TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	An Open Label, Non-comparative, Multicenter Study to Assess the Pharmacokinetics, Safety and Efficacy of Tafenoquine (SB-252263, WR238605) in the Treatment of Pediatric Subjects with Plasmodium vivax Malaria

Compound Number: SB252263

Development Phase: II B

Effective Date: 06-NOV-2018

Protocol Amendment Number: 3

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N207627_00	2015-MAR-02	Original
2014N207627_01	2016-SEP-02	Amendment No. 1/SS-1 (218704)
Amendment No. 1 is a site-specific amendment, and applies to one site in Thailand: center PPD At this center, the following changes will be implemented: An inclusion criterion will be added to state that the subject is of Thai nationality (Section 5.1; Inclusion Criteria). Vital signs will be measured and a physical examination will be conducted at every visit. The appropriate revisions have been made to Section 7.1 (Time and Events Table), Section 7.5.3 (Physical Exams) and Section 7.5.4 (Vital Signs) of the protocol.		
GlaxoSmithKline Document Number	**Date**	**Version**
2014N207627_02	2017-SEP-20	Amendment No. 2
Amendment No. 2 is a global amendment. The information contained applies to all centers with the exception that the site-specific information in the previous local amendment will be carried over into this amendment and text added to identify site applicability, thus superseding Amendment No. 1. The following new changes were implemented: Based on results from cohort 1, changes were made to the tafenoquine dose banding scheme (Section 6.1; Treatment Assignment). Change of Secondary Medical Monitor A newly-described risk, Nervous System & Psychiatric Disorders, was added to the Risk Assessment Table (Section 4.6.1; Risk Assessment) A typographical error was corrected in the inclusion criteria regarding approved methods of contraception (Section 5.1; Inclusion Criteria).		

GlaxoSmithKline Document Number	**Date**	**Version**
2014N207627_03	2018-NOV-06	Amendment No. 3
Amendment No. 3 is a site-specific amendment, and applies to one center in Brazil (Center PPD; Manaus, Brazil). Revisions to the protocol were made for this center to conduct ophthalmic assessments of subjects at screening and prior to randomization, at the Day 120 visit, and at withdrawal as applicable.		

SPONSOR SIGNATORY

PPD

06/NOV/2018

Andrew Skingsley, MD
Global Health Physician
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Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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

Regulatory Agency Identifying Number: IND Number 101471

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol TAF113577

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

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

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

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

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1. PROTOCOL SYNOPSIS FOR STUDY TAF113577

Rationale

Infants, children and adolescents account for a significant proportion of *P. vivax* infections worldwide. In regions with high intensity of transmission, the incidence of *P. vivax* malaria peaks in subjects before the age of 2 years while in low intensity transmission areas *P. vivax* infection and disease occurs in all pediatric age groups.

Many similarities exist in the clinical manifestations of *P. vivax* infection among adult and pediatric populations. In India, fever and chills were the most commonly reported clinical symptoms in both populations. Tender splenomegaly and anemia are also common findings in patients with chronic or recurrent disease caused by *P. vivax*. As in adults, relapses frequently occur months to years after the initial infection unless appropriate treatment to eradicate the hepatic phase of the parasite is administered. Since severe anemia is a relatively common consequence of *P. vivax* infection in younger children, pediatric *P. vivax* patients are at risk of blood transfusion-associated infections (e.g., HIV, hepatitis B and C) and are at an increased probability of death from the clinical consequences of the anemia.

A strong exposure-efficacy response relationship has been identified for tafenoquine (TQ) in adult patients in part 1 of Study TAF112582. A clinically relevant systemic exposure (AUC) of TQ, 56.4 µg.h/mL, was derived using a Classification and Regression Tree (CART) analysis. Subjects with TQ exposure ≥ 56.4 µg.h/mL were likely to have significantly lower relapses compared to subjects with < 56.4 µg.h/mL. Based on simulations, the probability of being recurrence-free at 6 months was 52% (95% CI: 44% to 61%) in subjects with a TQ AUC < 56.4 µg.h/mL compared to 85% (95% CI: 80% to 90%) in subjects with a TQ AUC ≥ 56.4 µg.h/mL. Additionally, 93% of subjects on the 300mg dose had a predicted AUC that exceeded 56.4 µg.h/mL.

The currently proposed doses for the pediatric study are derived from a population pharmacokinetic (PK) model built using the systemic TQ exposure data from adults in part 1 of Study TAF112582. The population PK model incorporated allometric scaling for bodyweight. Based on this population PK model, a 60 kg adult on 300mg dose will have a median AUC(0-∞) of 96 µg.h/mL (95% prediction interval 55-162 µg.h/mL). The proposed starting doses for this pediatric study are predicted to achieve a similar target exposure after accounting for the subjects' bodyweight. The lower prediction limit AUC(0-∞) of 55 µg.h/mL from the model is also consistent with the cut-off obtained from the CART analysis (AUC(0-∞) of 56.4 µg.h/mL) and therefore provides a high degree of confidence in the efficacy in the pediatric population using this PK bridging approach.

Therefore the primary objective of this study is to generate systemic exposure data to enable the modelling of the pharmacokinetics of TQ in infants, children and adolescents with *P. vivax* to identify and recommend doses for pediatric subjects that achieve similar TQ AUC (0-∞) to the selected adult dose of 300 mg. If achieved, this will provide a bridge for dose selection with extrapolation of the adult efficacy data to infants, children and adolescents aged 6 months to <16 years. In addition, the safety and the clinical and

parasitological efficacy of TQ will be studied in pediatric subjects receiving TQ and chloroquine (CQ).

Objectives/Endpoints

Objectives	Endpoints
Primary	
• To evaluate the pharmacokinetics (PK) of tafenoquine in children and adolescents aged ≥2 years to <16 years (weighing ≥5 kg) with *P. vivax* in order to identify appropriate doses that achieve a similar exposure to that of the tafenoquine adult dose of 300 mg.	• AUC(0-∞) of TQ by weight band from a population PK model in pediatric subjects aged ≥2 years to <16 years (weighing ≥5 kg).
Secondary	
• To assess the safety of tafenoquine when administered to pediatric subjects with *P. vivax* malaria.	• Description of key safety data in the study population.
• To assess the clinical and parasitological efficacy of tafenoquine as a radical cure for pediatric subjects with *P. vivax* malaria when co-administered with chloroquine.	• Recurrence-free efficacy at four months post-dosing.
• To assess the PK of tafenoquine in infants aged ≥6 months to <2 years (weighing ≥5 kg) with *P. vivax* (if data permit)	• AUC(0-∞) of TQ by weight band from a population PK model in infants aged ≥6 months to <2 years (weighing ≥5 kg).

Overall Design

- TAF113577 is a prospective, open-label, multicenter, non-comparative, single-arm study. All subjects will receive CQ and open-label TQ.

- Potential subjects can be identified, pre-screened, and begin off-study treatment with CQ, after which sites will have up to 48 hours to obtain full consent/assent, as applicable. Upon consent, subjects will be treated with tafenoquine on Day 1, then attend seven follow-up visits (Days 3, 8, 15, 29, 60, 90 and 120). The total follow-up period will be 120 days.

- Subjects must have a blood smear that is positive for *P. vivax* at pre-screening. Blood smears will be taken at Day 1 (screening) and at Day 8 to confirm the parasite has cleared. Additional parasitological assessments will be conducted on visit Days 29, 60, 90 and 120.

- 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. All subjects must have a minimum G6PD assay value of 70% to be enrolled.

- A subject is considered to have completed the study if they attend all treatment and follow-up visits. A PK evaluable subject is defined as one with a minimum of one PK sample from Days 3, 15, 29 and 60.
- The final safety analysis will take place when all 60 enrolled subjects have completed the study.
- Safety data will be collected on all subjects who receive a dose of TQ.

Treatment Arms and Duration

In this single-arm study, potential subjects who are slide-positive for *P. vivax* will be started by the site on CQ per local/national guidelines. Sites will have up to 48 hours to obtain consent. Once full consent is provided, all subjects will be screened and, if eligible, receive TQ, given as a single dose on Day 1. All study medication should be taken with food. After the treatment period, subjects will attend up to 7 follow-up visits through Day 120.

Type and Number of Subjects

Approximately 240 subjects aged <16 years with *P. vivax* malaria will be screened to achieve 60 completed subjects. A subject is considered to have completed the study if they attend all treatment and follow-up visits. A PK evaluable subject is defined as one with a minimum of one PK sample from Days 3, 15, 29 and 60, with accurate dosing and sample time histories.

Initially, subjects ≥2 years to <16 years of age will be enrolled into the study. Recruitment to an additional cohort of infants aged ≥6 months to <2 years (weighing ≥5 kg) may begin following completion of the first interim analysis. This lower age cohort are included as part of the 60 completed subjects.

Analysis

There are no hypotheses tested in this study. The study is designed to characterize TQ exposures in pediatric subjects. A population PK modelling and simulations-based approach was utilized to support appropriate study sample size and PK sampling times for the proposed population PK bridging study. Based on these simulations, a sample size of 16 subjects and a sparse sampling scheme of four time points per subject are considered sufficient for the evaluation of the primary PK objective of estimating TQ apparent systemic clearance (CL) and thus exposure [AUC(0-∞) = Dose/CL] within each weight band in pediatric subjects aged ≥2 years to <16 years. Up to two interim analyses (at 16 and 32 subjects) have been planned so that sparse PK sampling may be stopped at the earliest opportunity, although all remaining subjects recruited into the study will have a minimum of two PK samples taken. Recruitment will continue for safety data accumulation.

The primary population PK model-based analysis to be performed will borrow some information from the adult model as appropriate. The sparse sampling in pediatric subjects is insufficient to independently characterize the absorption phase. Consequently the information about absorption from the adult model will be used as prior information to feed into the pediatric PK model with the assumption that the absorption processes are similar in adults and pediatric subjects. The pediatric population PK model will aim to reliably estimate the TQ clearance and thus the exposures in pediatric population. The clearance estimate for each subject generated from the model-based analysis will be used to determine the subject's TQ AUC(0-∞) [AUC(0-∞) = Dose/CL].

2. INTRODUCTION

Tafenoquine (TQ; SB-252263 and WR238605) 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 analogue of primaquine (PQ) and is currently being developed for the radical cure of acute *Plasmodium vivax* malaria, to be administered as a single dose along with standard doses of the anti-malarial chloroquine (CQ). Of note, TQ possesses activity against all stages of the Plasmodium lifecycle, including the dormant *P. vivax* hypnozoite.

2.1. Study Rationale

2.1.1. Pediatric *P. vivax* Malaria

Infants, children and adolescents account for a significant proportion of *P. vivax* infections worldwide. In regions with high intensity of transmission, the incidence of *P. vivax* malaria peaks in subjects before the age of 2 years while in low intensity transmission areas *P. vivax* infection and disease occurs equally in all pediatric age groups [World Global Malaria Programme, 2013; Anstey, 2012]. Congenital *P. vivax* infection does not require treatment with radical cure drugs, apparently because sporozoites do not enter the fetal circulation, preventing the development of hypnozoites in the fetus [Menendez, 2007]. By contrast, vector-borne *P. vivax* infections in the pediatric population behave broadly similarly to adults and thus treatment is required to prevent relapses from hypnozoites.

As transmission rates are low in most regions where *P. vivax* is prevalent, affected populations do not achieve high levels of immunity (or premunition) to this parasite and people of all ages are at risk of infection [Crawley, 2010]. Many similarities exist in the clinical manifestations of *P. vivax* infection among adult and pediatric populations. For example, in a study of adult and pediatric patients with vivax malaria in India, fever and chills were the most commonly reported clinical symptoms in both populations [Singh, 2013a]. Tender splenomegaly and anemia are also common findings in patients with chronic or recurrent disease caused by *P. vivax*. As in adults, relapses frequently occur months to years after the initial infection unless appropriate treatment to eradicate the hepatic phase of the parasite is administered [Summer, 2005].

