for example 6/6, 6/7.5, or 6/9.5. These values will be used to derive a logMAR score for the statistical analysis, where logMAR = -1x $\log_{10}$ (ratio score). Thus, a ratio score of 6/9.5 corresponds to a logMAR score of 0.20.
- logMAR changes from baseline are classified as:
  - no change: <0.12
  - possible change: ≥0.12 to <0.3
  - definite change: ≥0.3

Vital Signs – Mean Arterial Blood Pressure

- To be calculated (to 1 decimal place) where systolic and diastolic blood pressure are both present at the same timepoint:

$$mean\ arterial\ blood\ pressure = \frac{(systolic\ blood\ pressure + 2(diastolic\ blood\ pressure)}{3}$$

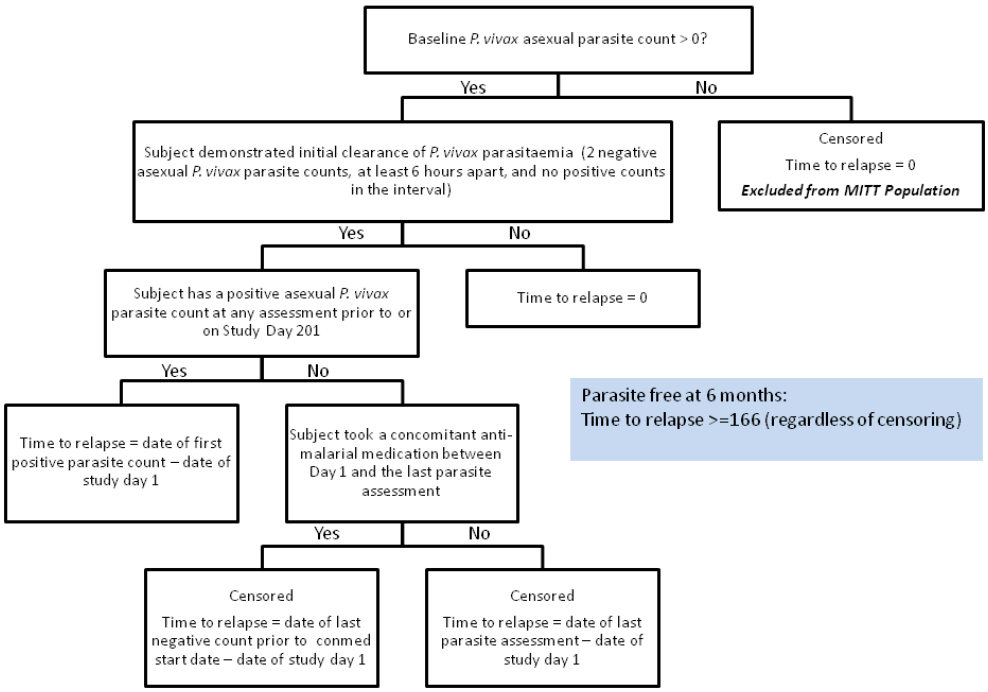
13.6.4. Efficacy

Relapse free efficacy and Time to Relapse
Six months

• A subject will be considered to have demonstrated relapse-free efficacy at 6 months for the purposes of the analysis if **all** of the following are true (also described in the flowchart below):
  ◦ Subject had a non-zero *P. vivax* asexual parasite count at baseline. Subjects with no asexual *P. vivax* parasites at this time point will be censored with time to relapse = 0 days.
  ◦ Subject demonstrated initial clearance of *P. vivax* parasitaemia. This is defined as two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval. Subjects who do not meet this criteria will be classified as relapses, with time to relapse = 0 days.
  ◦ Subject has no positive asexual *P. vivax* parasite count at any assessment prior to or on Study Day 201 following initial parasite clearance. Subjects who do have a positive count will be classified as relapses, with time to relapse = (date of first positive count) – (date of Study Day 1) days.
  ◦ Subject did not take a concomitant medication with anti-malarial activity at any point between Study Day 1 and their last parasite assessment. A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified accordingly. 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 last negative parasite assessment prior to concomitant medication start) – (date of Study Day 1).
  ◦ Subject is parasite-free at 6 months. This is defined as a negative asexual *P. vivax* parasite count at the first parasite assessment performed on or after Study Day 166.
• Subjects who do not have a positive asexual *P. vivax* parasite count following initial clearance but where the final parasite count occurred before Study Day 166 will not have been classified by the preceding rules. These subjects will be considered to be censored, with time to relapse censored at (Date of final parasite assessment) – (date of Study Day 1).
• If a subject has a relapse outcome and a censored outcome, they will be considered to be a relapse, even if the time point of the relapse is later than the time point of censoring. For example, a subject who took a medication with anti-malarial activity at Study Day 32, but remained parasite-free after initial clearance until Study Day 68 will be treated as a relapse at Study Day 68.

Relapse free efficacy and Time to Relapse

Flow chart of algorithm:



Four months

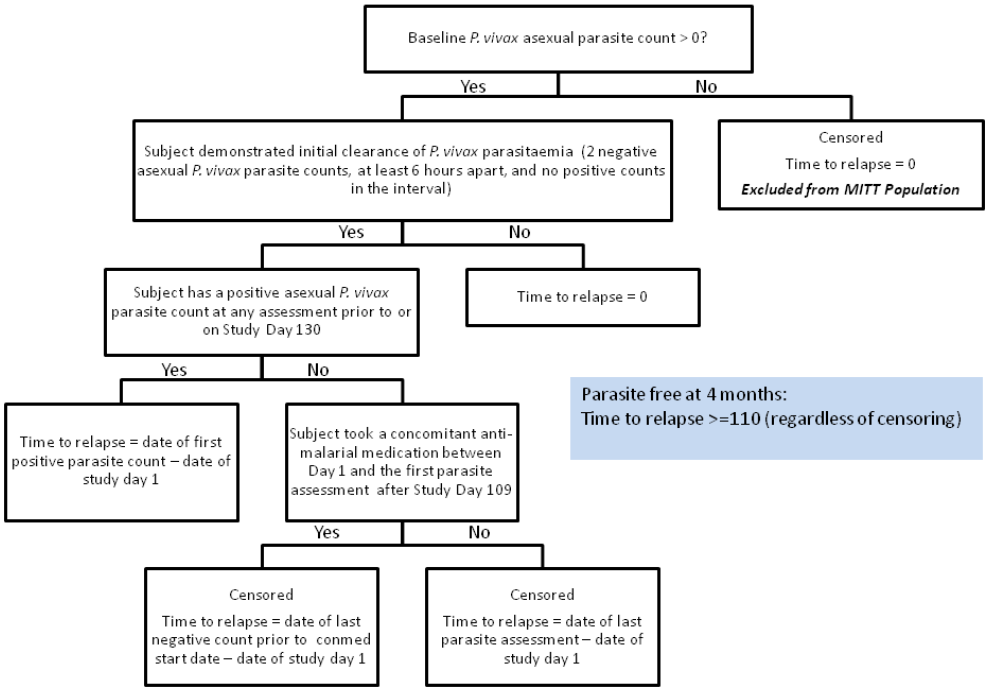
- A subject will be considered to have demonstrated relapse-free efficacy at 4 months for the purposes of the analysis if **all** of the following are true (also described in the flowchart below)::
  - Subject had a non-zero *P. vivax* asexual parasite count at baseline. Subjects with no asexual *P. vivax* parasites at this time point will be censored with time to relapse = 0 days.
  - Subject demonstrated initial clearance of *P. vivax* parasitaemia. This is defined as two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval. Subjects who do not meet this criteria will be classified as relapses, with time to relapse = 0 days.
  - Subject has no positive asexual *P. vivax* parasite count at any assessment prior to or on Study Day 130 following initial parasite clearance. Subjects who do have a positive count will be classified as relapses, with time to relapse = (date of first positive count) – (date of Study Day 1) days.
  - Subject did not take a concomitant medication with anti-malarial activity at any point between Study Day 1 and their first parasite assessment after Study Day 109. A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified accordingly. 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 last negative parasite assessment prior to concomitant medication start) – (date of Study Day 1).
  - Subject is parasite-free at 4 months. This is defined as a negative asexual *P. vivax* parasite

Relapse free efficacy and Time to Relapse

count at the first parasite assessment performed after Study Day 109.

- Subjects who do not have a positive asexual *P. vivax* parasite count following initial clearance but where the final parasite count occurred on or before Study Day 109 will not have been classified by the preceding rules. These subjects will be considered to be censored, with time to relapse censored at (Date of final parasite assessment) – (date of Study Day 1).
- If a subject has a relapse outcome and a censored outcome, they will be considered to be a relapse, even if the time point of the relapse is later than the time point of censoring. For example, a subject who took a medication with anti-malarial activity at Study Day 32, but remained parasite-free after initial clearance until Study Day 68 will be treated as a relapse at Study Day 68.

Flow chart of algorithm:



Relapse free efficacy at 6 months missing=failure definition

- In addition to those with a positive asexual *P. vivax* parasite count at any assessment prior to or on Study Day 201, the following subjects will also be defined to have relapsed:
  - Subject did not demonstrate initial clearance of *P. vivax* parasitaemia (i.e. did not have two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval)
  - Subject took a concomitant medication with anti-malarial activity at any point between Study Day 1 and their last parasite assessment. A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified

Relapse free efficacy and Time to Relapse
accordingly. o Subject does not have a parasite assessment between Study Day 166 and 201. • Subjects with a zero *P. vivax* asexual parasite count at baseline will be excluded from the analysis.
Relapse free efficacy at 6 months missing on or after Day 29=failure definition
• In addition to those with a positive asexual *P. vivax* parasite count at any assessment prior to or on Study Day 201, the following subjects will also be defined to have relapsed: • Subject did not demonstrate initial clearance of *P. vivax* parasitaemia (i.e. did not have two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval) • Subject took a concomitant medication with anti-malarial activity at any point between Study Day 1 and their last parasite assessment. A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified accordingly. • Subject with a missing parasite assessment on or after Study Day 29 • Subjects with a zero *P. vivax* asexual parasite count at baseline will be excluded from the analysis
Relapse free efficacy at 4 months missing=failure definition
• In addition to those with a positive asexual *P. vivax* parasite count at any assessment prior to or on Study Day 130, the following subjects will also be defined to have relapsed: o Subject did not demonstrate initial clearance of *P. vivax* parasitaemia (i.e. did not have two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval) o Subject took a concomitant medication with anti-malarial activity at any point between Study Day 1 and their last parasite assessment. A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified accordingly. o Subject does not have a parasite assessment between Study Day 110 and 130. • Subjects with a zero *P. vivax* asexual parasite count at baseline will be excluded from the analysis.

Incidence of recrudescence
Recrudescence
• A subject will be considered to have had a recrudescence if both of the following are true: • Subject had a positive *P. vivax* asexual parasite count at baseline and at least one subsequent zero asexual parasite count within Study Days 1-5. • Subject has a positive genetically homologous asexual *P. vivax* parasite count, after their zero count in days 1 to 5, but on or before Study Day 32. • The following subjects will have a censored time to recrudescence of 0 days: • Subject had no asexual *P. vivax* parasites at baseline.

Incidence of recrudescence
• Subject had a positive *P. vivax* asexual parasite count at baseline but had no subsequent zero asexual parasite count within Study Days 1-5. • If a subject does not meet the definition of recrudescence, but took a concomitant medication with anti-malarial activity between Study Day 1 and Study Day 32, they will be censored, with time to recrudescence censored at (date of last negative parasite assessment prior to concomitant medication start) – (date of Study Day 1). • All other subjects will be censored with time to recrudescence censored at their last parasite assessment on or before Study Day 32, with time to recrudescence = (Date of final parasite assessment) – (date of Study Day 1).

Clearance time
Parasite (PCT)
• Defined as: time needed to clear asexual parasite from the blood i.e. parasite numbers falling below the limit of detection in the thick blood smear and remaining undetectable ≥6 hours later. • If a subject has a non-zero asexual *P. vivax* parasite count at baseline, and prior to Study Day 8 has two negative counts with at least 6 hours between the counts and no positive parasite counts within this time period, parasite clearance time will be defined as the time elapsed between the first dose of study medication (including CQ) and the first of these negative counts (measured in hours). • Subjects with a negative parasite count at baseline will be censored with a parasite clearance time of 0 hours. All other subjects will be censored at the time of the last non-missing assessment prior to Study Day 8.
Fever (FCT)
• Defined as: time from first dose of treatment to the time when body temperature falls to normal within Study Days 1-4 and remains normal for at least 48 hours up to the Day 8 visit. • Any subject who does not have a temperature in excess of 37.4^0C at any point prior to the first dose of study medication (including CQ) on Study Day 1 will be censored with a fever clearance time of 0 hours. Subjects will also be censored at time 0 if the method of temperature measurement is not consistent throughout Study Days 1 to 4 (i.e., method is not consistently oral, tympanic, or axillary). • Fever clearance is considered to have been achieved once an initial temperature of >37.4^0C is reduced to a value ≤37.4^0C, in the absence of value >37.4^0C in the following 48 hours up to the Day 8 visit. • Subjects who do not demonstrate this endpoint prior to final assessment of Study Day 4 will be censored at that time point. • Subjects with missing data in Study Days 1-4 will be censored at the last available temperature assessment, if they do not meet the definition of fever clearance before the Day 8 visit.
Gametocyte (GCT)
• Defined as: time from first dose until the first slide that was gametocyte negative and remained so at the next slide reading. • Any subject with negative *P. vivax* gametocytes at baseline will be censored with a time to gametocyte clearance of 0 days. • For all other subjects, gametocyte clearance will be considered to have been achieved once a

Clearance time
negative gametocyte value has been seen, unless the next gametocyte count is positive. Time to clearance will then be defined as (time to first negative value) – (time of first dose of study medication including CQ). • Subjects who fail to reach this endpoint will be censored at the visit of their final gametocyte assessment.

Gametocyte emergence
• Gametocyte emergence is defined as the presence of *P. vivax* gametocytes at a post-baseline visit, where the subject did not have gametocytes at baseline

Early Failure

• An early failure is defined as a subject who either:
  • Did not demonstrate initial clearance of *P. vivax* parasitaemia (i.e. did not have two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval), OR
  • Demonstrates initial clearance and has a subsequent non-zero asexual *P. vivax* parasite count on or before Study Day 32.

13.6.5. Healthcare Resource Use

Currency Conversion

- To convert local currencies into a comparable combinable unit, all currencies will be converted into US Dollars (USD), at the exchange rate obtained from xe.com reported for 15 February 2015 (accessed on 23JUL2016). This date was chosen as a midpoint in the study.

Currency	USD per unit
Brazilian Real	0.3528270266
Peruvian Sol	0.3272251315
Colombian Peso	0.0004193751
Thai Baht	0.0306701426
Vietnamese Dong	0.0000468165

13.6.6. Exploratory G6PD and CYP-2D6 Genotype Analyses

G6PD Mutations
Emory Genetics Laboratory will provide a description of the G6PD mutation (such as Vanua Lava (c.383T>C, p.L128P- exon 5) het). In addition, the WHO classification of G6PD enzyme deficiency will be provided for each mutation observed
CPD2D6 Activity and Metabolizer Phenotype
• Quest Nichols laboratory will provide CYP2D6 *alleles which will be used to derive metabolizer

G6PD Mutations
Emory Genetics Laboratory will provide a description of the G6PD mutation (such as Vanua Lava (c.383T>C, p.L128P- exon 5) het). In addition, the WHO classification of G6PD enzyme deficiency will be provided for each mutation observed
CPD2D6 Activity and Metabolizer Phenotype

class (PM, IM, EM, UM)
• Each of the two CYP2D6 *alleles, comprising the genotype, will be assigned a value relative to its activity compared to the *1 reference allele:
  • Value of 0 for null activity alleles: *3, *4, *4xN, *5, *6, *7, *8, *11, *12,*13, *15, *16, *19, *20, *21, *38, *40, *42, *56B
  • Value of 0.5 for reduced activity alleles: *9, *10, *17, *29, *41
  • Value of 1 for fully functional alleles: *1, *2, *33, *35
  • Value of 2 for fully functional alleles carrying gene duplications: *1xN, *2xN, *33xN, *35xN
  • For all *alleles that are not captured above, the activity score will be determined prior to unblinding the data.
• Alleles denoting gene duplications, represented by 'xN', will receive double the non-duplicated value. For example *1xN will receive a value of 2 whereas *1 receives a value of 1.
• The CYP2D6 Activity Score (AS) [Gaedigk, 2008] is then calculated as the sum of activity values from the two alleles comprising the genotype. For example, a subject with 2 null alleles will have an AS of 0; one null and one reduced activity allele will have a score of 0.5; or one null allele and one fully functional allele will have an AS of 1.
• The CYP2D6 phenotype will be classified based on the AS and follows the Dutch Pharmacogenomics Working Group [DPWG] classification scheme.
  • Poor metabolizer (PM) if AS = 0
  • Intermediate metabolizer (IM) if AS = 0.5 or 1
  • Extensive metabolizer (EM) if AS is 1.5 or 2
  • Ultrametabolizer (UM) if AS ≥2.5

13.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

13.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion is defined as a subject that does not withdraw from the study and attends the Day 180 visit. • Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

13.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument : o These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects with outlying results may be excluded in additional *ad hoc* summaries and/or statistical analyses. These will be documented along with the reason for exclusion in the clinical study report, but the primary conclusions will remain based on the full population sets.

13.7.2.1. Handling of Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• It is not possible to record partial dates in the eCRF for AEs. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • AEs with entirely missing or unknown start dates will be assumed to be treatment emergent for reporting. • AEs with missing end dates are not anticipated to affect reporting.
Concomitant medications	• Where the start or stop date of a concomitant medication record is entirely unknown and is totally missing at the time of reporting, the eCRF flags 'Taken prior to study?' and 'Ongoing medication?' will be used in order to derive whether it is prior or concurrent. • If these flags are also missing, then it will be assumed that it is concurrent.

Element	Reporting Detail
	• In the event that use of the same medication is recorded at more than one visit (and if this has not been collapsed to one record), the eCRF flags will be cross-checked for both records.

13.7.2.2. Handling of Partial Dates

Element	Reporting Detail

Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
	• The recorded partial date will be displayed in listings.

Adverse Events	• It is not possible to record partial dates in the eCRF for AEs.
Date of birth	• Where a subject's date and month of birth is not known, the investigator has been asked to enter them as 30th June, and where month is known but date is unknown, the investigator has been asked to enter the 15th. • Thus all subjects should have an actual or an assumed date of birth entered on the eCRF. • In the event that any partial dates do occur for date of birth, age should be calculated using 30th June for an unknown date and month, and 15th for an unknown date only. • Only the year will be displayed in listings.

13.7.2.3. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Incidence of Haemolysis	• For the primary analysis only observed data will be used. • A sensitivity analysis will be performed where missing haemolysis data before Study Day 17 will be imputed as 'haemolysis=YES'.
Relapse-free efficacy and time to event endpoints	• For all analyses of the mITT population, subjects will not be excluded from any statistical analyses. • From the Day 29 assessment onwards, subjects who have not relapsed but fail to have an evaluable parasite smear within the visit window for every scheduled visit will be excluded from the PP population. • See Section 13.6.4 for further details on how missing assessments will be censored.
Derived variables	• For derived variables, details of how any missing eCRF data will be handled are provided in Section 13.6.

13.8. Appendix 8: Values of Potential Clinical Importance

13.8.1. Laboratory Values

Element	Reporting Detail
F1 flag	• Denotes a value that falls outside the normal range. • Used by the laboratory and provided directly by the site for inclusion on the database.
F2 flag	• Denotes a value that has increased or decreased from baseline by more than a specified amount. • Defined below

F3 flag	• Denotes a value that falls outside an extended normal range.
	• This range is independent of direction of change or other values.
	• F3 range is calculated as:
	  • Absolute: pre-specified limits.
	  • Proportional: upper and lower limits are defined by multiplying the normal range limits by different factors
	• Defined below

General	• If a subject has both 'high' and 'low' values flagged for a parameter during the study, they will be reported once under each category.

Haematology				
Laboratory Parameter	Units	Category	Clinical Concern Range	
			Low Flag (< x)	High Flag (>x)
Haemoglobin	G/L	F2	Max(baseline – >30 g/L, ≥30% decline from baseline)	
Platelets	10^9/L	F3	50	
Leukocytes	10^9/L	F3	2	
Neutrophils, segmented	10^9/L	F3	1	
Eosinophils	10^9/L	F3		1.5
Lymphocytes	10^9/L	F3	0.5	4
Methaemoglobin	%	F3		10
Reticulocytes	10^12/L	F3		1xULN

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Creatine kinase [a]	IU/L	F3		5x ULN
Creatinine[a]	μmol/L	F2		3x baseline
		F3		3x ULN
Urea [b]	mmol/L	F3		11.067
Estimated glomerular filtration rate[a]	ml/sec/ 1.73m^2	F3	0.4843	
Alanine aminotransferase	IU/L	F3		3x ULN
Aspartate aminotransferase	IU/L	F3		3x ULN
Total bilirubin	μmol/L	F3		1.5x ULN
Indirect bilirubin	μmol/L	F3		1.5x ULN
Alkaline phosphatase	IU/L	F3		2.5xULN

a. CTC AE criteria
b. FDA industry toxicity grading scale for healthy volunteer adults and adolescents in preventative vaccine trials

13.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	**Upper**
Absolute			
Absolute QTc Interval	msec		> 480
Change from Baseline			
Increase from Baseline QTc	msec		> 60

Note: both criteria (absolute and change from baseline) must be met to be of clinical concern.

13.9. Appendix 9: Multicenter Studies

13.9.1. Methods for Handling Centres

- In this multicentre global study, enrolment will be presented by investigative site and country.
- Regions are defined geographically for inclusion as covariates as:

Region	Countries
South America	Brazil, Peru, Colombia
Asia	Thailand, Vietnam

Centers will be pooled for assessing the primary assessment of incidence of clinically relevant hemolysis.

13.10. Appendix 10: Examination of Covariates, Subgroups & Other Strata

13.10.1. Handling of Covariates, Subgroups & Other Strata

Region is defined as in Section 13.9.1. Section 8.1.2 details how the impact of region will be assessed.

13.11. Appendix 11: Multiple Comparisons & Multiplicity

13.11.1. Handling of Multiple Comparisons & Multiplicity

No multiple comparisons will be performed in this study and so no adjustments for multiplicity are required.