Among patients with severe disease, the most frequent manifestations for both adults and children are severe anemia and acute respiratory distress. Less commonly, cerebral malaria, kidney injury, shock, and coagulopathy have also been reported [Baird, 2012]. *P. vivax* infection may also present with thrombocytopenia, which is a well-documented and frequent complication in both adult and pediatric patients with vivax malaria [Rodriguez-Morales, 2014], occurring with similar frequency in both age groups. In a review of 9 studies of patients with vivax malaria, thrombocytopenia was reported in 22.5% to 93.3% of adults [George, 2010; Kashinkunti, 2013; Kochar, 2009; Srivastava, 2011], and 22.2% to 95.6% of children [Mahgoub, 2012; Rodriguez-Morales, 2006; Bhattacharjee, 2013; Singh, 2011; Singh, 2013b].

Since severe anemia is a relatively common consequence of *P. vivax* infection in younger children, pediatric *P. vivax* patients are at risk of blood transfusion-associated infections (e.g., HIV, hepatitis B and C) and are at an increased probability of death from the clinical consequences of the anemia itself; however, the risks of severe disease and case fatality rates for *P. vivax* infection varies and have not been firmly established. In addition, there is accumulating evidence that *P. vivax* malaria impairs weight gain and growth as well as school performance, underlying the chronic, insidious impact that repeated relapses have on individuals and communities.

Besides parasite and host-related factors, severe anemia and acute renal failure could result from severe hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient children being treated with PQ. Although this is rarely described in the literature under-reporting is likely to occur. Fortunately diagnosis of G6PD deficiency in the pediatric population is identical to that in adults. Normal G6PD activity has been found to be higher in newborns (<7 days) than in adults but this does not affect diagnosis of complete G6PD deficiency, as G6PD deficient newborns show identical low levels to those of deficient adults but further complicates identification of heterozygote individuals.

2.1.2. Adult Tafenoquine Program and Design Rationale

A phase III program is ongoing to study TQ in adult subjects (≥16 years of age) with *P. vivax* malaria. This program is comprised of two studies:

1. Study TAF112582 [GlaxoSmithKline Document Number RM2010/00052/04] is a seamless phase II/III study in which the phase II portion has completed and an efficacious dose of TQ with a clinically acceptable safety profile has been selected; a single 300 mg dose. The phase III portion of TAF112582 will test the efficacy and safety of the selected TQ/CQ regimen in the radical cure of *P. vivax* malaria.

2. Study TAF116564 [GlaxoSmithKline Document Number 2012N152563_01] will characterize the incidence of hemolysis with TQ/CQ, and compare this to the incidence of hemolysis with PQ/CQ. In particular, a subset of adult female subjects will be enrolled that display a moderate deficiency in G6PD activity (G6PD heterozygous deficiency; susceptible to being misclassified as having "normal" G6PD activity by G6PD tests) so that the potential for hemolysis can be studied using the selected TQ/CQ regimen.

A strong exposure-efficacy response relationship has been identified for TQ in adult patients in part 1 of Study TAF112582. A clinically relevant systemic exposure (AUC) of TQ, 56.4 µg.h/mL, was derived using a Classification and Regression Tree (CART) analysis. Subjects with TQ exposure ≥ 56.4 µg.h/mL were likely to have significantly lower relapses compared to subjects with < 56.4 µg.h/mL. Based on simulations, the probability of being recurrence-free at 6 months was 52% (95% CI: 44% to 61%) in subjects with a TQ AUC < 56.4 µg.h/mL compared to 85% (95% CI: 80% to 90%) in subjects with a TQ AUC ≥ 56.4 µg.h/mL. Additionally, 93% of subjects on the 300mg dose had a predicted AUC that exceeded 56.4 µg.h/mL.

Therefore the primary objective of this study is to generate systemic exposure data to enable the modelling of the PK of TQ in infants, children and adolescents with *P. vivax* to identify and recommend doses for pediatric subjects that achieve similar TQ AUC (0-∞) to the selected adult 300 mg dose. If achieved, this will provide a bridge for dose selection with extrapolation of the adult efficacy data to children. In addition, the safety and the clinical and parasitological efficacy of TQ will be studied in pediatric subjects receiving TQ/CQ.

2.2. Brief Background

Tafenoquine has been shown to have an acceptable safety profile in the treatment and prevention of plasmodial infections in pre-clinical models and during Phase I, II and III clinical studies in >4000 subjects aged ≥16 years old.

All members of the 8-aminoquinoline class of drugs, including TQ and PQ, induce hemolysis in subjects with G6PD deficiency. G6PD is a housekeeping enzyme responsible for protection against oxidant stress. The effects of oxidant stress in subjects with G6PD deficiency are most apparent in red blood cells. Tafenoquine is thus being developed for treatment of patients with sufficient levels of G6PD enzyme activity.

Tafenoquine has a long half-life, and as such can be administered as a single oral dose. This is in contrast to PQ, which requires 14 days dosing. It must be determined if improved compliance with TQ could also lead to improved clinical outcomes. 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.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the pharmacokinetics (PK) of tafenoquine in children and adolescents aged ≥2 years to <16 years (weighing ≥5 kg) with *P. vivax* in order to identify appropriate doses that achieve a similar exposure to that of the tafenoquine adult dose of 300 mg.	• AUC(0-∞) of TQ by weight band from a population PK model in pediatric subjects aged ≥2 years to <16 years (weighing ≥5 kg).
Secondary	
• To assess the safety of tafenoquine when administered to pediatric subjects with *P. vivax* malaria.	• Description of safety data in the study population. Key safety endpoints of interest are: ➢ Gastrointestinal tolerability, and ➢ Clinically relevant drops in hemoglobin. ➢ Additionally, the incidence and severity of adverse events and abnormal laboratory observations.
• To assess the clinical and parasitological efficacy of tafenoquine as a radical cure for pediatric subjects with *P. vivax* malaria when co-administered with chloroquine.	• Recurrence-free efficacy at four months post-dosing.
• To assess the PK of tafenoquine in infants aged ≥6 months to <2 years (weighing ≥5 kg) with *P. vivax* (if data permit)	• AUC(0-∞) of TQ by weight band from a population PK model in infants aged ≥6 months to <2 years (weighing ≥5 kg).

With regard to the secondary efficacy endpoint, it should be noted that it is not possible to determine if a subject's recurrence of malaria is a relapse (liver stage treatment failure) or a re-infection (i.e., new infection), even when using current genetic techniques. Likewise, it is not possible to determine if a recurrence is a re-infection or recrudescence (blood stage treatment failure). For the purposes of this protocol, the term 'recurrence' will be used to represent any type of malaria treatment failure. Recurrence is defined as a positive blood smear with or without vivax malaria symptoms.

4. STUDY DESIGN

- TAF113577 is a prospective, open-label, multicenter, non-comparative, single-arm study. All subjects will receive CQ and open-label TQ.

- Potential subjects can be identified, pre-screened, and begin off-study treatment with CQ, after which sites will have up to 48 hours to obtain full consent/assent, as applicable. Upon consent, subjects will be treated with tafenoquine on Day 1, then attend seven follow-up visits (Days 3, 8, 15, 29, 60, 90 and 120). The total follow-up period will be 120 days.

- During the follow-up period, sites have the option of performing non-PK visits (Days 8, 90 and 120) at the subject's home.

- Subjects must have a blood smear that is positive for *P. vivax* at pre-screening. Blood smears will be taken at Day 1 (screening) and at Day 8 to confirm the parasite has cleared. Additional parasitological assessments will be conducted on visit Days 29, 60, 90 and 120.

- 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. All subjects must have a minimum G6PD assay value of 70% to be enrolled.

- A total of 60 pediatric subjects will be enrolled. The main cohort will consist of subjects aged ≥2 years to <16 years with no restriction on gender. Subjects will be dosed according to four weight bands.

- Within the total of 60 enrolled pediatric subjects, a second cohort of up to 6 infants aged ≥6 months to <2 years (weighing ≥5 kg) may be recruited following completion of a planned first interim analysis (see below).

- An interim analysis will be conducted once sufficient data from 16 subjects is available to assess PK and safety parameters. If needed, a second interim analysis may be conducted after a total of 32 subjects have enrolled. The primary analysis population will be the PK evaluable population.

- A subject is considered to have completed the study if they attend all treatment and follow-up visits. A PK evaluable subject is defined as one with a minimum of one PK sample from Days 3, 15, 29 and 60.

- The final safety analysis will take place when all 60 enrolled subjects have completed the study.

- A population PK model will be used to estimate the clearance and thus exposure of TQ for each of the weight bands in the main cohort [AUC(0-∞) = Dose/Clearance (CL)].

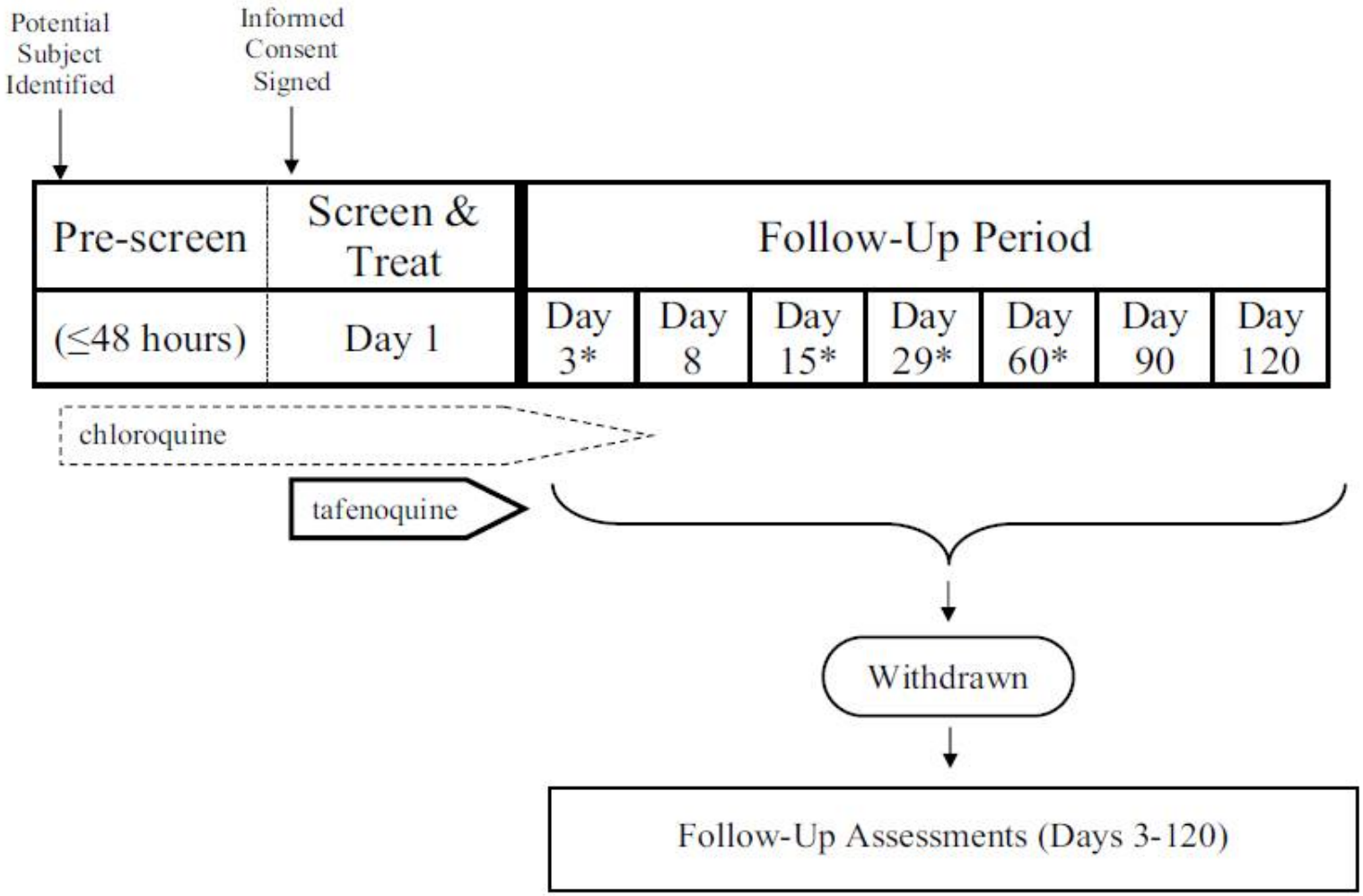
- Safety data will be collected on all subjects who receive their dose of TQ.
- A single center (PPD; Manaus, Brazil) will perform ophthalmic safety assessments at selected visits to monitor subjects for changes in the eye.