13.12. Appendix 12: Model Checking and Diagnostics for Statistical Analyses

13.12.1. Statistical Analysis Assumptions

If models are not deemed appropriate following the checks described below, alternative appropriate methods (e.g. Fisher's exact test) will be additionally performed.

13.12.1.1. Cox proportional hazards model

The proportional hazards assumption should be assessed including a check of the Kaplan-Meier curves. The shape of the curves should be similar for the 2 treatment groups with the separation between the curves remaining proportional across time. A complementary log-log plot may also be used to check the proportional hazards assumption.

13.12.1.2. Logistic Regression

Model checking may include goodness of fit tests and residual plots (Pearson and deviance residuals to detect outliers and/or influential points).

13.13. Appendix 13 – Abbreviations & Trade Marks

13.13.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
A&R	Analysis and Reporting
AS	Activity Score
BMI	Body Mass Index
Bun	Blood Urea Nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CQ	Chloroquine
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DRE	Disease-Related Event
DP	Decimal Places
DPWG	Dutch Pharmacogenomics Working Group
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
eGFR	Estimated Glomerular Filtration Rate
FCT	Fever Clearance Time
G	Gram
G6PD	Glucose-6-phosphate dehydrogenase
GCSP	Global Safety and Pharmacovigilance
GCT	Gametocyte Clearance Time
GSK	GlaxoSmithKline
Hb	Haemoglobin
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IVRS	Interactive Voice Recognition System
ITT	Intent-To-Treat
GUI	Guidance
kg	Kilogram
L	Litre
LFT	Liver Function Tests
mITT	Microbiologic Intent To Treat
m	Metre

Abbreviation	Description
MedDRA	Medical Dictionary for Regulatory Activities
MetHb	Methaemoglobinemia
MPV	Major Protocol Deviation
mg	Milligram
msec	Millisecond
PCI	Potential Clinical Importance
PCR	Polymerase Chain Reaction
PCT	Parasite Clearance Time
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
P. falciparum	*Plasmodium falciparum*
PGx	Pharmacogenetics
PK	Pharmacokinetic
PP	Per Protocol
PQ	Primaquine
P. vivax	*Plasmodium vivax*
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RBC	Red Blood Cell
RUCAM	Roussel Uclaf Causality Assessment Method
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	Standard Operation Procedure
SPM	Study Procedures Manual
TA	Therapeutic Area
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures & Listings
TQ	Tafenoquine
ULN	Upper Limit of Normal
USD	United States Dollars
V/F	Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organisation

13.13.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

13.14. Appendix 14: List of Data Displays

13.14.1. Data Display Numbering

Section	Tables	Figures
Study Population	1.1 to 1.22	None
Efficacy	2.1 to 2.32	2.1 to 2.4
Safety	3.1 to 3.56	3.1 to 3.48
Pharmacogenetics	5.1 to 5.4	None
Health Outcomes	6.1 to 6.12	None
Section	**Listings**	
ICH Listings	1 to 19	
Other Listings	20-38	

13.14.2. Deliverable

Delivery	Description
SAC	Final Statistical Analysis Complete
Headline	Headline Results

13.14.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Populations Analysed					
1.1.	All Subjects Screened	SA1	Summary of Analysis Populations	IDSL	Headline
Subject Disposition					
1.2.	Safety	IE1	Summary of Inclusion/Exclusion Criteria Deviations		SAC
1.3.	Safety	ES1	Summary of Subject Disposition	ICH E3, GSK CTR, FDAAA, EudraCT	SAC
1.4.	Safety	SA3	Summary of Discontinuation of Study Medication		SAC
1.5.	Safety	SA2	Summary of Study Recruitment – Number of Subjects by Country and Centre	EudraCT	Headline
1.6.	Safety	ES6	Summary of Reasons for Screen Failure	Journal Requirements Add footnote: 'G6PD normal females screened after randomisation was closed to normal females had reason recorded as Investigator Discretion.'	SAC
Protocol Deviations					
1.7.	Safety	DV1B	Summary of Important Protocol Deviations	ICH E3	SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Demographic and Baseline Characteristics					
1.8.	Safety	DM1	Summary of Demographic Characteristics	ICH E3, GSK CTR, FDAAA, EudraCT Include age, sex, ethnicity, weight, height, BMI, respiratory rate, G6PD enzyme activity, G6PD enzyme activity (as % of site median). Height, Weight, BMI, and respiratory rate are collected in DMDATA. VITALS where VISITNUM=10 and PTMNUM=20. G6PD enzyme activity is collected in DMDATA.LAB where VISITNUM=10 and LBTESTCD='G6PD_BLC'. All other parameters are collected on DMDATA.DEMO	Headline
1.9.	Safety	DM5	Summary of Race and Racial Combinations	ICH E3, GSK CTR, FDA, FDAAA, EudraCT	SAC
1.10.	Safety	DM6	Summary of Race and Racial Combinations Details	ICH E3, FDA	SAC
Prior and Concomitant Medications and Conditions					
1.11.	Safety	CM1	Summary of Prior Medications	Add footnote 'Only medications taken prior to the start date and time of first dose of study medication, and within 30 days of Study Day 1 are included.' ICH E3	SAC
1.12.	Safety	CM1	Summary of Concomitant Medications	ICH E3	Headline
1.13.	Safety	CM1	Summary of Paracetamol Usage		SAC
1.14.	Safety	SA4	Summary of Malarial Signs and Symptoms		SAC
1.15.	Safety	MH1	Summary of Current Medical Conditions by Body System	ICH E3	SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.16.	Safety	MH1	Summary of Past Medical Conditions by Body System	ICH E3	SAC
1.17.	Safety	MH4	Summary of Current Specific Medical Conditions		SAC
1.18.	Safety	MH4	Summary of Past Specific Medical Conditions		SAC
1.19.	Safety	SA5	Summary of Splenomegaly at Baseline		SAC
1.20.	Safety	SA6	Summary of Previous Episodes of Malaria		SAC
Exposure and Treatment Compliance					
1.21.	Safety	SA7	Summary of Study Medication Compliance and Exposure	ICH E3	Headline – excluding PQ PK data SAC – including PQ PK data
Diagnostic					
1.22.	All subjects screened	SA8	Comparison of G6PD point of care test versus G6PD enzyme activity test		SAC

13.14.4. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Parasite counts					
2.1.	mITT	SA9	Summary of *P.vivax* Asexual Parasites at all Timepoints (count per ml)		SAC
2.2.	mITT	SA10	Summary of Other Malarial Asexual Parasites at all Timepoints (count per ml)	Page by parasite	SAC
2.3.	mITT	SA10	Summary of *P.vivax* Gametocytes at all Timepoints (count per ml)		SAC
2.4.	mITT	SA10	Summary of Other Malarial Gametocytes at all Timepoints (count per ml)	Page by gametocyte	SAC
Relapse-free efficacy					
2.5.	mITT	SA11	Summary of Relapse-Free Efficacy at 6 Months		SAC
2.6.	PP	SA12	Summary of Relapse-Free Efficacy at 6 Months		SAC
2.7.	mITT	SA13	Summary of Relapse-Free Efficacy at 4 Months		SAC
2.8.	PP	SA14	Summary of Relapse-Free Efficacy at 4 Months		SAC
2.9.	mITT	TTE6	Analysis of Relapse-Free Efficacy at 6 Months (Cox Proportional Hazards Methodology)		Headline
2.10.	PP	TTE6	Analysis of Relapse-Free Efficacy at 6 Months (Cox Proportional Hazards Methodology)		Headline
2.11.	mITT	TTE6	Analysis of Relapse-Free Efficacy at 4 Months (Cox Proportional Hazards Methodology)		Headline
2.12.	PP	TTE6	Analysis of Relapse-Free Efficacy at 4 Months (Cox Proportional Hazards Methodology)		Headline

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.13.	mITT	SA15	Analysis of Relapse-Free Efficacy at 6 Months (Logistic Regression) (Subjects Censored Prior to 6 Months Excluded)		Headline
2.14.	mITT	SA15	Analysis of Relapse-Free Efficacy at 4 Months (Logistic Regression) (Subjects Censored Prior to 4 Months Excluded)		Headline
2.15.	mITT	SA15	Analysis of Relapse-Free Efficacy at 6 Months (Logistic Regression) (Missing=Failure Analysis)	Add footnotes: "Subjects who do not demonstrate initial clearance, take a concomitant medication with anti-malarial activity or have a missing Day 180 assessment are counted as relapses." "Subjects with a zero *P. vivax* asexual parasite count at baseline are excluded from the analysis."	Headline
2.16.	mITT	SA15	Analysis of Relapse-Free Efficacy at 4 Months (Logistic Regression) (Missing=Failure Analysis)	Add footnotes: "Subjects who do not demonstrate initial clearance, take a concomitant medication with anti-malarial activity or do not have an assessment between Study Day 110 and 130 are counted as relapses." "Subjects with a zero *P. vivax* asexual parasite count at baseline are excluded from the analysis."	Headline

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.17.	mITT	SA15	Analysis of Relapse-Free Efficacy at 6 Months (Logistic Regression) (Missing on or after Study Day 29=Failure Analysis)	Add footnotes: "Subjects who do not demonstrate initial clearance, take a concomitant medication with anti-malarial activity or have a missing assessments on or after Day 29 are counted as relapses." "Subjects with a zero P. vivax asexual parasite count at baseline are excluded from the analysis."	
2.18.	mITT	TTE6	Analysis of Relapse-Free Efficacy at 6 Months (Cox Proportional Hazards Methodology) – by Genetic Classification (Homologous / Heterologous)	Include genetic classification as a by-group	SAC
2.19.	mITT	TTE6	Analysis of Relapse-Free Efficacy at 4 Months Cox Proportional Hazards Methodology) - by Genetic Classification (Homologous / Heterologous)	Include genetic classification as a by-group	SAC
2.20.	mITT	SA37	Analysis of Subjects with Relapse-Free Efficacy at 6 Months - Treatment by Region Interaction		SAC
Time to Event endpoints					
2.21.	mITT	TTE3	Analysis of Time to Relapse	Give time in days Exclude hazard ratio section and footnote	SAC
2.22.	mITT	TTE3	Analysis of Parasite Clearance Time	Give time in hours	SAC
2.23.	mITT	TTE3	Analysis of Fever Clearance Time	Give time in hours	SAC
2.24.	mITT	TTE3	Analysis of Gametocyte Clearance Time	Give time in days	SAC
Other efficacy endpoints					
2.25.	mITT	SA23	Summary of *P. vivax* Gametocyte Emergence		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.26.	mITT	TTE7	Analysis of Recrudescence (Blood Stage Failure) Rates		SAC
2.27.	mITT	SA24a	Summary of Early Failures		SAC
2.28.	mITT	SA24b	Summary of Genetic Classification by PCR of Relapse Infections Occurring on or After Study Day 33		SAC
2.29.	mITT	SA25	Summary of *P. falciparum* Asexual Parasite Emergence	Change display to a listing if 5 or fewer subjects in total	SAC
CYP2D6					
2.30.	PGx	SA45	Analysis of Subjects with Relapse-Free Efficacy at 6 Months by CYP2D6 Metaboliser Class – Logistic Regression – PM and IM vs EM+UM		SAC
2.31.	PGx	SA45	Analysis of Subjects with Relapse-Free Efficacy at 6 Months by CYP2D6 Metaboliser Class – Logistic Regression – IM vs EM		SAC
2.32.	PGx	SA37	Effect of CYP2D6 Activity Score (AS) on Relapse-Free Efficacy at 6 Months – Logistic Regression		SAC

13.14.5. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Relapse-free efficacy					
2.1.	mITT	SF4	Kaplan-Meier Survival Curves for Relapse-Free Efficacy at 6 Months		Headline
2.2.	PP	SF4	Kaplan-Meier Survival Curves for Relapse-Free Efficacy at 6 Months		SAC
2.3.	mITT	SF4	Kaplan-Meier Survival Curves for Relapse-Free Efficacy at 6 Months – by Genetic Classification (Homologous / Heterologous)	One plot for each classification (page by)	SAC
2.4.	mITT	SF5	Frequency (95% Confidence Interval) of Genetically Homologous and Genetically Heterologous Infections Occurring on or After Study Day 33		SAC

13.14.6. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Incidence of haemolysis					
3.1.	Safety	SA40	Analysis of Incidence of Haemolysis		Headline
3.2.	Safety	SA40	Analysis of Incidence of Haemolysis (Missing data sensitivity analysis)	Exclude 'Missing' row. Add footnote to say 'Missed visits up to Study Day 17 have been imputed as Yes'	Headline
Adverse Events (AEs)					
3.3.	Safety	AE1	Summary of All Treatment Emergent Adverse Events by Treatment by System Organ Class	ICH E3 Add footnote: 'Events are ordered based on Total incidence'	SAC
3.4.	Safety	AE3	Summary of Common Treatment Emergent Adverse Events (>=5% in Any Treatment Group) by Preferred Term	ICH E3, GSK CTR Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	Headline
3.5.	Safety	AE15	Summary of Common (>=5% in Any Treatment Group) Non-serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC
3.6.	Safety	AE3	Summary of All Drug-Related Treatment Emergent Adverse Events by Treatment by Preferred Term	GSK CTR Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	Headline
3.7.	Safety	AE5	Summary of Treatment Emergent Adverse Events by Maximum Intensity	Add footnote: 'Events are ordered based on Total incidence'	SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.8.	Safety	AE3	Summary of All Treatment Emergent Adverse Events by Treatment by Preferred Term	Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	SAC
3.9.	Safety	AE3	Summary of Treatment Emergent Adverse Events with Onset On or Prior to Study Day 29	Add footnote: 'Events are ordered based on Total incidence'	Headline
3.10.	Safety	AE3	Summary of Treatment Emergent Adverse Events with Onset Date in Month 2 or 3	Add footnote: 'Events are ordered based on Total incidence'	SAC
3.11.	Safety	AE3	Summary of Treatment Emergent Adverse Events with Onset On After Month 3	Add footnote: 'Events are ordered based on Total incidence'	SAC
Serious and Other Significant Adverse Events					
3.12.	Safety	AE3	Summary of Fatal Serious Treatment Emergent Adverse Events	GSK CTR Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	SAC
3.13.	Safety	AE1	Summary of Serious Treatment Emergent Adverse Events by System Organ Class	GSK CTR, IDSL Add footnote: 'Events are ordered based on Total incidence'	SAC
3.14.	Safety	AE3	Summary of Serious Treatment Emergent Adverse Events by Preferred Term	GSK CTR Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	Headline

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.15.	Safety	AE3	Summary of Drug-Related Treatment Emergent Serious Adverse Events by Preferred Term	GSK CTR Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	SAC
3.16.	Safety	AE3	Summary of Drug-Related Fatal Serious Treatment Emergent Adverse Events by Preferred Term	GSK CTR Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	SAC
3.17.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAA, EudraCT	SAC
3.18.	Safety	AE3	Summary of Treatment Emergent Adverse Events Leading to Withdrawal from the Study	IDSL Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	Headline
3.19.	Safety	AE3	Summary of Treatment Emergent Adverse Events Leading to Discontinuation of Study Treatment	IDSL Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	Headline
3.20.	Safety	AE1	Summary of Treatment Emergent Adverse Events Considered to be Haematologically-Related	Add footnote: 'Events are ordered based on Total incidence'	Headline
3.21.	Safety	AE3	Summary of Grade 3 and Grade 4 Treatment-Emergent Adverse Events by Preferred Term	Include Grade 3 and Grade 4 events only. Order events in descending order by incidence in TQ+CQ arm only. Add footnote: 'Events are ordered based on incidence in TQ+CQ arm'	SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Laboratory: Chemistry					
3.22.	Safety	SA35	Summary of Clinical Chemistry Data by Treatment and Time	Remove sex column	Headline
3.23.	Safety	SA36	Summary of Change from Baseline in Clinical Chemistry Data by Treatment and Time	ICH E3 Remove sex column	Headline
3.24.	Safety	LB2	Summary of Clinical Chemistry Laboratory Data Outside the Reference Range (F3)		SAC
Laboratory: Haematology					
3.25.	Safety	SA35	Summary of Haematology Data by Treatment, Time and Sex		Headline
3.26.	Safety	SA36	Summary of Change from Baseline in Haematology Data by Treatment, Time and Sex	ICH E3	Headline
3.27.	Safety	LB2	Summary of Haematology Laboratory Data Outside the Reference Range (F3)		SAC
3.28.	Safety	SA26	Summary of Categories of Change from Baseline Haemoglobin (G/L)) Data by Treatment and Time		SAC
3.29.	Safety	SA26	Summary of Categories of Change from Baseline Haemoglobin (G/L)) Data by Treatment, Time and Sex	Add sex column	Headline
3.30.	Safety	SA41	Summary of Haemoglobin Declines over First 29 Days		SAC
3.31.	Safety	SA41	Summary of Haemoglobin Declines over First 29 Days by Sex	Add sex column	SAC
Laboratory: Urinalysis					
3.32.	Safety	SA35	Summary of Urine Concentrations Changes from Baseline by Treatment and Time	ICH E3 Remove gender column	SAC
3.33.	Safety	UR1	Summary of Urinalysis Dipstick Results	IDSL	SAC
Hepatobiliary (Liver)					
3.34.	Safety	LIVER1	Summary of Liver Events Assessment	IDSL	SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.35.	Safety	LIVER2	Summary of Time on Treatment Before Liver Event		SAC
3.36.	Safety	LIVER3	Summary of Liver Biopsy Details		SAC
3.37.	Safety	LIVER4	Summary of Liver Imaging Details		SAC
ECG					
3.38.	Safety	EG1	Summary of ECG Findings	IDSL	SAC
3.39.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL At baseline, 12 hours post-first dose of randomised study medication, Day 29	SAC
3.40.	Safety	SA27	Summary of QTcF Values by Category and Visit	At baseline, 12 hours post-first dose of randomised study medication, Day 29	Headline
3.41.	Safety	CP_EG12	Summary of Maximum Change from Baseline QTcF up to 72 hours Post Randomised Treatment		Headline
Vital signs					
3.42.	Safety	VS1	Summary of Absolute Values in Vital Signs by Visit	ICHE3 Include Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Blood Pressure, Heart Rate, Respiratory Rate and Temperature	SAC
3.43.	Safety	VS1	Summary of Change From Baseline in Vital Signs by Visit	ICHE3 Include Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Blood Pressure, Heart Rate, Respiratory Rate and Temperature	SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Ophthalmic Assessments					
3.44.	Ophthalmic Safety	SA29	Summary of Keratopathy	If no keratopathy is reported, display should be blank with 'No subjects reported keratopathy displayed'	SAC
3.45.	Ophthalmic Safety	SA30	Summary of Slit Lamp Assessments		SAC
3.46.	Ophthalmic Safety	SA30	Summary of Humphrey Perimetry Assessments		SAC
3.47.	Ophthalmic Safety	SA32	Summary of Colour Perception Assessments		SAC
3.48.	Ophthalmic Safety	SA33	Summary of Best Corrected Visual Acuity Test Scores		SAC
3.49.	Ophthalmic Safety	SA34	Summary of Best Corrected Visual Acuity Classification		SAC
3.50.	Ophthalmic Safety	SA28	Summary of Hyperpigmentation		SAC
3.51.	Ophthalmic Safety	SA28	Summary of Hypopigmentation		SAC
3.52.	Ophthalmic Safety	SA28	Summary of Appearance of Retinal Vessel		SAC
3.53.	Ophthalmic Safety	SA28	Summary of Optic Nerve Pallor		SAC
3.54.	Ophthalmic Safety	SA28	Summary of Confounding Abnormalities		SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.55.	Ophthalmic Safety	SA28	Summary of Retinal Changes from Baseline	Exclude baseline rows. Categories will be 'no change', 'questionable change', 'definite change', 'cannot grade'	SAC
Blood Transfusions					
3.56.	Safety	SA38	Summary of Blood Transfusions		SAC

13.14.7. Safety Figures

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Incidence of haemolysis					
3.1.	Safety	SF3	Incidence of Haemolysis by Treatment Group		SAC
Adverse Events					
3.2.	Safety	AE10	Plot for Common Adverse Events (>=5% in Any Treatment Group) by Overall Frequency	IDSL	SAC
Clinical laboratory endpoints					
3.3.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Eosinophils		SAC
3.4.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Haemoglobin		SAC
3.5.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Haematocrit		SAC
3.6.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Lymphocytes		SAC
3.7.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Mean Corpuscle Volume		SAC
3.8.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Methaemoglobin (%)		SAC
3.9.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Segmented Neutrophils		SAC
3.10.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Platelet Count		SAC

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.11.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Erythrocytes		SAC
3.12.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Reticulocytes		SAC
3.13.	Safety	LB9	Boxplot of Haematological Parameters by Visit and Treatment Group – Leukocytes		SAC
3.14.	Safety	LB9	Boxplot of Haemoglobin by Visit and Treatment Group – Males		SAC
3.15.	Safety	LB9	Boxplot of Haemoglobin by Visit and Treatment Group – Females		SAC
3.16.	Safety	LB9	Boxplot of Change from Baseline in Haemoglobin by Visit and Treatment Group		SAC
3.17.	Safety	LB9	Boxplot of Methaemoglobin by Visit and Treatment Group – Males		SAC
3.18.	Safety	LB9	Boxplot of Methaemoglobin by Visit and Treatment Group – Females		SAC
3.19.	Safety	LB9	Boxplot of Reticulocytes by Visit and Treatment Group – Males		SAC
3.20.	Safety	LB9	Boxplot of Reticulocytes by Visit and Treatment Group – Females		SAC
3.21.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Indirect Bilirubin		SAC
3.22.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Total Bilirubin		SAC
3.23.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Creatine Kinase		SAC

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.24.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Urea		SAC
3.25.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Creatinine		SAC
3.26.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Alkaline Phosphatase		SAC
3.27.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Alanine Amino Transferase		SAC
3.28.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group – Aspartate Amino Transferase		SAC
3.29.	Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Treatment Group - G6PD enzyme activity		SAC
3.30.	Safety	LB9	Boxplot of Change from Baseline in Clinical Chemistry Parameters by Visit and Treatment Group - G6PD enzyme activity		SAC
3.31.	Safety	LB9	Boxplot of Total Bilirubin by Visit and Treatment Group – Males		SAC
3.32.	Safety	LB9	Boxplot of Total Bilirubin by Visit and Treatment Group – Females		SAC
3.33.	Safety	LB9	Boxplot of Indirect Bilirubin by Visit and Treatment Group – Males		SAC
3.34.	Safety	LB9	Boxplot of Indirect Bilirubin by Visit and Treatment Group – Females		SAC
3.35.	Safety	SF1	Maximum Fall in Haemoglobin over First 29 Days by Enzyme Activity and Treatment Group	Subjects with decline of >20g/L in haemoglobin only	SAC