Hospitalization of subjects is not required for this study; however, subjects may be hospitalized as warranted by their condition, and at the discretion of the investigator.

4.1. Overall Design

Study TAF113577 is a prospective, open-label, single arm, multicenter study enrolling 60 pediatric subjects aged 6 months to <16 years of age. The study schematic (Figure 1) summarizes the study visits.

Figure 1 TAF113577 Study Design Schema



* Pharmacokinetic sampling days

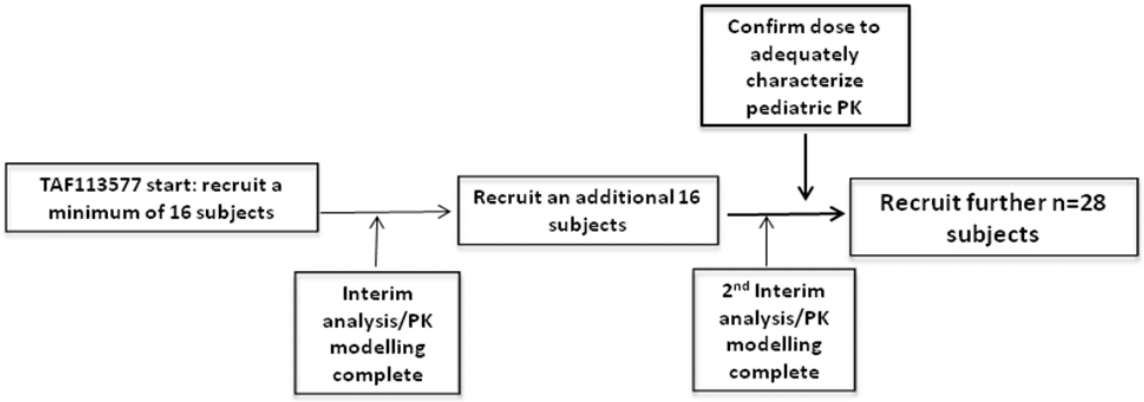
4.2. Treatment Arms and Duration

In this single-arm study, potential subjects who are slide-positive for *P. vivax* will be started by the site on CQ per local/national guidelines. Sites will have up to 48 hours to obtain consent. Once full consent is provided, all subjects will be screened and, if eligible, receive TQ, given as a single dose on Day 1. All study medication should be taken with food. After the treatment period, subjects will attend up to 7 follow-up visits through Day 120.

Due to the large variation in weight for the same age anticipated across various countries, pediatric subjects will have TQ dosed by weight instead of by age. This approach with weight based dosing is also more relevant since various enzymatic processes that may be involved in drug metabolism generally reach adult maturation levels post 6 months of age. The current study does not enrol subjects less than 6 months of age. TQ doses within weight bands were selected by using a population PK modelling and simulation approach based on adult data and incorporation of allometric scaling (see Appendix 8, Section 12.8, Tafenoquine Pediatric Dose Extrapolation). Based on these simulations there will be four weight bands of ≥5 to ≤10 kg, >10 to ≤20 kg, >20 to ≤35 kg and >35 kg with proposed starting doses for pediatrics from 100 to 300 mg TQ (see Section 4.5). Enrollment into all weight bands will be conducted in parallel. Although no minimum enrollment is required in any single weight band prior to the interim analyses, efforts will be made to enrol subjects across all weight bands.

An interim population PK analysis will be performed once data from 16 subjects is obtained (Figure 2). The TQ clearance estimate (CL) for each subject generated from the population model based analysis will be used to determine the subject's TQ exposure; i.e., AUC(0-∞) [AUC(0-∞) = Dose/CL]. The model based pediatric exposure predictions will be compared to the corresponding adult exposures at the 300mg dose that have been shown to be efficacious. If the data is sufficient to make reliable predictions for dose recommendations, full PK sampling in the trial will be stopped. If the data are deemed insufficient, the PK sampling will continue to collect PK data from another set of 16 pediatric subjects where after the modelling and simulation activity will be repeated at the second interim analysis. Once the full PK assessments are completed and sufficient data is available to reliably characterize pediatric TQ PK, all remaining enrolled subjects will provide two PK samples at Day 15 and Day 29 to provide data for the final population PK analysis of TQ to be conducted at the end of the study. If during the analysis it is realized that exposures are greater than 275 µg.hr/mL, the dosing strategy will be revised. Refer to Section 4.6.1 for details.

Figure 2 TAF113577 Recruitment Scheme



4.3. Type and Number of Subjects

Approximately 240 subjects aged <16 years with *P. vivax* malaria will be screened to achieve 60 enrolled subjects. Initially, subjects ≥2 years to <16 years of age will be enrolled into the study. Recruitment to an additional cohort of infants aged ≥6 months to <2 years (weighing ≥5 kg) may begin following completion of the first interim analysis.

A subject is considered to have completed the study if they attend all treatment and follow-up visits. A PK evaluable subject is defined as one with a minimum of one PK sample from Days 3, 15, 29 and 60, with accurate dosing and sample time histories. The key PK parameter to be estimated is the drug's clearance.

4.4. Design Justification

Study TAF113577 is an open-label single-arm study and will not include a control arm. This pediatric PK bridging and safety study will test appropriate doses of TQ in pediatric subjects selected to achieve similar levels of exposure observed in adults treated with 300mg TQ. The dosing regimen in the pediatric population is based on allometric scaling and targeting a systemic exposure comparable to the 300 mg exposures in adults. Given the evidence suggests that the disease process in adults and children is similar, it is appropriate to draw conclusions from our emerging adult data set to inform our pediatric study design. This assumption allows the use of this pharmacokinetic bridging study to support the dose selection in infants, children and adolescents aged 6 months to <16 years.

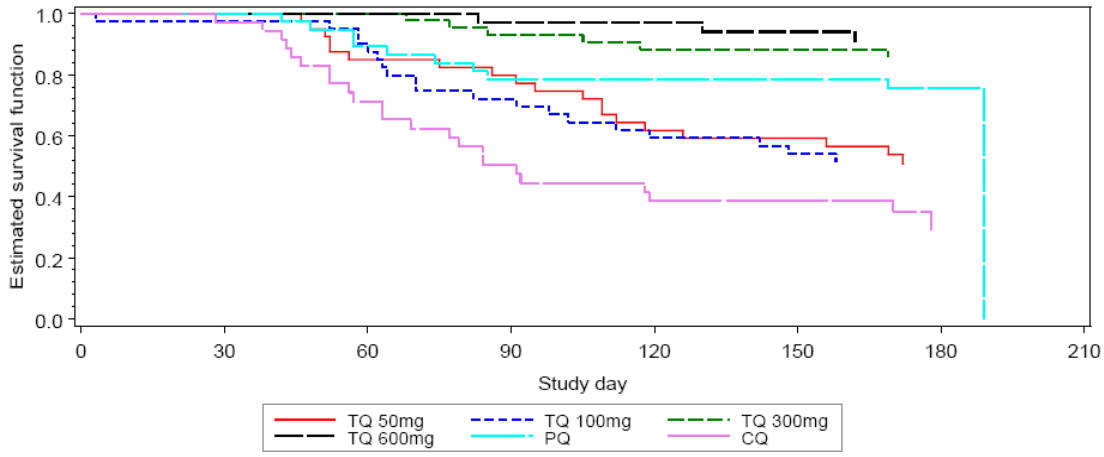
The study will recruit a target of 60 subjects. Safety data will be collected for the entire study (up to 120 days, as the half-life of TQ is 2–3 weeks). With regard to efficacy, the study is being conducted in areas with known high recurrence rates in adults. Therefore, high efficacy in this study is not indicative of low background recurrence rates.

Pharmacokinetic samples will be collected in order to achieve the primary objective of the study. However, in order to minimize distress in this pediatric population, a sparse sampling scheme will be used to reduce the frequency and volume of blood collected and a population PK modelling and simulation approach will be utilized. Small volume venous sampling (≤1 mL whole blood) and/or microsampling (70 µL whole blood) will

be employed to minimize volume of blood taken from subjects. Furthermore, up to two interim analyses have been included in this study, so that full PK sampling can be stopped as soon as sufficient data have been collected. As mentioned in Section 4.1, once full PK sampling is stopped, two samples will be collected from each remaining enrolled subject at Day 15 and Day 29 to provide data for the final population PK analysis of TQ to be conducted at the end of the study. Simulations were used to identify appropriate sampling times and total study sample size (See Appendix 9, Section 12.9, Tafenoquine Pediatric Population-PK Trial Simulation). The primary objective of this PK bridging study is to adequately characterize the systemic TQ exposure in the pediatric population. Consequently, a sparse PK sampling scheme is selected to reliably estimate TQ clearance (CL) and thereby characterize exposure, i.e., AUC [AUC (0-∞) = dose/CL]. Other information that cannot be obtained from the pediatric data owing to the sparse sampling design, e.g. absorption rate, will be obtained from the adult exposure data and population PK model.

In the phase 2 adult TQ program, efficacy was measured at 4 months and 6 months [GlaxoSmithKline Document Number 2013N160035_00]. The majority of the recurrences across all treatment groups were observed prior to 4 months and efficacy of TQ 300 dose at 4 months was significantly higher than placebo (Figure 3). To allow for a shorter follow up period in the pediatric study population, recurrence-free efficacy will be measured at four months rather than at four and six months as measured in the adult studies.

Figure 3 Kaplan-Meier Survival Curves for Time to *P. vivax* Recurrence (Intent-to-Treat Population)



Number of subjects at risk during the interval

TQ 50mg	40	33	31	24	22	6
TQ 100mg	39	36	28	23	21	5
TQ 300mg	43	43	40	37	37	15
TQ 600mg	36	36	33	32	30	9
PQ	37	33	28	28	28	10
CQ	34	24	17	13	13	5

4.4.1. Dose Justification in Cohort Aged <2 years

There is no lower age limit below which infants and children are not susceptible to vivax malaria. There is, however, a balance to be struck in terms of collecting data sufficient to define an appropriate dose for infants, versus limiting the number of study related assessments to which this highly vulnerable group are subjected. Where possible, PK data from an additional cohort of six infants aged ≥6 months to <2 years (weighing ≥5 kg) will be obtained to define dosing in infants down to 6 months. Available data from this cohort will be combined with data obtained from the main cohort as part of the final population PK analysis. The lower age of 6 months is based on the age at which G6PD enzyme activity reaches maturity. The pediatric population PK model used for dose prediction has been developed based on adult patient data and includes an allometric function for weight-based dosing. Allometric scaling accounts for size differences only and not age-related changes in metabolizing enzymes or renal function. However, the generalized functional immaturity in metabolizing enzyme activity and renal function approach adult levels about 6 months after birth [Kearns, 2003]. Thus, the model is appropriate for dose prediction in this cohort.

The decision to enrol subjects aged ≥6 months - <2 years will be based on a review of exposure data as well as of safety results from the first interim analysis. Particular attention will be paid to the reporting of adverse events related to decreases in hemoglobin (Hb), methemoglobin (metHb) levels, increases in creatinine, and any reports of phototoxicity.

4.5. Dose Justification

As mentioned above, subjects will be dosed based on weight (see Section 6.1). The pediatric dose rationale is based on achieving a target median TQ exposure AUC(0-∞) of 96 µg.h/mL. The term AUC listed throughout this document refers to the AUC(0-∞) unless specified otherwise and is estimated based on model predicted post hoc CL estimates [AUC (0-∞) = dose/CL].

The currently proposed doses for the pediatric study are derived from a population PK model built using the systemic TQ exposure data from adults in part 1 of Study TAF112582. The population PK model incorporated allometric scaling for bodyweight. Based on this population PK model, a 60 kg adult on 300mg dose will have a median AUC(0-∞) of 96 µg.h/mL (95% prediction interval 55-162 µg.h/mL). The proposed starting doses for this pediatric study are predicted to achieve a similar target exposure after accounting for the subjects' bodyweight.