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.36.	Safety	SF1	Maximum Fall in Haemoglobin over First 29 Days by Enzyme Activity and Treatment Group - Females	Subjects with decline of >20g/L in haemoglobin only	SAC
3.37.	Safety	SF1	Maximum Fall in Haemoglobin over First 29 Days by Enzyme Activity and Treatment Group – G6PD Deficient Males	Subjects with decline of >20g/L in haemoglobin only	SAC
3.38.	Safety	SF2	Mean Change from Baseline in Haemoglobin by Treatment Group, Visit and G6PD status (Subjects with Known G6PD Genotype)		SAC
3.39.	Safety	SF2	Mean Change from Baseline in Haemoglobin by Treatment Group and Visit (Male Subjects with Unknown G6PD Genotype)		SAC
3.40.	Safety	LB11	LFT Profile Plots	Only for subjects with >3 ULN in ALT or AST. Add footnote to this effect. The subject ID, treatment group, sex, age and race should be included as a header for each subject's plot.	SAC
3.41.	Safety	LB11	Haematology Profile Plots	Only for subjects with a >20g/L decline from baseline haemoglobin or is a female who was genotyped and found to be G6PD deficient Add footnote to this effect. The subject ID, treatment group, sex, age and G6PD status should be included as a header for each subject's plot.	SAC

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.42.	Safety	LB11	Clinical Chemistry Profile Plots	Only for subjects with >3 ULN in ALT or ASTor change from baseline in urea or creatinine > 50% Add footnote to this effect. The subject ID, treatment group, sex, age and race should be included as a header for each subject's plot.	SAC
3.43.	Safety	LB11	G6PD Enzyme Activity Profile Plots	Only for G6PD deficient females	SAC
3.44.	Safety	LB10	Distribution of Maximum LFTs by Treatment Group		SAC
3.45.	Safety	LB7	LFT Shift from Baseline to Maximum Value		SAC
3.46.	Safety	LB8	Matrix Display of Maximum LFT Values		SAC
ECG					
3.47.	Safety	LB9	Boxplot of Changes in QTcF by Visit and Treatment Group		SAC
Vital Signs					
3.48.	Safety	LB9	Boxplot of Mean Arterial Blood Pressure by Visit and Treatment Group		SAC

13.14.8. PharmacogeneticTables

Pharmacogenetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PGx General Summaries					
5.1.	PGx	GN1	Summary of Subject Accountability for PGx	Categories to use under Genotype sample status: • Collected and evaluable • Collected but consent withdrawn • Collected but not evaluable • Not collected Change 'Genotype data status' to 'Genetic data status' and include: • G6PD • CYP2D6	SAC
5.2.	PGx	GN2	Summary of Genetic Consent Not Obtained/Withdrawn		SAC
5.3.	PGx	GN5	Summary of Allele Frequency by Treatment		SAC
5.4.	PGx	GN5	Summary of Allele Frequency by Treatment and Region		SAC

13.14.9. Health Outcomes Tables

Health Outcomes: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Cost of Illness Survey					
6.1	Safety	COI1	Summary of Costs Associated with the Initial Episode of *P. vivax* Malaria - By Country and Visit		SAC

Health Outcomes: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
6.1	Safety	COI1	Summary of Costs Associated with a Relapse Episode of P. *vivax* Malaria - By Country and Visit		SAC
6.2	Safety	COI1	Summary of Costs Associated with a Haemolysis Event - By Country and Visit		SAC
6.3	Safety	COI2	Summary of Medication Costs Associated with the Initial Episode of *P. vivax* Malaria - By Country and Visit		SAC
6.4	Safety	COI2	Summary of Medication Costs Associated with a Relapse Episode of *P. vivax* Malaria - By Country and Visit		SAC
6.5	Safety	COI2	Summary of Medication Costs Associated with a Haemolysis Event - By Country and Visit		SAC
6.6	Safety	COI3	Summary of Time Lost Due to the Initial Episode of *P. vivax* Malaria - By Country and Visit		SAC
6.7	Safety	COI3	Summary of Time Lost Due to a Relapse Episode of *P. vivax* Malaria - By Country and Visit		SAC
6.8	Safety	COI3	Summary of Time Lost Due to a Haemolysis Event - By Country and Visit		SAC
6.9	Safety	COI4	Summary of Actions Associated with the Initial Episode of *P. vivax* Malaria - By Country and Visit		SAC
6.10	Safety	COI4	Summary of Actions Associated a Relapse Episode of *P. vivax* Malaria - By Country and Visit		SAC
6.11	Safety	COI4	Summary of Actions Associated with a Haemolysis Event - By Country and Visit		SAC

13.14.10. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population - Subject Disposition					
1.	Safety	BL1	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	SAC
2.	Safety	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
Study Population - Protocol Deviations					
3.	Safety	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
4.	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Study Population - Populations Analysed					
5.	Safety	SA3a	Listing of Subjects Excluded from Any Population	ICH E3	SAC
Study Population - Demographic and Baseline Characteristics					
6.	Safety	DM2	Listing of Demographic Characteristics	ICH E3	SAC
7.	Safety	DM9	Listing of Race and Racial Combinations	ICH E3	SAC
Study Population - Exposure					
8.	Safety	LA7a	Listing of Exposure Data	ICH E3	SAC
Safety - Adverse Events					
9.	Safety	AE8	Listing of All Adverse Events	ICH E3 Include flag for treatment emergent	SAC
10.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
Safety - Serious and Other Significant Adverse Events					
11.	Safety	AE8	Listing of Fatal Adverse Events	ICH E3 Include reasons for considering AE to be serious	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
12.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3 Include reasons for considering AE to be serious	SAC
13.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal From Study	ICH E3	SAC
14.	Safety	AE8	Listing of Disease Related Events	ICH E3	SAC
Safety - All Laboratory endpoints					
15.	Safety	LB5	Listing of Laboratory Data with Abnormalities of Potential Clinical Importance	ICH E3	SAC
16.	Safety	LB5	Listing of Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance	ICH E3	SAC
17.	Safety	UR2a	Listing of Urinalysis Data	ICH E3 All subjects	SAC
Safety - Hepatobiliary (Liver)					
18.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Criteria	IDSL	SAC
Safety - Vital Signs					
19.	Safety	VS4	Listing of Vital Signs	Include mean arterial BP	SAC

13.14.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population - Subject Disposition					
20.	Safety	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
21.	Safety	TA1	Listing of Planned and Actual Treatments	IDSL	SAC
Study Population - Demographic and Baseline Characteristics					
22.	Safety	LA1	Listing of Malaria Signs and Symptoms at Baseline		SAC
23.	Safety	MH2	Listing of Past and Current Medical Conditions		SAC
Study Population - Concomitant Medication					
24.	Safety	CM2	Listing of Prior and Concomitant Medications	Include concomitant medications and prior medications taken within 30 days of first dose of study medication	SAC
Study Population - Compliance					
25.	Safety	LA7b	Listing of Compliance Data		SAC
Efficacy					
26.	mITT	LA4	Listing of Results of Efficacy Endpoints		SAC
27.	mITT	LA5	Listing of Malarial Parasite Counts		SAC
28.	mITT	LA6	Listing of Time to Fever Clearance Data		SAC
Safety - Adverse Events					
29.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms and Verbatim Text	IDSL	SAC
Safety - All Laboratory endpoints					
30.	Safety	LA8	Listing of Haemoglobin Drops for G6PD Deficient Subjects		

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Safety - Hepatobiliary (Liver)					
31.	Safety	LIVER5	Listing of Liver Event Results and Time of Event Relative to Treatment		SAC
32.	Safety	LIVER6	Listing of Liver Event Information for RUCAM Score		SAC
33.	Safety	LIVER7	Listing of Liver Imaging Details		SAC
Safety - ECG					
34.	Safety	EG3	Listing of ECG Values		SAC
35.	Safety	EG5	Listing of ECG Findings		SAC
Safety - Ophthalmic Assessments					
36.	Ophthalmic Safety	LA2	Listing of Ophthalmic Assessments		SAC
37.	Ophthalmic Safety	LA3	Listing of Retinal Examination		SAC
Health Outcomes – Cost of Illness Survey					
38.	Safety	LA9	Listing of Cost of Illness Survey		SAC

Summary of changes: Reporting and analysis plan

TAF116564

Title	:	Reporting and Analysis Plan for TAF116564: A Randomized, Double-Blind, Double Dummy, Comparative, Multicenter Study to Assess the Incidence of Haemolysis, Safety, and Efficacy of Tafenoquine (SB-252263, WR238605) versus Primaquine in the Treatment of Subjects with *Plasmodium vivax* Malaria.
Compound Number	:	SB-252263
Effective Date	:	21-FEB-2017

RAP Section	Amendment Details
Reporting and Analysis Plan_StudyTAF115654_Final [05-AUG-2016]	
Reporting and Analysis Plan_StudyTAF115654_Final_Amend 1 [21-FEB-2017]	
1.0, 4, 8.1.2, 10, 13.14.4, 13.14.8	Removal of Pharmacogenetics population – not required. mITT and Safety populations are sufficient as CYP2D6 and G6PD genotyping are collected under the main Informed Consent.
7.1.2	Correction of Newcombe upper confidence limit equation
8.1.2, 13.14.4, 13.14.5, 13.14.11	Secondary Statistical Analyses: Re-design of efficacy analysis tables to display Cox Proportional Hazard and Kaplan-Meier results in one display Sensitivity Analyses: By Genetic Classification: re-design of analyses to look at heterologous and homologous infections separately with new censoring rules Sensitivity Analyses: Chloroquine Supply: Additional analyses included to investigate the effect of chloroquine supplied before and after a cut-off date Secondary Statistical Analyses: Early Failures: Inclusion of category of early failures where the parasite genetics are missing; listing added Secondary Statistical Analyses: CYP2D6: minor changes to the output statistics
8.2.2, 13.14.6	Urine concentration change from baseline removed as no continuous urinalysis data is collected
13.6.3	Laboratory Parameters: Standard text on handling non-detectable lab values added
13.6.4	Relapse-free efficacy at 6 months and 4 months definitions: censoring added to account for subjects that take a concomitant medication with anti-malarial action prior to clearance plus clarification to the time periods assessed for 4 months Genetic classification of relapse definition: added to include censoring rules Recrudescence definition: clearance definition updated in line with other efficacy endpoints Fever clearance definition: updated to reflect Time and Events schedule of temperature collection
13.10.1	Addition of chloroquine supply covariate
Various	Typographical errors corrected

Division: Worldwide Development
Retention Category: GRS019
Information Type: Meta-Analysis Plan

Title:	Meta-Analysis Plan for 207581: Comparing the efficacy of 300 mg single dose tafenoquine with 14-day primaquine 15 mg treatment regimen for the prevention of *P. vivax* relapse: a non-inferiority analysis.

Compound Number: SB252263

Effective Date: 30-MAR-2017

Description: This document described the planned meta-analysis for tafenoquine, comparing the efficacy of the 300mg single dose of tafenoquine to that of the 15mg primaquine once daily dose for 14 days

Subject: tafenoquine, primaquine, chloroquine, meta-analysis, non-inferiority, hazard ratio

Author:

PPD Principal Statistician	30-MAR-2017

PPD Principal Statistician	30-MAR-2017

Approved by:

PPD Director, Statistics	05-APR-2017

TABLE OF CONTENTS

PAGE

ABBREVIATIONS

CDISC	Clinical Data Interchange Standards Consortium
CQ	Chloroquine
mITT	Microbiologic Intent to Treat
P. vivax	*Plasmodium vivax*
PP	Per Protocol
PQ	Primaquine
TQ	Tafenoquine

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
SAS

1. INTRODUCTION

Plasmodium vivax malaria is a neglected tropical disease and a major cause of uncomplicated malaria (~50% cases malaria worldwide). In addition, recent evidence suggests that the severity of disease that can be caused by *P. vivax* has been underestimated. *P. vivax* malaria has significant economic impact primarily in South & South East Asia, Latin America and the horn of Africa, where the majority of the estimated 130-390 million annual clinical cases occur, many of whom are children.

The current gold standard for treatment of *P. vivax* malaria in many areas of the world is chloroquine (CQ); typically 600 mg day one, 600 mg day two, 300 mg day three for clearance of the acute parasitaemia immediately followed by primaquine (PQ) 15 mg once daily x 14 days to clear the liver stages of the parasite and prevent disease relapse. The PQ dose is typically increased to 22.5 mg or 30 mg once daily x 14 days in areas where PQ tolerant hypnozoites are present. The 14-day regimen for PQ has presented major compliance problems, resulting in a significant degree of *P. vivax* malaria relapses in treated populations. Shorter courses (e.g., seven days) are sometimes utilised, but there is no evidence that they are effective[1]. Consequently, anti-relapse therapy for *P. vivax* malaria is impractical in most endemic regions due to duration of treatment resulting in poor compliance.

There is a need to provide alternative treatments to manage vivax relapse over and above PQ. Tafenoquine (TQ, SB-252263 and WR 238605), is a new 8-aminoquinoline anti-malarial drug being co-developed by GlaxoSmithKline and the Medicines for Malaria Venture with the assistance and historic support of the Walter Reed Army Institute of Research. It is a synthetic analogue of PQ. Tafenoquine has shown to be well-tolerated in the treatment and prevention of plasmodial infections in pre-clinical models and during Phase 1, 2 and 3 clinical studies in >4000 subjects and is currently in phase 3 for a radical cure indication in *P. vivax* malaria. Of note, TQ possesses activity against all stages of the *Plasmodium* lifecycle, including the dormant *P. vivax* hypnozoite.

A phase III program is currently underway to study TQ in adult subjects with *P. vivax* malaria. This program is comprised of two studies: TAF112582, a seamless phase II/III study in which the phase II portion has completed and an efficacious and well-tolerated single dose of 300mg TQ has been selected for the two ongoing trials. Both the phase III portion of TAF112582 and phase III study TAF116564 will assess the efficacy and safety of the selected TQ+CQ regimen in the radical cure of *P. vivax* malaria compared to CQ only.

PQ and TQ are both 8-aminoquinolines that have demonstrated (PQ+CQ)/ hope to demonstrate (TQ+CQ) efficacy over CQ only (which is akin to placebo for prevention of relapse) in the radical cure of *P. vivax* malaria. However, a clinical study to directly assess the treatment difference between PQ+CQ and TQ+CQ has not been conducted - it is expected that compliance with PQ treatment in a clinical trial setting will be notably better than in a real world use setting, necessitating an unfeasibly large study to test a superiority hypothesis. Similarly, a non-inferiority study with a credible non-inferiority margin would require a large study and subsequent delay to launch of TQ in endemic

countries. Therefore, a meta-analysis of the phase 2b/3 studies is proposed to establish non-inferiority of TQ+CQ to PQ+CQ in the clinical trial setting.

All decisions regarding final analysis, as defined in this Meta-Analysis Plan document, have been made prior to the database lock of both the phase III portion of TAF112582 and the phase III study TAF116564.

2. OBJECTIVE(S) AND ENDPOINT(S)

2.1. Objective(s)

To conduct a meta-analysis testing the hypothesis that TQ+CQ is non-inferior to PQ+CQ for the prevention of relapse over the six month post-dosing period. The upper 95% confidence bound of the TQ+CQ versus PQ+CQ hazard ratio will be compared to a pre-specified non-inferiority margin.

Superiority of TQ+CQ over PQ+CQ will be claimed if there is a statistically significant difference, in favour of TQ+CQ, for the time to relapse, at the 5% level.

2.2. Endpoint(s)

The primary endpoint is the time-to-relapse in the six month post-dosing period and the treatment difference will be assessed as a hazard ratio.

The rationale behind using survival analysis and a hazard ratio to assess the treatment difference for non-inferiority is that it makes the most use of the individual patient data that will be available, including the time to relapse. In addition, the survival analysis methodology allows for the censoring of subjects who had not relapsed at the end of their follow up in the study.

The secondary endpoint is the proportion of relapse. In the event that the proportional hazards assumption is violated for the primary endpoint (see Section 9.4) the odds ratio will be assessed for non-inferiority (see Section 9.5). An additional sensitivity analysis will also be performed, where some subjects with missing data will be classified as having relapsed in an additional Missing on or after Day 29=Failure sensitivity analysis (see Section 8.2).

3. DATA SOURCES/STUDIES INCLUDED

- The individual patient data from the PQ+CQ and CQ only arms of the DETECTIVE Part 1 study will be used alongside published data and clinical opinion to define the non-inferiority limit (further details in Section 9.2)

- The individual patient data from the TQ+CQ and PQ+CQ arms of the DETECTIVE Part 2 and GATHER studies will be used to calculate a combined hazard ratio and 95% confidence interval (further details in Section 9.4).

DETECTIVE Part 1

TAF112582 (DETECTIVE) is a seamless phase II/III, multi-centre, double-blind, double-dummy, parallel group, randomised, active control study. In Part 1 (phase 2b) of the study, all subjects were treated with CQ on Days 1 to 3 (600 mg, 600 mg, 300 mg) to treat the blood stage malaria infection. Subjects were randomised to one of six groups (ratio 1:1:1:1:1:1):

- Placebo (CQ only),
- Single dose TQ 50mg,
- Single dose TQ 100mg,
- Single dose TQ 300mg,
- Single dose TQ 600mg, or
- 15mg PQ od for 14 days.

A total of 329 subjects were enrolled in this study. Subjects were followed up for six months to assess the proportion of subjects who remained relapse free in that time.

DETECTIVE Part 2

The Part 2 of TAF112582 is a Phase III confirmatory trial which is currently ongoing and has enrolled 522 subjects. All subjects received open label CQ for the first three days of the study to treat the blood stage of the infection. Subjects were randomised to one of three groups (ratio 2:1:1):

- Single dose TQ 300mg,
- PQ 15 mg od for 14 days, or
- Placebo (CQ only).

The primary endpoint (% relapse-free efficacy over six months) is the same as for Part 1 (phase 2b) of the study.

GATHER

The phase III study TAF116564 (GATHER) is similar in design to pivotal Part 2 of DETECTIVE. It is a prospective, double-blind, multicenter study where a total of 251 subjects have been randomised. All subjects received open label CQ for the first three days of the study to treat the blood stage of the infection. Subjects were randomised to one of two groups (ratio 2:1):

- Single dose TQ 300mg, or
- PQ 15mg od for 14 days.

This study does not contain a placebo arm, as the primary endpoint is safety, and efficacy is a secondary endpoint. However, efficacy assessment methodology and timings, and duration of follow-up are identical to DETECTIVE.

4. PLANNED ANALYSES

The individual patient data meta-analysis will be conducted after the datasets from the individual studies have been integrated according to CDISC standards.

5. ANALYSIS POPULATIONS

Microbiologic Intent to Treat (mITT) Population: all randomized subjects who receive at least one dose of blinded study medication and have microscopically-confirmed *P. vivax* parasitemia. Subjects will be analyzed according to their randomized treatment.

Per Protocol (PP) Population: all subjects in the mITT population for whom there were no major protocol violations within the individual studies.

The PP population will be the primary population for the non-inferiority analysis and the mITT population will be used for sensitivity/supporting analysis.

The rationale behind looking at both the mITT and PP populations is that we want to be able to claim superiority, if it exists. The PP population is considered more conservative for non-inferority analysis, where any existing treatment differences are not underestimated due to the presence of protocol violators. Conversely, the the mITT population is considered more conservative for a superiority analysis, so we are stating up-front an intention to look at both.

The datasets will contain flags to identify which analysis populations subjects are eligible for. Inclusion in the mITT and PP populations was determined for individual patients within the DETECTIVE Part 2 and GATHER studies prior to the unblinding of the studies. The populations used for this meta-analysis will be consistent with the studies, and details of major protocol violations resulting in exclusion from the PP population are provided in the study reporting and analysis plans.

6. TREATMENT COMPARISONS

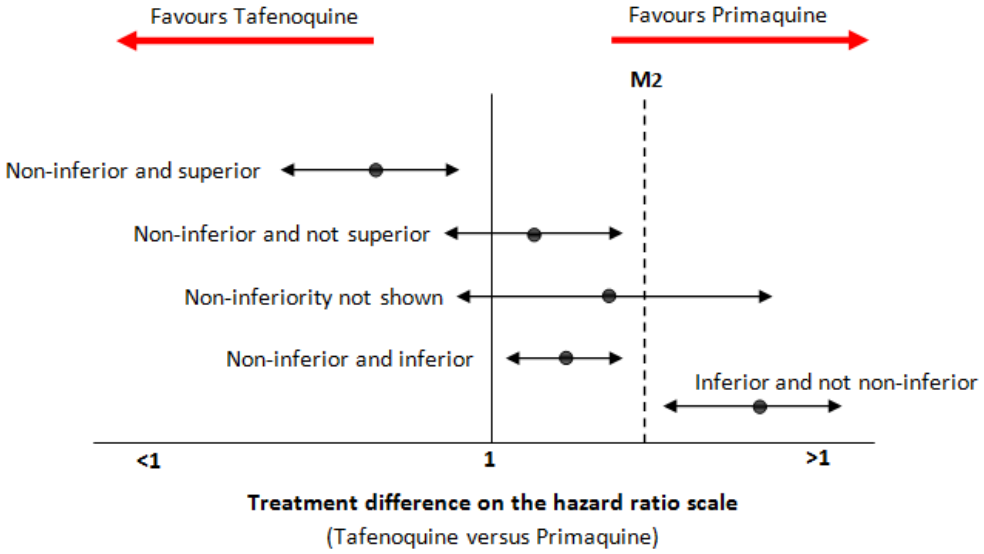
The primary comparison of interest is TQ+CQ versus PQ+CQ on the risk of relapse over the six month period post-dosing, with a primary objective of assessing non-inferiority. Superiority of TQ+CQ over PQ+CQ will be claimed if it exists.