The lower prediction limit of AUC(0-∞) of 55 µg.h/mL from the population PK model is consistent with the cut-off obtained from the CART analysis (AUC(0-∞) of 56.4 µg.h/mL). The CART analysis conducted with exposure – efficacy/response data from part 1 in Study TAF112582 identified a clinically relevant TQ AUC of 56.4 ug.hr/mL. Subjects with TQ AUC ≥ 56.4 ug.hr/mL were likely to have significantly lower relapses compared to subjects with < 56.4 ug.hr/mL TQ AUC. This population PK model based dose rationale therefore provides a high degree of confidence in the efficacy in the pediatric population using such PK bridging approach.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with TQ (SB-252263) can be found in the Investigator's Brochure The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) – SB-252263		
Hemolysis in G6PD-deficient subjects (PRIMARY RISK)	Tafenoquine is an 8-aminoquinoline, a class of drug known to exert oxidative effects on 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.	• All subjects with <70% G6PD activity will be excluded. Subjects with Hb levels <8 g/dL will also be excluded. • Protocol-defined SAE criteria will be adopted; defined as, ≥ 3.0 g/dL or 30% decline in Hb from the baseline value, or a Hb value <6 g/dL, to aid in safety monitoring. • Recommendations for clinical management of hemolysis will be provided as part of investigator training.
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. The doses recommended for this study, designed to achieve similar levels of exposure observed in adults treated with 300mg TQ, should pose minimal risk of causing elevations of metHb of clinical concern.	• Methemoglobin percentage will be monitored non-invasively at selected times throughout the study.
High Systemic Exposure to TQ	In a cohort of patients taking 600 mg TQ (first part of Study TAF112582) the highest AUC(0-∞) observed was 275 µg.h/mL.	• The presence of an observed AUC(0-∞) in any subject of >275 µg.h/mL will trigger a review of dosing in the study.
Liver Transaminase Elevations	Preclinical repeat dose toxicology studies observed liver changes that were fully or partially reversible. During the TQ thorough QT study (TAF114582)	• Conduct liver function tests – baseline and Day 8. • TQ dose limited to 300mg total dose equivalent in pediatric subjects.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	two adult 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. However, based on data from TAF112582 Part 1 there is no safety signal for hepatoxicity for doses of 600mg and 300mg.	
Keratopathy	No ophthalmological changes were observed in preclincial species. Reversible vortex keratopathy was observed in clinical trials at higher doses and/or longer duration of treatment than are being studied here. Keratopathy was not observed in a limited number of adult patients (n=15) who underwent ophthalmological exams at 300mg dose in TAF112582 Part 1 study.	• This risk will be mitigated in other studies within the tafenoquine program • Appropriate training will be provided at investigator meetings on these potential ophthalmological changes
Retinal Toxicity	No ophthalmological changes have been observed in preclinical species. Previous clinical studies (057, 058 and TAF 106491) have included substantive ophthalmic assessments. No evidence of retinal toxicity associated with TQ was observed in any of the TQ-treated subjects in these studies as per conclusion of Ophthalmic Advisory board Nov ’09. Irreversible retinopathy has been reported with a potential combination partner - CQ (and hydroxychloroquine). 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 falciparum malaria is reported in the literature but rare in vivax.	• This risk will be mitigated in other studies within the tafenoquine program • Appropriate training will be provided at investigator meetings on these potential ophthalmological changes

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
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. A preclinical assessment of inhibition of renal transporters has demonstrated that TQ inhibits organic cation transporter 2 (OCT2), multidrug and toxin extrusion 1 transporter (MATE1) and multidrug and toxin extrusion 2K transporter (MATE-2K). The changes in serum creatinine are thought to be related to this tubular transporter interaction.	• Conduct renal function testing in the proposed pediatric study – baseline and Day 8. • Include drugs that are excreted via these transporters in the list of prohibited medications.
Nervous system & psychiatric disorders	Phase 3 results in adult patients showed mild to moderate self-limiting nervous system & psychiatric disorders including dizziness, anxiety & insomnia.	• Consider excluding patients with a history of serious psychiatric disorders such as psychosis, depression and suicidal ideation.
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 G6PDd and risk to breastfed infants whose G6PD status may be unknown.	• Pregnant or lactating women are excluded from the study.
Phototoxicity	Pre-clinical studies concluded that there was a possibility that TQ was phototoxic. However,	• Routine AE information will be collected and the incidence and frequency of rash

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	this information was superseded by safety data collected in clinical trials in which over 4000 subjects were exposed to TQ, some of them for a long time period. The clinical data indicated that there was no pattern in incidence of rash associated with TQ treatment and this risk is considered to be low.	will continue to be reviewed for signs of photoirritancy in this patient population.
Study Procedures		
Volume of Blood Draws from Pediatric Subjects	A plasma assay has been used to analyze PK samples (preclinical and clinical) throughout the development of TQ. Blood collection to obtain the plasma has been via venipuncture.	• Small volume venous sampling (≤1 mL whole blood) and/or microsampling (70 µL whole blood) will be employed to minimize volume of blood taken from subjects.

4.6.2. 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 has 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 as well as causing bystander hemolysis, 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 asymptomatic anemia (resulting in transfusion).

Due to its long half life, TQ 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 recurrence rates.

4.6.3. Overall Benefit:Risk Conclusion

Tafenoquine is being developed with the aim of a benefit:risk profile which is at 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.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Tafenoquine Investigator Brochure [GlaxoSmithKline Document Number GM2007/00152/08], and the locally-approved label for chloroquine.

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

5.1. Inclusion Criteria

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

[1] AGE
1. Subject is ≥2 years to <16 years of age at the time of signing of the assent and/or informed consent. An additional cohort of subjects aged ≥6 months to <2 years may be recruited following the first interim analysis.

[2] TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. The subject is of Thai nationality **(applicable only to subjects at center** PPD **).** 3. The subject has a positive malarial smear for *P. vivax*. 4. The subject has a history of fever within 48 hours prior to enrollment. 5. The subject has a glucose 6-phosphate dehydrogenase (G6PD) value (measured by a quantitative spectrophotometric phenotype assay) ≥70% of the site median value for G6PD normal adult males. 6. The subject has a screening hemoglobin (Hb) value ≥8 g/dL.

[3] WEIGHT
7. The subject has a body weight ≥5 kg.

[4] SEX
8. Males and females are eligible to enter the study. A female is eligible to enter and participate in this study if she is non-pregnant, non-lactating and if she is of: a. Non-childbearing potential (i.e., premenstrual); 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: i. Use of oral contraceptive, either combined or progestogen alone used in conjunction with double barrier method as defined below. ii. Use of an intrauterine device with a documented failure rate of <1% per year. iii. Use of depo provera injection iv. Double barrier method consisting of spermicide with either condom or diaphragm v. Male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female.

vi. 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.

[5] INFORMED CONSENT

9. The subject and/or the subject's parent(s)/legal guardian(s) agree to G6PD genotyping in the context of a subsequent hemolytic anemia adverse event.
10. The subject and parent(s)/legal guardian(s) are willing and able to comply with the study protocol.
11. In accordance with regional/local laws and regulations, the parent(s)/legal guardian(s) has given written informed, dated consent; and the subject has given written assent, if applicable, to participate in the study.

5.2. Exclusion Criteria

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

[1] CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)

1. The subject has a mixed malaria infection (identified by a malarial smear or rapid diagnostic test).
2. The subject has a condition that may affect absorption of study medication, such as severe vomiting (no food or inability to take food during the previous 8 hours).
3. The subject has a liver ALT >2 time the upper limit of normal (ULN).
4. The subject has a clinically significant concurrent illness (e.g., pneumonia, meningitis, septicaemia, coagulopathy, severe hemorrhage), pre-existing condition (e.g., renal disease, malignancy, malnutrition, known pre-existing HIV), febrile convulsions prior to consent, or clinical signs and symptoms of severe cardiovascular disease (e.g., congenital heart disease).
5. The subject has a history of porphyria, psoriasis, or epilepsy.

[2] CONCOMITANT MEDICATIONS

6. The subject has taken anti-malarials (e.g., artemisinin-based combination therapies, mefloquine, primaquine, or any other 4- or 8-aminoquinoline) or drugs with antimalarial activity within 30 days prior to study entry.
7. The subject has received treatment with any investigational drug within 30 days of study entry, or within 5 half-lives, whichever is longer.
8. The subject has taken or will likely require during the study the use of:
   - histamine-2 blockers
   - antacids
   - anti-diabetic drugs of the biguanide class (i.e., phenformin, buformin)

• anti-arrhythmic agents dofetilide, procainamide, pilsicainide 9. The subject has a serum creatinine above the upper limit of normal and is currently taking metformin.

[3] CONTRAINDICATIONS
10. The subject has a history of allergy or intolerance to chloroquine, mefloquine, tafenoquine, primaquine, or to any other 4- or 8-aminoquinoline. 11. The subject has previously enrolled in this study.

[4] DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
12. The subject has severe *P. vivax* malaria as defined by WHO criteria (see Appendix 6, Section 12.6). 13. The subject has any retinal abnormality in the macular region, either pre-existing or identified at the baseline visit (Center PPD only).

5.3. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently dosed. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information will be reported including Demography, Screen Failure details (including G6PD results), Eligibility Criteria, and any Serious Adverse Events.

5.4. Withdrawal/Stopping Criteria

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

A subject or their parent/legal guardian(s) 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 120 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 120.

Subjects and/or their parent/legal guardian 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 for the Withdrawal visit as applicable.

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

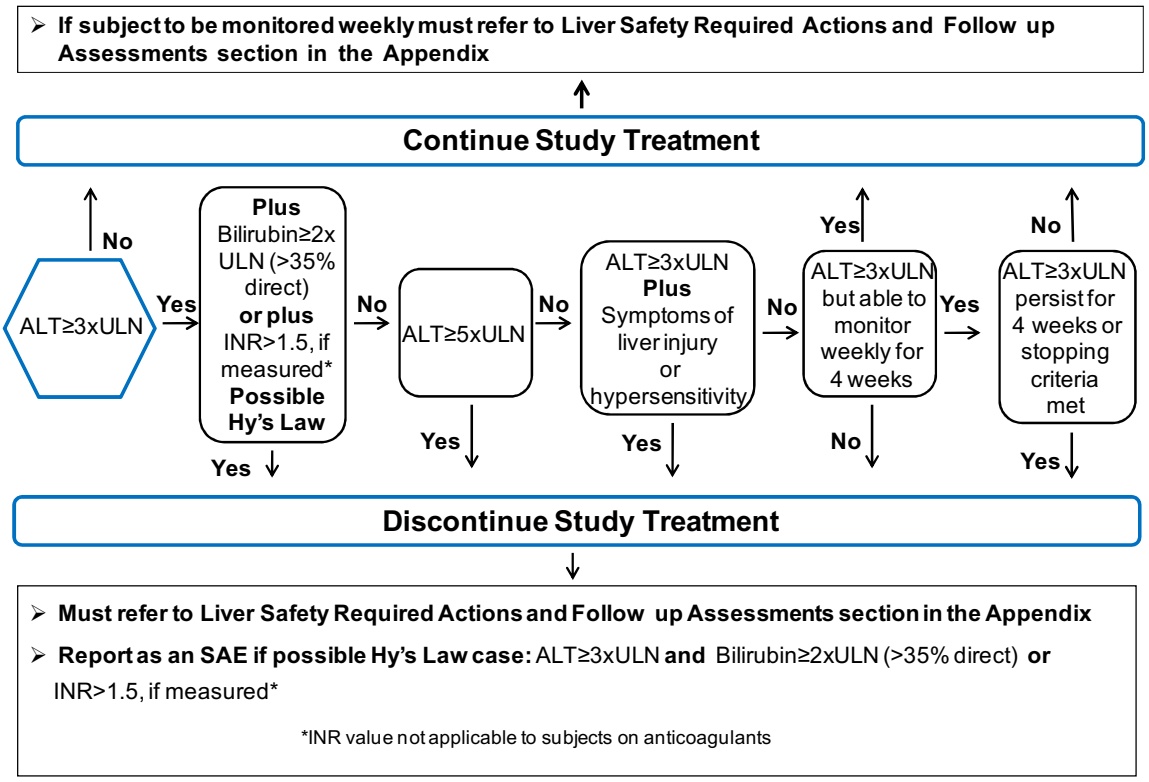
- The site must attempt to contact the parent/legal guardian of the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject and/or parent/legal guardian on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes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

5.4.1. Liver Chemistry Increased Monitoring Criteria

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

Figure 4 below presents the algorithm for evaluating and monitoring liver chemistry data. It should be noted that, given TQ is administered as a single dose, there will be no opportunity to discontinue study treatment. However, liver event follow-up assessments would still apply if liver increased monitoring criteria are met.