The upper 95% confidence bound of the hazard ratio will be compared to a pre-specified non-inferiority margin (further details in Section 9). If the upper bound is:

- Less than one, then TQ+CQ will be declared both non-inferior and superior to PQ+CQ.
- Less than the non-inferiority limit and greater than one, then TQ+CQ will be declared non-inferior to PQ+CQ.
- Either equal to or greater than the non-inferiority limit, then non-inferiority between TQ+CQ and PQ+CQ has not been demonstrated.

Figure 1 shows the graphical interpretations of the possible TQ+CQ versus PQ+CQ hazard ratios and 95% confidence intervals.

Figure 1 Interpretation of the TQ+CQ versus PQ+CQ hazard ratio and 95% confidence interval (M2 represents the pre-determined non-inferiority margin).



For data displays, and throughout this document, treatment groups are defined using the following descriptors:

Treatment Group	Short Label Descriptor
Tafenoquine 300 mg + chloroquine	TQ+CQ
Primaquine + chloroquine	PQ+CQ
Chloroquine	CQ only

7. GENERAL CONSIDERATIONS FOR DATA ANALYSES

All statistical summaries and analyses will be performed using SAS software version 9.3 on a UNIX or LINUX platform, unless otherwise specified.

No multiple comparisons will be performed in this analysis and so no adjustments for multiplicity are required.

8. DATA HANDLING CONVENTIONS

8.1. Premature Withdrawal and Missing Data

Both premature study withdrawal and missing data are accounted for in the survival analysis by censoring (see Section 8.2).

Subjects censored prior to six months will be excluded from the secondary endpoint i.e. the logistic regression analysis of the binary outcome of relapse. However if the proportional hazards assumption is violated, see Section 9.4, then some of these subjects will be classified as having relapsed in an additional Missing on or after Day 29=Failure sensitivity analysis (see Section 8.2).

8.2. Derived and Transformed Data

The datasets of both the DETECTIVE Part 2 and GATHER studies will contain key variables that have been derived using the definitions specified below.

Baseline

Randomisation may occur at the Day 1 visit or the Day 2 visit. The last assessment performed prior to the first dose of study medication (CQ or randomised treatment) will be considered baseline.

Six month time to relapse

Relapse is defined by a positive blood smear with or without *P. vivax* symptoms.

- A subject will be considered not to have relapsed at six months for the purposes of the analysis if **all** of the following are true (also described in Figure 2):

  - Subject had a non-zero *P. vivax* asexual parasite count at baseline. Subjects with no asexual *P. vivax* parasites at this time point will be censored with time to relapse = 0 days.

  - Subject demonstrated initial clearance of *P. vivax* parasitaemia. This is defined as two negative asexual *P. vivax* parasite counts, with at least six hours between the counts, and no positive counts in the interval. Subjects who do not meet this criteria will be classified as relapses, with time to relapse = 0 days.

  - Subject has no positive asexual *P. vivax* parasite count at any assessment prior to or on Study Day 201 following initial parasite clearance. Subjects who do have a positive count will be classified as relapses, with time to relapse = (date of first positive count) – (date of Study Day 1) days.

  - Subject did not take a concomitant medication with anti-malarial activity at any point between Study Day 1 and their last parasite assessment. A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding

the study, and classified accordingly. 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 last negative parasite assessment prior to concomitant medication start) – (date of Study Day 1). If a subject has not had a negative assessment prior to the concomitant medication start date, they will be censored at 0.

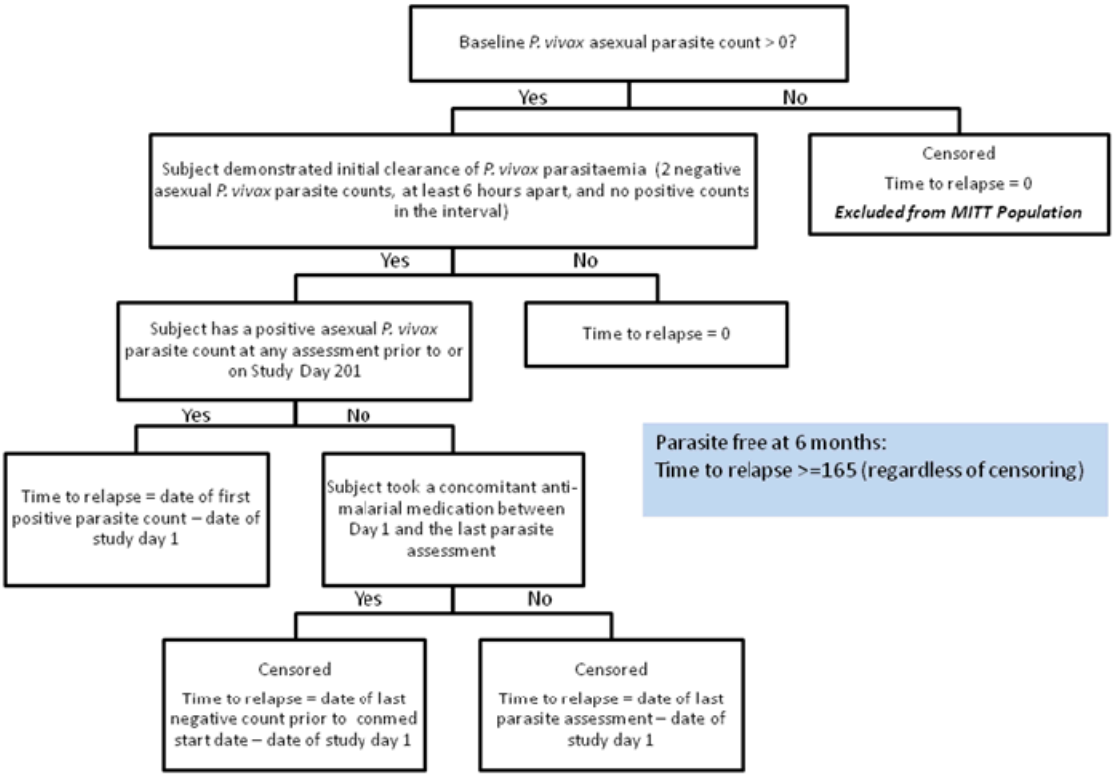
- Subject is parasite-free at six months. This is defined as a negative asexual *P. vivax* parasite count at the first parasite assessment performed on or after Study Day 166.

- Subjects who do not have a positive asexual *P. vivax* parasite count following initial clearance but where the final parasite count occurred before Study Day 166 will not have been classified by the preceding rules. These subjects will be considered to be censored, with time to relapse censored at (date of final parasite assessment) – (date of Study Day 1).

If a subject has a relapse outcome and a censored outcome, they will be considered to be a relapse, even if the time point of the relapse is later than the time point of censoring. For example, a subject who took a medication with anti-malarial activity at Study Day 32, but remained parasite-free after initial clearance until Study Day 68 will be treated as a relapse at Study Day 68.

Flow chart of algorithm:

Figure 2 Flowchart of algorithm for six month time to relapse



Missing on or after Day 29=Failure definition

In the event that the proportional hazards assumption is violated (see Section 9.4), resulting in the odds ratio being assessed for non-inferiority (see Section 9.5), then the following Missing on or after Day 29=Failure definititon will be used in an additional sensitivity analysis.

- In addition to those with a positive asexual *P. vivax* parasite count at any assessment prior to or on Study Day 201, the following subjects will also be defined to have relapsed:

    - Subject did not demonstrate initial clearance of *P. vivax* parasitaemia (i.e. did not have two negative asexual *P. vivax* parasite counts, with at least six hours between the counts, and no positive counts in the interval)

    - Subject took a concomitant medication with anti-malarial activity at any point between Study Day 1 and their last parasite assessment. A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified accordingly.

- Subject with a missing parasite assessment on or after Study Day 29.

- Subjects with a zero *P. vivax* asexual parasite count at baseline will be excluded from the analysis.

All data summaries of the mITT population will be performed with no replacement of missing electronic case report form (eCRF) efficacy and safety data.

Exposure and Treatment Compliance

For the first three days of the study, all study medication will be administered in the presence of the Investigator or study nurse, and ingestion confirmed.

On any day of in-clinic dosing, a subject will be classified as compliant with daily administered dose if they do not vomit the initial dose or if they are successfully re-dosed. A subject is considered to be compliant in clinic if they retain all study medication given to them on all three days of dosing.

Subjects will also take PQ or PQ placebo outside of the clinic to a total of 14 days of PQ/PQ placebo dosing, where administration is not directly observed. Compliance for this study medication will be summarised using the final pill count and PQ PK data.

Compliance determined using Day 8, Day 15, Day 8 or Day 15, Day 8 and Day 15 carboxyPQ PK samples will also be captured.

8.3. Assessment Windows

The following assessment windows were used in both DETECTIVE Part 2 and GATHER.

Visit	Analysis Window	
	Beginning Timepoint	Ending Timepoint
Day 1	Study Day 1	Study Day 1
Day 2	Study Day 2	Study Day 2
Day 3	Study Day 3	Study Day 4
Day 29	Study Day 26	Study Day 32
Day 180	Study Day 166	Study Day 201

Unscheduled and withdrawal visit data will be slotted into a scheduled visit window, if no competing visit exists within the window. If there are multiple assessments within the same window which are not unscheduled visits, the earliest result will be used in the summaries.

Study Day 180 refers to a time point exactly 179 days after Study Day 1 (when the first dose of study medication including CQ was taken), whereas the 'Day 180 visit' refers to the nominal Day 180 assessments which did not necessarily occur on Study Day 180.

8.4. Subgroup and Covariate Definitions

Both study and region will be included as covariates. The randomisation was not stratified for both DETECTIVE Part 2 and GATHER, so no additional covariate adjustment is required.

Breakdown of countries within each study

Countries	DETECTIVE Part 2	GATHER
Brazil	x	x
Peru	x	x
Thailand	x	x
Philippines	x	
Ethiopia	x	
Cambodia	x	
Colombia		x
Vietnam		x

Regions are defined geographically for inclusion as a covariate as:

Region	Countries
South America	Brazil, Peru, Colombia
Asia	Thailand, Vietnam, Cambodia, Philippines
Africa	Ethiopia

9. ANALYSES

9.1. The non-inferiority margin

The time to relapse hazard ratio and 95% confidence interval for CQ only versus PQ+CQ in DETECTIVE Part 1 is 3.68 (1.84 to 7.35). This can be considered a comparison of PQ versus placebo given CQ only treats the acute parasitemia, so does not prevent relapse. Table 1 presents a range of preserved effects (preserving the difference versus placebo) based on the lower bound of the 95% confidence interval of 1.84. For example, a preserved effect of 50% would result in a non-inferiority margin of 1.42.

Table 1 Non-inferiority margins for a range of preserved effects.

No preserved effect	50%	66%	75%	80%	100%
1.84	1.42	1.29	**1.21**	1.17	1.00

The binary relapse/relapse-free data at six months, which contributes to the overall hazard ratio of 1.21, translates to an odds ratio of 1.45 (see Section 9.5).

The combined DETECTIVE Part 2 and GATHER sample size is expected to be 642, with 428 on TQ+CQ and 214 on PQ+CQ. Based on these figures, if the PQ+CQ efficacy is 60.3% then an odds ratio of 1.45 equates to a PQ+CQ minus TQ+CQ efficacy difference of 9.1%. Table 2 shows the PQ+CQ minus TQ+CQ percentage differences for a range of efficacies.

Table 2 PQ+CQ minus TQ+CQ percentage differences for a range of efficacies (based on an odds ratio of 1.45).

PQ efficacy (%)	TQ efficacy (%)	Difference (%)
40.2	31.8	8.4
50.0	40.9	9.1
60.3	**51.2**	**9.1**
70.1	61.9	8.2
80.4	73.8	6.5

During discussions with the clinical team on 7th September 2016 a preserved effect of 75% was chosen, resulting in a non-inferiority margin of 1.21. This value is considered not to represent a clinically meaningful difference. Section 9.2 contains details about the statistical reasoning underpinning the selection of the non-inferiority margin.

9.2. How the non-inferiority margin was defined

The data from DETECTIVE Part 1 was used to select the non-inferiority margin as a hazard ratio using the following steps.

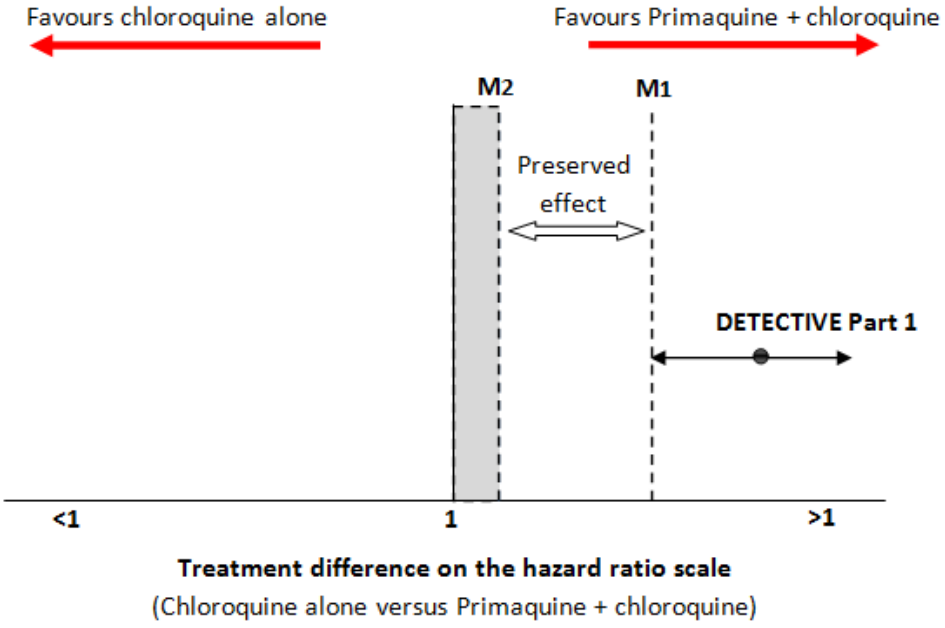
Step 1: The hazard ratio and 95% confidence interval for CQ only versus PQ+CQ was determined from a Cox proportional hazards model using region as a covariate. India was excluded from the primary efficacy analyses in the study due to very low relapse rates across all study treatment groups.

Step 2: The lower bound of the confidence interval identified an amount, M_1, which acted as the starting point for determining the non-inferiority margin.

Step 3: The non-inferiority margin, M_2, was then chosen to ensure a specified preserved effect of PQ+CQ over CQ only that translates to a value considered not to represent a clinically meaningful difference.

The approach taken to define the non-inferiority limit is shown graphically in Figure 3 and is based on the methods described in Schumi (2011).

Figure 3 **Determining the non-inferiority margin (M2 represents the non-inferiority margin and M1 represents the lower bound of the 95% confidence interval of the hazard ratio comparing CQ only versus PQ+CQ in DETECTIVE Part 1).**



The results from DETECTIVE Part 1 have been used to determine the non-inferiority margin as a hazard ratio because similar comparisons of PQ+CQ in the published literature are limited.

An alternative approach would have been to perform the primary comparison as a binary (relapse/no relapse) endpoint. The decision was taken to base the primary approach using survival analysis as this makes the most use of the individual patient level data available.

9.3. Is the non-inferiority margin reasonable?

To ensure the non-inferiority margin selected from DETECTIVE Part 1 is consistent with published literature on PQ+CQ the odds and risk ratios, adjusted for region, for PQ+CQ versus CQ only relapse in DETECTIVE Part 1 were also calculated.

Based on all subjects who completed six months of follow-up in DETECTIVE Part 1 there were 12/40 relapses in the PQ+CQ arm and 30/42 relapses in the CQ only arm. This translates to an adjusted odds ratio (95% confidence interval) of 0.12 (0.04 to 0.36) and an adjusted risk ratio (95% confidence interval) of 0.42 (0.21 to 0.82).

- In the Worldwide Antimalarial Resistance Network's (WWARN) Primaquine Review[3] the odds ratio (95% confidence interval) for low dose PQ was 0.14 (0.06 to 0.35).

- In the Cochrane systematic review[4] of 'Primaquine for preventing relapse in people with *Plasmodium vivax* malaria treated with chloroquine' the risk ratio (95% confidence interval) for supervised 14-day PQ treatment with follow-up for less than or equal to 6-months was 0.40 (0.23 to 0.68).

The DETECTIVE Part 1 results are consistent with the published literature, and support the use of the study to determine the non-inferiority margin as a hazard ratio for use in the planned meta-analysis.

9.4. Meta-analysis

Using the individual subject level data from the TQ+CQ and PQ+CQ arms of DETECTIVE Part 2 and GATHER, a Cox proportional hazards model will be fitted with region, study and treatment as covariates. The hazard ratio of TQ+CQ versus PQ+CQ, plus the associated 95% confidence interval and p-value, will be presented. The upper bound of the 95% confidence interval will be compared to the non-inferiority limit of 1.21 and interpreted as outlined in Section 6.

Interactions between study and treatment, and region and treatment will be assessed at the 10% (2-sided) level of significance. If any significant interactions are identified from the Cox proportional hazards model, they may be further investigated by presentation of the time-to-relapse hazard ratios and 95% confidence intervals for each study and/or region separately.

A Kaplan-Meier survival curve with 95% confidence bands and a log-log plot will be produced.

An important assumption underpinning the Cox proportional hazards model is that of proportional hazards. The proportional hazards assumption will therefore be assessed and will include a visual check of the Kaplan-Meier curves. The shape of the curves should be similar for the TQ+CQ and PQ+CQ treatment groups with the separation between the curves remaining proportional across time. A complementary log-log plot will also be used to check the proportional hazards assumption. In this plot both treatment group lines should appear approximately linear.

In the event that the proportional hazards assumption is considered violated the primary comparison will be based on a logistic regression model. The treatment difference will then be assessed for non-inferiority based on the upper bound of the 95% confidence interval surrounding the odds ratio. Further details in Section 9.5.

9.5. Odds ratio

The odds ratio, adjusted for study and region, will be presented along with the 95% confidence interval. However it will **only** be formally assessed for non-inferiority **if** the proportional hazards assumption (described in Section 9.4) is violated.

The non-inferiority margin for the odds ratio has been calculated using the same methodology described for the hazard ratio in Section 9.2. In brief, the lower bound of the DETECTIVE Part 1 CQ only versus PQ+CQ odds ratio is used to identify M1, the

starting point for identifying the non-inferiority margin. The non-inferiority limit, M2, has then been selected to maintain a specified preserved amount that translates to a value considered not to represent a clinically meaningful difference.

Table 3 shows the odds ratio non-inferiority margin for a range of preserved effects. The non-inferiority margin for the odds ratio is 1.45 (for the 75% preserved effect, consistent with that used for defining NI margin for the survival analysis). These values were agreed by the clinical team at a meeting on 7th September 2016.

Table 3 Odds ratio non-inferiority margin for a range of preserved effects

Actual (PQ+CQ vs CQ only)			Reciprocal (CQ only vs PQ+CQ)			Preserved Effects					
Ratio	LB	UB	Ratio	LB	UB	No	50%	66%	75%	80%	100%
0.12	0.04	0.36	8.66	2.80	26.85	2.80	1.90	1.61	**1.45**	1.36	1.00

The odds ratio will be adjusted for both study and region using a logistic regression model. Interactions between study and treatment, and region and treatment will be assessed at the 10% (2-sided) level of significance. If any significant interactions are identified they may be further investigated by presentation of the odds ratio and 95% confidence intervals for each study and/or region separately.

10. REFERENCES

Galappaththy GNL, Tharyan P, Kirubakaran R. Primaquine for preventing relapse in people with Plasmodium vivax malaria treated with chloroquine. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD004389. DOI: 10.1002/14651858.CD004389.pub3.

John GK, Douglas NM, von Seidlein L et al. Primaquine radical cure of *Plasmodium vivax*: a critical review of the literature. Malaria Journal 2012; 11:280 doi: 10.1186/1475-2875-11-280

Schumi J, Wittes J. Through the looking glass: understanding non-inferiority. Trials 2011; 12:106 doi: 10.1186/1745-6215-12-106

WHO. Guidelines for the Treatment of Malaria - 3rd Edition, 2015. ISBN 978 92 4 154912 7

11. ATTACHMENTS

11.1. List of Trials

- DETECTIVE Part 2 (details in Section 3)
- GATHER (details in Section 3)

11.2. Table of contents for Data Display Specifications

Population	Format	Example Shell	Title	Notes
All subjects randomised	Table	Table 1	Summary of Analysis Populations	
mITT and PP	Table	Table 2	Summary of Study Recruitment (by Study, Region and Country)	
mITT and PP	Table	Table 3	Summary of Demographic Characteristics	
mITT and PP	Table	Table 4	Analysis of time to relapse	
mITT and PP	Table	Table 5	Summary of Covariate and Interaction Significance from the Cox Proportional Hazards Model	
mITT and PP	Figure	Figure 1	Time-to-Relapse in the 6-month post-dosing period: Kaplan-Meier Survival Curves	
mITT and PP	Figure	Figure 2	Time-to-Relapse in the 6-month post-dosing period: log(-log(survival) versus log(time)	
mITT and PP	Table/Figure	Table 6	Adjusted Hazard Ratio and 95% Confidence Interval Forest Plot	

Population	Format	Example Shell	Title	Notes
mITT and PP	Table	Table 7	Analysis of Relapse during the 6-month post-dosing period (Missing on or after Day 29=Failure Sensitivity Analysis)	Only to be produced if proportional hazards assumption is violated for the time to relapse endpoint.
mITT and PP	Table	Table 8	Summary of Covariate and Interaction Significance from the Logistic Regression Model	
mITT and PP	Table	Table 8	Summary of Covariate and Interaction Significance from the Logistic Regression Model (Missing on or after Day 29=Failure Sensitivity Analysis)	Only to be produced if proportional hazards assumption is violated for the time to relapse endpoint.
mITT and PP	Table/Figure	Table 9	Adjusted Odds Ratio and 95% Confidence Interval Forest Plot	
mITT and PP	Table/Figure	Table 9	Adjusted Odds Ratio and 95% Confidence Interval Forest Plot (Missing on or after Day 29=Failure Sensitivity Analysis)	Only to be produced if proportional hazards assumption is violated for the time to relapse endpoint.
mITT and PP	Table	Table 10	Summary of Study Medication Compliance and Exposure	

11.3. Data Display Specifications

Data displays are detailed in the separate 'Meta Analysis Plan shell tables 05Dec16' document.