Figure 4 Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



For further details, refer to the Liver Safety Required Actions and Follow up Assessments Section in Appendix 2 (Section 12.2).

5.4.2. QTc Stopping Criteria

QTc stopping criteria will not be employed in this study.

A TQ definitive QTc study, Study TAF114582 [GlaxoSmithKline Document Number 2012N145359_00], demonstrated a lack of effect on QTcF elongation at adult clinical doses (300 and 600mg). CQ does have a propensity to cause QTc prolongation; however, in TQ drug-drug interaction (DDI) Study TAF106491 [GlaxoSmithKline Document Number WD2009/01503/00] no difference was seen in PK and QTcF changes between CQ/TQ groups with all groups showing the same pattern of elongation as with CQ alone, for both frequency and magnitude of changes.

The DDI study concluded that there was no trend over time for increased QTc intervals in those treated with TQ alone. Therefore, no ECG monitoring is planned for this study.

5.5. Subject and Study Completion

A completed subject is one who attends all treatment and follow-up visits.

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

6. STUDY TREATMENT

Chloroquine will be provided to subjects outside the parameters of this study, and according to local/national treatment guidelines. Potential subjects who are slide-positive for *P. vivax* will begin CQ treatment and sites will have 48 hours to obtain full subject consent and assent, as applicable. Consented subjects will be screened, randomized and dosed with TQ on Day 1. Two formulations of TQ will be made available; a 150 mg film-coated tablet (TQ adult tablet), and a 50mg fast-dispersing film coated tablet (TQ pediatric tablet; Table 1). Instructions for preparation and administration of the TQ formulations will be provided in the SRM.

Table 1 Study Treatments

	Study Treatment	
Product name:	tafenoquine adult tablet	tafenoquine pediatric tablet
Formulation description:	Film-coated tablet	Fast-dispersing film coated tablet
Dosage form:	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	150 mg	50 mg
Route of Administration:	Oral	Oral
Dosing instructions:	Single dose on Day 1	Single dose on Day 1
Physical description:	Dark pink capsule-shaped	Round normal concave-shaped
Method for individualizing dosage:	Subject weight	Subject weight

6.1. Treatment Assignment

This is an open-label, single arm study, and all subjects will receive CQ and TQ. Subjects will be dosed based on weight, with the goal to achieve a median TQ exposure of 96 µg.h/mL, the median exposure observed in adults following administration of a 300 mg dose of TQ. The TQ doses presented in Table 2 below were selected using a population PK model based on adult data and incorporation of allometric scaling.

Table 2 Tafenoquine Dosing

Weights	Tafenoquine Dose[a]	Dosing Regimen
>45 kg	300 mg	2 × 150 mg or 6 × 50 mg
>40–≤45 kg	300 mg	2 × 150 mg or 6 × 50 mg
>35–≤40kg	300 mg	2 × 150 mg or 6 × 50 mg
>30–≤35kg	200 mg	4 × 50 mg
>25–≤30 kg	200 mg	4 × 50 mg
>20–≤25 kg	200 mg	4 × 50 mg
>15–≤20 kg	100 mg	2 × 50 mg
>10–≤15 kg	100 mg	2 × 50 mg
≥5–≤10 kg	50 mg	1 × 50 mg

a. The TQ dose is based on achieving a target AUC(0–∞) of 96 µg.h/ml.

The single dose of TQ will be administered at the investigator site. Subjects >35 kg have the choice of taking the TQ adult tablet or the TQ pediatric tablet. All 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 6.9.1.2.

6.2. Planned Dose Adjustments

The TQ doses and weight banding may be refined after a planned interim analysis of at least 16 subjects and based on safety and predicted exposures for the pediatric population. The observed pediatric exposure data will be compared with corresponding adult exposures that have been shown to be efficacious in order to help inform the need for any dose adjustments.

6.3. Blinding

This will be an open-label study and investigators have direct access to the subject's individual study treatment.

6.4. Packaging and Labeling

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

6.5. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

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

Precautions will be taken to avoid direct contact with the study treatment. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

6.6. Compliance with Study Treatment Administration

Compliance with TQ will be assessed in all subjects by directly observing the taking of medication while at the investigator center. Despite being administered outside of this study, CQ compliance should be monitored by the site and recorded in the subject's source documentation.

6.7. 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 does occur, individuals should be managed with appropriate supportive measures

and clinical judgement. Immediate induction of emesis and/or gastric lavage is not recommended. Hemodialysis is unlikely to be clinically useful as tafenoquine is highly protein-bound.

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

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.

In the event of an overdose the investigator should:

1. contact the Medical Monitor immediately
2. closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until TQ and/or CQ can no longer be detected systemically (at least 90 days for TQ and 28 days for CQ)
3. document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

6.8. Treatment after the End of the Study

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 6.9.1.2.

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

6.9. Concomitant Medications and Non-Drug Therapies

6.9.1. Permitted Medications and Non-Drug Therapies

6.9.1.1. Concomitant Medications

All subjects can be given paracetamol 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.

6.9.1.2. 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 through the Day 120 visit to ensure 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.

6.9.2. Prohibited Medications and Non-Drug Therapies

The following drugs are prohibited for use from 30 days prior to entry in the study through Day 120:

- Anti-malarials and other medicines with known anti-malarial activity (with the exception of CQ being given to potential subjects prior to randomization).

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 TQ.

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

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

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

See Appendix 7 in Section 12.7 for a non-exhaustive list of prohibited medicines for guidance.

7. STUDY ASSESSMENTS AND PROCEDURES

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

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

7.1. Time and Events Table

Protocol Activity	**Visit Day**									
	Screen & Treat	**Follow-Up Period**							**Recurrence Visit[a]**	**Withdrawal Visit[b]**
	Day 1[c]	**Day 3**	**day 8**	**Day 15**	**Day 29**	**Day 60**	**Day 90**	**Day 120**	**Recurrence**	**Withdrawal**
Window		**+2d**	**-/+2d**	**-/+3d**	**-/+5d**	**-/+10d**	**-/+10d**	**-/+10d**		
Informed Consent Process	X									
Demographic Information	X									
Initial History Only [d]	X									
Physician Assess. Malaria Signs & Symptoms	X									
Inclusion/Exclusion Criteria	X									
Efficacy Assessments										
Parasitological Assessment (blood smear)	X		X		X	X	X	X	X	X
Plasmodium PCR genotyping	X								X	
Safety Assessments										
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Vital Signs [e,f]	X	X		X	X	X			X	X
Brief Physical Examination [f]	X	X	X		X	X	X	X	X	X
Adverse Events Assessment [g]	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events [h]	X	X	X	X	X	X	X	X	X	X
G6PD (phenotyping) [i]	X									
G6PD (genotyping)	X [j]									
Ophthalmological Exam (qualified site only)	X							X		X

Protocol Activity	**Visit Day**									
	Screen & Treat	**Follow-Up Period**							**Recurrence Visit[a]**	**Withdrawal Visit[b]**
	Day 1[c]	**Day 3**	**day 8**	**Day 15**	**Day 29**	**Day 60**	**Day 90**	**Day 120**	**Recurrence**	**Withdrawal**
Window		**+2d**	**-/+2d**	**-/+3d**	**-/+5d**	**-/+10d**	**-/+10d**	**-/+10d**		
Laboratory Assessments										
Hematology [k]	X	X	X							
Clinical Chemistry [l]	X		X							
Methemoglobin	X		X							
Pregnancy Test [m]	X				X	X	X		X	X
Pharmacokinetic Assessments										
Pharmacokinetic Sampling		X[n]		X[o]	X[o]	X			X	
Investigational Product										
Dispense Open Label tafenoquine	X									
Treatment Compliance Int. - Invest.	X									
IVRS Registration	X									

a. Subjects who have a recurrence will continue to be monitored for safety and efficacy at all scheduled visits through day 120. Recurrence is defined by a positive blood smear with or without vivax malaria symptoms.
b. If a subject withdraws, the site should offer to conduct safety assessments through Day 120.
c. Visit Day 1 includes all screening procedures and treatment with tafenoquine.
d. Includes medical, disease and therapy histories.
e. Vital signs include height and weight (screening only), blood pressure, temperature, heart rate and respiratory rate. Refer to Section 7.5.4 for additional details.
f. At Center PPD, Vital Signs and Brief Physical Examination will be performed at every visit.
g. Adverse events are recorded from the time of the first dose of study medication.
h. Serious adverse events are recorded from the time of consent in order to fulfil international regulatory requirements.
i. 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.
j. A blood sample for G6PD genotyping will be collected only from subjects who experience a SAE due to hemoglobin decline. Subjects with hemoglobin decline should continue to attend all visits through Day 120 to monitor Hb status.
k. Hematology includes hemoglobin, hematocrit, red blood cell/white blood cell/platelet counts, mean cell volume, white blood cell differential and reticulocyte count.
l. Clinical Chemistry includes CPK, BUN, serum creatinine, total and indirect bilirubin and liver clinical chemistry.
m. Pregnancy testing is only for females of child-bearing potential. Use a urine pregnancy test that is routinely used at the site with a test sensitivity for human chorionic gonadotropin (hCG) level ≤ 25 mIU/mL.
n. Day 3 PK sample must be taken 24-96 hours post TQ dose.
o. Once full PK sampling has completed, remaining enrolled subjects will provide two PK samples at Day 15 and Day 29.

7.2. Screening and Critical Baseline Assessments

Study site personnel must obtain written, dated informed consent from the parent(s) or legal guardian(s) of the subject, as well as assent from the subject, if applicable, prior to the initiation of any screening procedures.

The following clinical and laboratory assessments will be conducted at screening (prior to the dose of TQ) as detailed in the Time and Events (Section 7.1):

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

- Medical history will be collected, including medical, disease and therapy histories; and, cardiovascular history and associated risk factors

- A brief 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 rigors, 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 the presence of Plasmodium species asexual parasites and gametocytes (see Section 7.4 and the SRM for further details). Given the subject may have already received one or more doses of CQ, the parasitological assessment at Day 1 may be negative.

- A blood sample will be collected on filter paper and stored for future plasmodium genotyping analysis.

- 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 SRM). 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 SRM.

- The following laboratory assessments will be performed by local laboratories at screening and prior to dosing TQ:

  - Hematology analysis will include: Hb, hematocrit (Hct), red blood cells (RBC), white blood cells (WBC), mean cell volume (MCV), differentiated 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 urine pregnancy test will be performed on females of childbearing potential that is routinely used at the site, provided the test has sensitivity for human chorionic gonadotropin (hCG) of ≤ 25 mIU/mL.

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

- Center PPD (Manuas, Brazil) only will perform the following ophthalmic assessments prior to randomization:

  - Visual acuity will be assessed by standard methods

  - Slit lamp examination of the cornea to evaluate for vortex keratopathy

  - Retinal digital imaging (color photographs, fundus autofluorescence and OCT)

7.3. Unscheduled Visits

Subjects who have one or more visits outside the allowable time window defined for each scheduled visit will undergo all the procedures and assessments described in the Time and Events Table (Section 7.1) 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 120-day study period. In addition, subjects must return to the clinic anytime they are experiencing a recurrence of malaria symptoms.

7.4. Efficacy

The study is not powered to produce precise estimates of efficacy. However, the estimates of recurrence-free efficacy at Day 120 will be reviewed at each interim and at the final analysis of the study. The doses in the pediatric study (Section 6.1) have been selected to match the exposure following an efficacious dose of TQ (300 mg) in adults,

and are therefore expected to provide similar levels of efficacy in the pediatric population.

Parasitology

Microscope blood slides will be prepared pre-dose at screening on Day 1 to confirm the presence (positive or negative) of *P. vivax* malaria (asexual parasites and gametocytes), and on Day 8 to confirm the parasite has cleared. Blood films will also be prepared during follow-up on Days 29, 60, 90 and 120. In addition, blood films should be obtained at the recurrence visit or withdrawal visit as applicable. At each time point two thick and one thin film slides 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 please refer to the SRM.

Parasite Genotyping

Two drops of peripheral blood will be collected onto pre-printed filter paper for subsequent DNA extraction and genetic analysis of Plasmodium species on all subjects on Day 1, prior to TQ dose and; if necessary, at the time of the first recurrence.

Analysis 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.

External quality control

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

7.5. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional details on specific assessments are provided below. Safety information will be reviewed on a monthly basis by a GSK/MMV safety review team.

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

The definitions of an AE or SAE can be found in Appendix 3 (Section 12.3.1 and Section 12.3.2). The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.5.1.1. Protocol-Defined SAE

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.

7.5.1.2. Time period and Frequency for collecting AE and SAE information

- AEs will be collected from the start of Study Treatment and SAEs will be collected from the time of consent. AEs and SAEs will continue to be collected until the follow-up contact (see Section 7.5.1.4), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 3 (Section 12.3.4 and Section 12.3.6).
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

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

7.5.1.3. Method of Detecting AEs and SAEs

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

- “How does your child seem to feel?”
- “Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?”
- “Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?”

7.5.1.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 3 (Section 12.3.5).

7.5.1.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 3 (Section 12.3.3) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

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

Occurrence of malaria is an efficacy endpoint for this study. Consequently malaria should not typically be reported as an AE/SAE and will not be subject to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of a serious adverse event). The occurrence of malaria and any associated signs and symptoms must instead be recorded on the 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/recurrence which should not be reported as AEs/SAEs but captured on the DRE page. However, this should be done ONLY IF confirmed with a positive slide reading for the presence of *P. vivax* malaria at the time symptoms are reported. If any of the following symptoms are reported and the slide read is negative, they should be reported as an AE or SAE as usual.

- Pyrexia
- Chills
- Rigor
- Headache

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

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

If the above condition is met then record the event on the SAE page rather than the DRE page and report promptly (i.e., expedited reporting, see Appendix 3, Section 12.3.6) to GSK.

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

7.5.1.7. Regulatory Reporting Requirements for SAEs

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

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

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

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

7.5.2. Pregnancy

Information on the occurrence of new pregnancies will be collected over the period starting at screening (Day 1) and ending at the Day 120 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.

If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 12.4).

7.5.3. Physical Exams

Physical examinations will be performed during the treatment period (Day 1), the follow-up period on Days 3, 8, 29, 60, 90 and 120 and if there is a relapse or premature withdrawal visit. (At center PPD physical examinations are required at all follow-up visits.) When conducting the exam, please note:

- A brief physical examination will include, at a minimum, assessments of the lungs, cardiovascular system, and abdomen (liver and spleen).

- Investigators should pay special attention to clinical signs related to previous serious illnesses

7.5.4. Vital Signs

Vital signs will be performed on the day of TQ treatment (Day 1), immediately prior to pharmacokinetic (PK) measurements, and if there is a recurrence or premature withdrawal visit. (At center PPD vital signs are to be performed at all follow-up visits.) Vital signs include height and weight (screening only), blood pressure, temperature, heart rate and respiratory rate.

7.5.5. Concomitant Medications

Information on concomitant medications will be collected at all scheduled treatment and follow-up visits, and if there is a recurrence or premature withdrawal visit.

7.5.6. Clinical Safety Laboratory Assessments

Clinical chemistry and hematology samples will be analyzed by local laboratories. All protocol required laboratory assessments must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule (Section 7.1).

Hematology tests will be conducted on the Day 1, 3 and 8 visits. Clinical chemistry tests will be conducted on the Day 1 and Day 8 visits. In addition, laboratory tests may be conducted at any time during the study, as warranted by the condition of the subject and at the investigator's discretion. All laboratory results that are considered clinically significant should be recorded as AEs. 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.

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

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, all additional hematology and clinical chemistry labs should be obtained immediately. In addition, a blood sample should be drawn for G6PD genotyping (see Section 7.7).

Methemoglobin status will be assessed at Day 1 and Day 8. Subjects with anemia may have symptomatic methemoglobinemia (e.g., blue discoloration of skin and lips, shortness of breath) at levels lower than subjects with normal hemoglobin levels

(symptoms typically do NOT occur with MetHb values <20% in subjects with normal hemoglobin levels).

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

7.5.7. Ophthalmic Assessments (Center PPD Only)

Ophthalmic assessments will be performed at Center PPD (Manaus, Brazil) at screening and prior to randomization, at Day 120 and at the withdrawal visit, if applicable. The Principal Investigator and site ophthalmologist will determine if the child is able to comply with the assessments, based on their malaria status and ability to reasonably cooperate with the assessments. Subjects who do not complete the ophthalmic examination at baseline, including interpretable retinal imaging, should not complete ophthalmic exams at follow-up or withdrawal. If a subject completes a portion of the ophthalmic exams at baseline, only those same exams should be completed at follow-up.

7.6. Pharmacokinetics

Blood samples for PK analysis of TQ will be collected at the time points indicated in the Time and Events Table (Section 7.1). The Day 3 sample should be taken 24-96 hours after TQ dosing and a concurrent set of vital signs should also be obtained. Sample(s) of 1 mL blood will be collected (via venipuncture) into blood tubes and/or 70 µL blood (via finger or heel prick) will be collected into capillary tubes. Each sample will be centrifuged to produce plasma and the plasma transferred into a tube for shipping to a central laboratory for analysis. The actual date and time of each blood sample collection will be recorded. The timing and collection of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure sufficient PK monitoring. In addition, concentrations of CQ will be determined. Details of the PK blood sample collection (both venipuncture and microsampling), processing, storage and shipping procedures are provided in the SRM.

Evaluation of correlation between venous and microsampling data will be made at each interim analysis. If microsampling data is deemed adequately representative of venous blood samples, any further PK sampling will switch predominantly to microsampling. However, up to two out of the four planned PK samples per subject may still be collected by both venous and microsampling methods. This will be as a back-up given the primary objective of this study is to adequately characterize the PK of TQ in the pediatric population. The PK data hence is of critical value. In the event that microsampling data is deemed an inadequate representation of venous samples, any further PK sampling will be only by venous sampling.

The sampling strategy of four PK samples per subject is designed to be sparse but adequately characterize the PK of TQ in the pediatric population. These four samples per subject will be reduced to two samples per subject at the earliest interim analysis once reliable characterization of TQ PK has been achieved.

7.6.1. Sample Analysis

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

7.7. Genetics

A 1 mL blood sample will be obtained from all subjects who experience hemoglobin decline during the study (see Section 7.5.6). Genetic research will be limited to G6PD genotyping.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

There are no hypotheses tested in this study. The study is designed to characterize the TQ exposures in pediatric subjects.

9.2. Sample Size Considerations

A minimum of 16 subjects are required to assess the clearance and hence exposures of TQ in pediatric subjects. However, a total of 60 subjects based on feasibility is required to assess overall safety in the pediatric population.

9.2.1. Sample Size Assumptions

A population PK modelling and simulations-based approach was utilized to support appropriate study sample size and PK sampling times for the proposed population PK bridging study. Based on these simulations, a sample size of 16 subjects and a sparse sampling scheme of four time points per subject (Day 3 (24 to 96 hours post TQ dose), Day 15, Day 29, and Day 60) are considered sufficient for the evaluation of the primary PK objective of estimating exposure within each weight band in pediatric subjects aged ≥2 years to <16 years.

Assuming that the rates of absorption and distribution in this population will be similar to the adult population, this sparse sampling scheme allows for adequate estimation of TQ clearance (coefficient of variation < 40% within each weight band as per regulatory recommendation) and thereby exposure within each weight band while obtaining a minimum number of samples for each subject (Appendix 9, Section 12.9).

9.2.2. Sample Size Sensitivity

Population PK simulations were performed to assess the adequacy of study sample sizes of 4, 8, 16, 32, 64 subjects and different sampling schemes to determine exposure with sufficient precision. With sparse sampling of 3-4 time points per subject, a minimum of n=16 subjects are deemed adequate. However, if the variability is higher than expected at the interim analysis, the PK sampling may be continued with a larger sample size to provide exposure assessments across weight bands with sufficient precision (Appendix 9, Section 12.9).

9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

9.3. Data Analysis Considerations

9.3.1. Key Analysis Populations

Safety Population:

This population includes all subjects who received at least one dose of study medication.

Primary PK Population:

This population will include all subjects with at least one PK sample taken at Days 3, 15, 29 and 60. The primary PK analysis to evaluate TQ exposure will be carried out using this population.

9.3.2. Interim Analysis

Up to two interim analyses have been planned so that serial but sparse (i.e., 4 PK timepoints) PK sampling may be stopped at the earliest opportunity. The first interim analysis will take place after a total of at least 16 subjects in the main cohort have PK evaluable data or 12 months post study initiation, whichever comes first. The second interim analysis will take place after a total of at least 32 subjects in the main cohort have evaluable PK data or at 24 months post study initiation, whichever comes first. The second interim analysis will take place only if serial but sparse PK sampling is continued after the first interim analysis.

At every interim analysis, the 95% prediction interval of AUCs based on the simulation with the population pharmacokinetic model will be generated for the mid-point of each weight band (at a population level). The population PK model predicted individual clearance estimates will be utilized to calculate exposure [AUC(0-∞) = Dose/CL]. If this interval lies within the 55-162 µg.hr/mL for the mid-point of each weight band, serial (but sparse) sampling can be stopped for any subjects enrolled further. These bounds were chosen because 95% of adult subjects dosed with the efficacious dose of 300 mg TQ in part 1 of Study TAF112582 had an AUC that fell within this range and the lower bound is consistent with the clinically relevant breakpoint of 56.4 µg.h/mL for the adult

Phase IIb data (TAF112582 Part1). Recruitment will continue for safety data accumulation with these subjects having a PK assessment at two timepoints.

If it is found that due to insufficient number of children being enrolled in the lowest weight band(s) the prediction intervals are wider in that lowest weight band, then further serial (but sparse) sampling may be limited to the children being enrolled in the lowest weight band. The analyses will then be repeated after next set of 4 subjects and so on until the 95% prediction intervals based on the population PK model simulations for that weight band are within the targeted 55-162 µg.hr/mL. Additionally, based on the available data post the two planned interim analyses, up to two samples will be collected in all children enrolled to provide data for the final population PK analysis of TQ to be conducted at the end of the study.

Although the volume of blood required for PK sampling is expected to be small, this study assessment does not form part of the routine standard-of-care for vivax malaria. It is therefore important that serial PK sampling not continue past the point when sufficient data have been collected to answer the primary study question. Recruitment to the additional cohort of infants aged ≥6 months to <2 years may begin following completion of the first interim analysis.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

The primary population PK model based analysis to be performed at the end of the study will borrow some information from the adult model. The sparse sampling in pediatric subjects is insufficient to independently characterize the absorption phase. Consequently the information about absorption from the adult model will be used as prior information to feed into the pediatric PK model with the assumption that the absorption processes are similar in adults and pediatric subjects. Similarly, other information from the adult PK model may also be borrowed in the pediatric model (e.g., distribution). The pediatric population PK model will aim to reliably estimate the TQ clearance and thus the exposures in the pediatric population [AUC(0-∞) = Dose/CL]. If data permit, other PK parameters such as apparent volume of distribution may also be estimated based on pediatric data; otherwise, the information will be borrowed from available adult data.

Such model based analyses utilizing prior information from the adult model may be implemented using one of the various options available within routinely used population PK software such as NONMEM [Beal, 2013] (ICON PLC, USA). The exposures in pediatric subjects across various weight bands will be simulated based on the population PK model developed from the pediatric PK data. The doses that provide target median exposures of 96 µg.hr/mL in each weight band with relevant precision (see Section 9.3.2) will be estimated using the population PK model. The details of the approach will be described in the study reporting and analysis plan.

The final analysis of the data will include modeling and simulation activity in order to provide dosing recommendations for pediatric subjects across different weight bands. The weight bands and doses may or may not be similar to the weight bands and doses currently proposed in the study. The final recommended dosing schedule across any

weight band will aim to provide the average target exposure of 96 µg.hr/mL and will take into account the safety and efficacy data from the pediatric study.

9.4.2. Secondary Analyses

The overall safety and particularly of key endpoints such as gastrointestinal tolerability, clinically relevant drops in hemoglobin and incidence of AEs will be assessed. The ophthalmic assessments of visual acuity, keratopathy and retinopathy will be summarized.

The recurrence-free efficacy at 4 months will be estimated at the interim and final analyses. The targeted exposure in the pediatric study population is expected to match the high level of recurrence free efficacy observed in adults. Although there is no control group to compare the background recurrence rates, the overall estimate of recurrence rates will help compare the exposure-efficacy response in this study to the observed response in the efficacy studies in adults.

If data has been acquired in infants aged ≥6 months to <2 years, it will be included in the main PK model and will contribute to the overall assessment of TQ exposure by weight band and dose setting in this age band.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

Prior to initiation of a 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, and with GSK policy.

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

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Signed informed consent to be obtained for each subject before participation in the study (and for amendments as applicable)

- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including 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 also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

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

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

10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all

relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

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

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

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

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

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

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

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

µg.h/mL	Microgram Hours per milliliter
µL	Microliters
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
CL	Clearance
CPK	Creatine Phosphokinase
CQ	Chloroquine
CRF	Case Report Form
CV	Cardiovascular
DDI	Drug-drug Interaction
DRE	Disease-Related Event
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
g	Grams
g/dL	Grams per Deciliter
G6PD	Glucose-6-phosphate Dehydrogenase
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
Hb	Hemoglobin
hCG	Human Chorionic Gonadotropin
Hct	Hematocrit
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
kg	Kilograms
LDH	Lactate Dehydrogenase
MCV	Mean Cell Volume
MetHb	Methemoglobin
mg	Milligrams
mL	Milliliters
MMV	Medicines for Malaria Venture
MSDS	Material Safety Data Sheet
PK	Pharmacokinetics

PQ	Primaquine
RBC	Red Blood Count
SAE	Serious Adverse Event
SRM	Study Reference Manual
TQ	Tafenoquine
ULN	Upper Limit of Normal
WBC	White Blood Count
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

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

Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR2	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (i.e., screening) (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained as soon as possible and within 24 hours after last dose[5] • 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 liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form

MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline (i.e., screening) • If at any time subject meets 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.

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

12.3.1. Definition of Adverse Events

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

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

Events NOT meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

12.3.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires hospitalization or prolongation of existing hospitalization NOTE: • In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

- Refer to Appendix 2 for the required liver chemistry follow-up instructions

12.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

12.3.4. Recording of AEs and SAEs

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

- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

12.3.5. Evaluating AEs and SAEs

Assessment of Intensity

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

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

Assessment of Causality

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

information, amending the SAE data collection tool accordingly.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

12.3.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

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

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

SAE reporting to GSK via PIMS

• Facsimile transmission of the following PIMS listings for the corresponding subject is the preferred method to transmit SAE information to the protocol contact:
  • SAE listing
  • Demographic listing
  • Study treatment listing
• In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of all required information sent by overnight mail.
• If the PIMS system is unavailable when the SAE occurs, the site will use the paper SAE form and fax that to the protocol contact. The site will enter the SAE data into PIMS as soon as the system becomes available.

12.4. Appendix 4: Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study

- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.

- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.

- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.

- A spontaneous abortion is always considered to be an SAE and will be reported as such.

- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described above. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

12.5. Appendix 5 - Country Specific Requirements

No country-specific requirements exist.

12.6. Appendix 6 - WHO Definition of Severe Malaria

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

In addition, the following may develop:

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

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

References

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

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

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

12.7. Appendix 7 – 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 provide 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 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:

- Phenformin
- Buformin
- Dofetilide
- Procainamide
- Pilsicainide

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.

12.8. Appendix 8 – Tafenoquine Pediatric Dose Extrapolation

Document Number: 2014N199461_03

Division: Worldwide Development

Retention Category: GRS019

Information Type: Clinical Pharmacology Modelling Report

Title:

Tafenoquine Paediatric Dose Extrapolation

Compound Number: SB-252263, Tafenoquine

Effective Date: 23/04/2014

Description:

Extrapolation of the adult population-PK modelling to paediatric dosing. Identification of doses and weight bands using random-space sampling with optimality.

Subject: Tafenoquine, paediatric, allometry, dose selection

Author's Name and Functional Area:

PPD & PPD
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Approved by:

PPD
Clinical Pharmacology Modelling & Simulation

Tafenoquine Paediatric Dose Extrapolation

PPD

23/04/2014

1. Introduction

Tafenoquine has been dosed in a Phase 2b dose-ranging study in adults with extensive pharmacokinetic data for single adult doses of 50, 100, 300 and 600 mg. A population PK analysis (to be reported) using a two-compartment model with first order absorption and random effects on volume and terminal phase half-life (beta) identified bodyweight to be a significant determinant of exposure. The allometric power for clearance was approximately 0.5, in contrast to traditional estimates of 0.75. The inclusion of bodyweight allometry into the model was highly statistically significant.

Assuming a target exposure equivalent to the adult dose of 300 mg, we propose using allometry to optimally select doses and weight bands that provide the best matching of paediatric AUC(0-inf) to that of adults. The justification for the selection of 300 mg will be discussed elsewhere. The proposal is to use the parameters for the adult model, and assume that there are no developmental effects on the apparent clearance of tafenoquine for the age (and weight) ranges to be treated.

2. Methods

The adult population pharmacokinetic model used to describe the Phase 2b dose ranging study was the standard two-compartment model with first order absorption. Bodyweight is part of the model and the full equation takes the form;

(t) = Dose*((BWT/60)**-pBWT)*(A*exp(-Alpha*t) + B*exp(-Beta*t) - (A+B)*exp(-KA*t)).

Bodyweight was centred on 60 kg in accordance with observation from the trial. The dose-normalized AUC(0-inf) for a 60 kg adult is therefore given by DNAUC(0-inf) = A/Alpha+B/Beta-(A+B)/KA = 0.316 ug.hr/ml/mg. The only other parameter required to extrapolate AUC(0-inf) for other doses and bodyweights is the allometric power, pBWT = 0.5217.

The pharmacokinetic model estimates between-subject variability for parameters A and B, and this can be used to derive 95% confidence limits for adult exposure and hence a target exposure to be maintained in children. Moreover, the variability in children is solely assumed to result from bodyweight, and hence 95% limits for children can also be derived.

We propose up to four weight bands with cut-off points and doses for each weight band. For each scenario, we can calculate AUC(0-inf) with 95% confidence limits across the weight range 0-100 kg. For each scenario, we derive the square error (deviation) from the idealized 300 mg adult exposure (for a 60 kg subject), then evaluate the root mean square error for the range 0-100 kg.

In order to evaluate scenarios, we begin with a proposal that has been optimized by trial and error. Doses are assumed to be 50, 100, 200 and 300 mg and weight bands are 0-4, 4-16, 16-40 and >40 kg. In the Phase 2b trials, the lowest recorded weight was 32kg. A cut-off of 30-40 kg is therefore reasonable.

To evaluate optimality we could, in principle, minimise the RMSE by changing weight bands and doses. In practice this is a hard optimization, so we propose an alternative. Four weight classes are defined and generated from uniform random distributions. The lowest dose range is defined randomly from 0-100 mg and subsequent doses selected using linear: 150*rand[0,1], and multiplicative: 4**rand[0,1] escalations. 100,000 scenarios are simulated and the RMSE calculated for each scenario. Optimization is performed manually by selecting the extreme (low) RMSE scenarios and comparing with the trial and error proposal. Finally a pseudo-optimal solution is presented graphically with a recommendation for dose strengths.

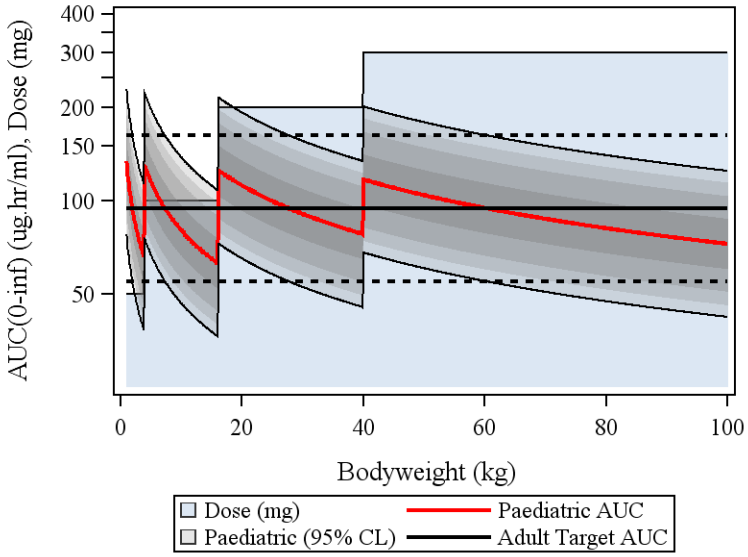
In principle, the full solution is soluble in closed form with integration of the RMSE function by dose and weight band in an eight dimensional phase space. The random sampling algorithm, whilst not the most efficient, is robust and should therefore be capable of finding very good solutions.

3. Results

3.1. Trial and Error

We begin by assuming that a 50 mg dose might be possible for the smallest children, and that we should try and avoid dosing on a mg/kg basis greater than 10 mg/kg. Doses are fixed to 50, 100, 200 and 300 mg, and weight bands were chosen manually and are 0-4, 4-16, 16-40 and >40 kg. The predicted AUC(0-inf), complete with dose bands and adult 300 mg target (for a 60 kg subject) are plotted below. The RMSE for this scenario is an impressive 14.6 ug.hr/ml, compared with a target of 95 ug.hr/ml, implying an over/under dosing of approximately 15%.

Figure 5 First Guess Paediatric AUC (0-inf) as a Function of Bodyweight and Dose

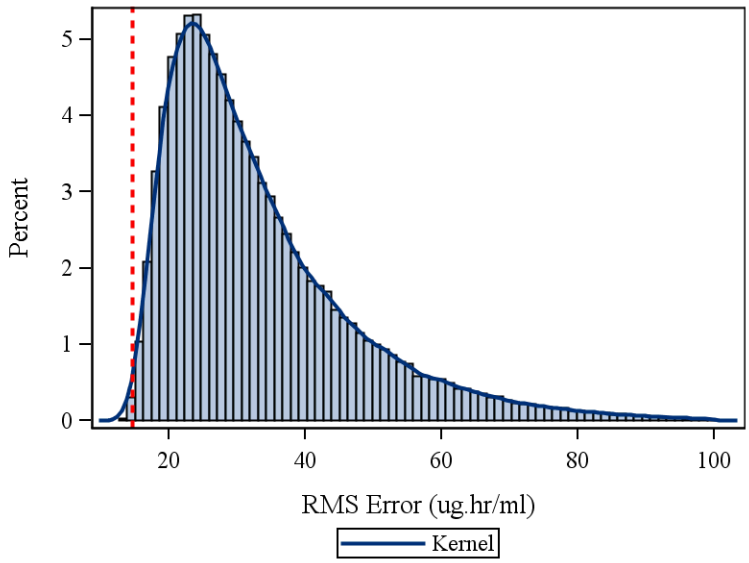


3.2. Simulations

We now conduct a simulation of 100,000 scenarios, selected at random with some structural components. First, the lowest dose is deemed to be between 0 and 100 mg and is uniformly distributed (i.e., the mean will be 50 mg). Second, the increment in dose for each weight band is 4**rand[0,1] (i.e., the mean fold increase will be two-fold). Finally we assume four uniform random weight bands of widths 10, 20, 30 and 20 kg, implying mean cut-offs of 0-5, 5-15, 15-30 and 30-40 kg, in keeping with the first proposal. These can be varied at will, as can the fold changes in dose per weight band.

The histogram below shows the RMSE for AUC(0-inf) compared with target. The dashed red line shows the RMSE for the first proposal and it is clearly close to optimal. Some selections will clearly under- or over-dose paediatric patients hugely!

Figure 6 Histogram of RMSE for Predicted Exposure



3.3. Optimality

Having simulated 100,000 scenarios, the histogram shows the distribution of RMSEs. The multiplicative dose escalation tended to produce many scenarios with large over- or under-dosing, when presented on a semi-log plot (not shown). The additive escalations show a log-normal distribution. We select the five smallest as a measure of optimality and compare with the trial proposal (Scenario 0). The table below shows original proposal compares well, but that a smaller RMSE available by tuning doses and weight bands accordingly. It is however entirely possible that the small difference in RMSE is of little clinical significance, and this can be tested with the exposure-relapse response logistic regression model we have used to analyse the efficacy data (not shown).

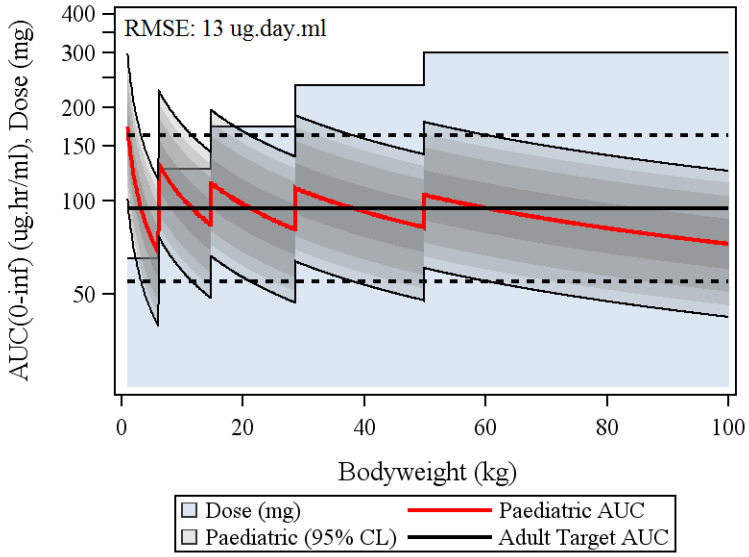
Table 5 Table of Scenarios with Lowest RMSE

Scenario	Lowest Value	Weight1	Weight2	Weight3	Weight4	Dose1	Dose2	Dose3	Dose4
0	14.6	4.0	16.0	40.0	40.0	50.0	100.0	200.0	300.0
6692	13.0	6.2	14.8	28.6	49.8	65.1	127.1	173.8	236.1
21313	13.2	2.5	9.1	21.2	49.4	46.9	72.7	140.3	223.8
87977	13.3	7.1	19.0	33.2	50.2	57.2	129.0	194.4	264.0
9445	13.3	6.3	16.6	23.1	46.3	62.3	123.0	156.0	208.3
88153	13.4	6.1	10.4	19.5	45.4	61.9	102.6	147.2	197.4

3.4. Optimal Exposure Prediction

Selecting the scenario with the lowest RMSE from the table and using the weight bands and doses for a final simulation of the predicted exposures. This is compared with the target AUC(0-inf) and range in adults in the Figure below.

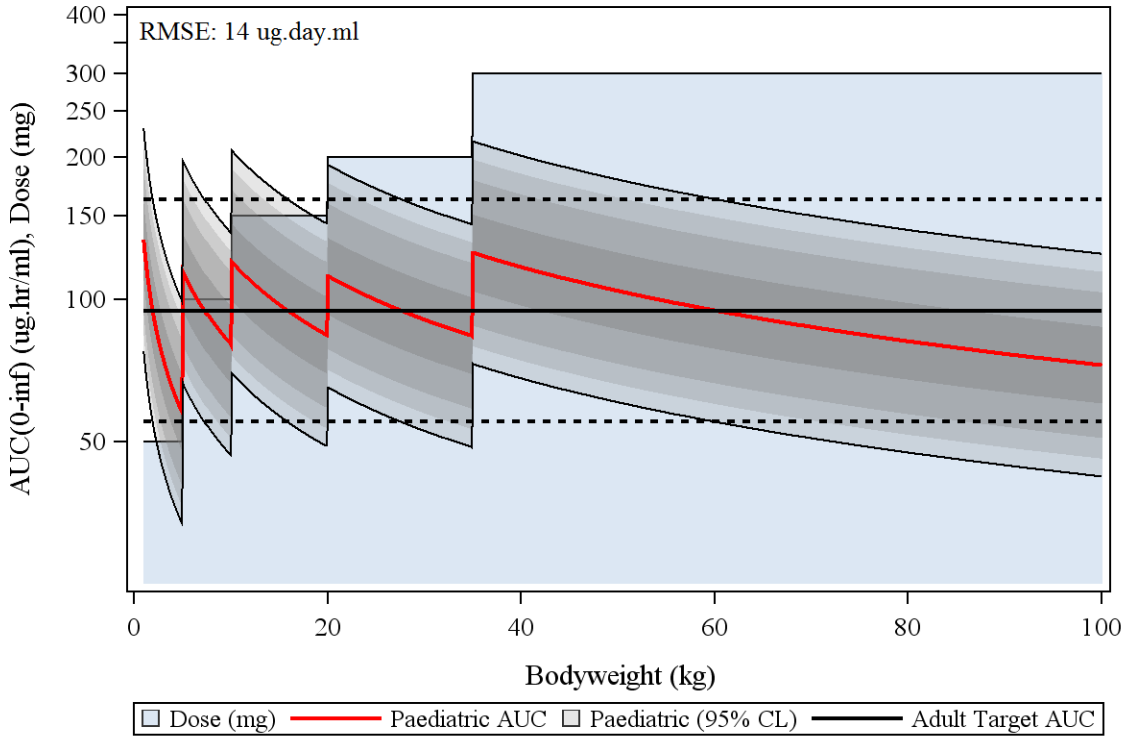
Figure 7 Optimal Paediatric AUC (0-inf) as a Function of Bodyweight and Dose



3.5. Proposed Paediatric Dose and Weight Bands

We assume that the paediatric formulation is only to be made available in one tablet strength, and that selection of dose and weight bands should be close to optimal. Table 5 suggests that a low dose of 50 mg and a low weight range of 0-5 kg is optimal. We therefore propose a tablet strength of 50 mg that provides for doses of 50, 100, 150, 200 and 250 mg, combined with the adult dosage form of 300 mg. Using the weight bands 0-5, 5-10, 10-20, 20-35 and >35 kg, we present a near optimal one-tablet dosing nomogram with RMSE 14.0 ug/day/ml (15% error). Subjects >35 kg receive the adult dosage form.

Figure 8 Paediatric AUC (0-inf) for Doses 50, 100, 150, 200, 300 mg, and Weight Bands 0-5, 5-10, 10-20, 20-35 and >35 kg



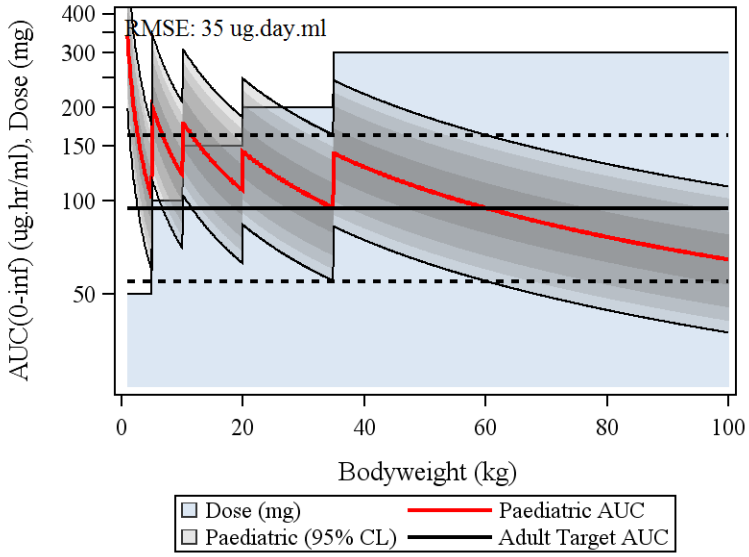
Bodyweight has been used as a covariate to predict exposure with an exponent estimated from the adult data. The lowest weight in the adult study was 32 kg, and it is possible the exponent, pBWT, although estimated with good precision, may be an underestimate. The conventional value for metabolic processes is 0.75, and we now consider model misspecification, should the true value (estimated from paediatric data) fall closer to the conventional value.

With all other parameters fixed, the RMSE for the conventional exponent of 0.75 increases to 34 ug.hr/ml (). Much of this error is, however, in the 0-5 kg weight range, which will not be treated in the proposed study. Once data is acquired, estimation of exposure in the treated subjects using the established population pharmacokinetic model in the first instance, will provide a better estimation of the allometric exponent down to 5 kg.

Table 6 RMSE for Proposed Nomogram with Estimated and Conventional Allometry

Scenario	pBWT	RMSE
Estimated	0.522	14.0
Theoretical	0.750	34.8

Figure 9 Paediatric AUC (0-inf) for the Proposed Dosing Nomogram Assuming a Conventional Allometric Exponent of 0.75



4. Conclusion

A simple closed-form solution that describes the effect of bodyweight on Tafenoquine exposure, which has in turn been related to the probability of relapse, has been used to extrapolate adult exposure down to paediatric populations. It is assumed that the only determinants of exposure are dose and bodyweight, and that the effects of bodyweight scale allometrically from 60 kg down to 1kg.

A range of weight bands and doses have been investigated, and these have been optimized using random phase space exploration. Simulation of 100,000 possible scenarios shows that a weight band of 0-5 kg is prudent, and that a low dose of 50 mg is optimal. If one tablet strength is desired for paediatric formulation, we propose 50, with four weight bands. This nomogram is very close to optimal, with a RMSE of less than 15% of the target exposure in adults.

Evaluation of model mis-specification shows that the proposed nomogram is robust, with a maximum RMSE of 36%. Since most of this error is in the smallest weight band that will not be treated in the proposed paediatric trial, and evaluation of exposure is planned after approximately 20 subjects have been dosed, the proposal is deemed to be sufficiently robust for evaulation in a clinical setting.

12.9. Appendix 9 - Tafenoquine Pediatric Population-PK Trial Simulation

Document Number: 2014N201728_01

Division: Worldwide Development

Retention Category: GRS019

Information Type: Clinical Pharmacology Modelling Report

Title:

Tafenoquine Paediatric Population-PK Trial Simulation

Compound Number: SB-252263, Tafenoquine

Effective Date: 27/04/2014

Description:

Simulation of paediatric trial and re-estimation of exposure using population-PK methods to evaluate different trial designs and sampling schemes.

Subject: Tafenoquine, paediatric, allometry, dose selection

Author's Name and Functional Area:

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Tafenoquine Paediatric Population-PK Trial Simulation

PPD

27/04/2014

1.Introduction

The pharmacokinetics of tafenoquine have been evaluated in adults in a Phase 2b dose-ranging study. A population PK analysis was used to extrapolate exposure to paediatric cases and a weight-based dosing nomogram proposed for the paediatric trial (see Appendix 8). Having evaluated suitable doses and weight bands, the purpose of this report is to consider how the paediatric trial should be designed to best evaluate exposure in a much small population whilst still maintain precision in estimation methods.

For the paediatric population we have proposed five weight bands; 0-5, 5-10, 10-20, 20-35 and >35 kg, with corresponding doses of 50, 100, 150, 200 and 300 mg. Analysis showed that this is a near optimal nomogram for maintaining predicted exposure within 15% of that of adults. Design parameters for the paediatric trial to confirm the suitability of this nomogram are; number of subjects in each weight band, total number of subjects and sample times.

In the adult study five pharmacokinetic samples were taken over 60 days. This scheme, coupled with the large number of subjects, meant that a two-compartment model with first-order absorption was well-estimated and described the observed data. Allometry was integrated into the model allowing for full paediatric extrapolation.

In this report we consider the effects of sparse sampling and reduced sample sizes. These restrictions are necessary on the grounds of practicality; minimising data collection in children is an important aim of paediatric extrapolation, but at the same time reduce the ability to estimate exposure accurately. Any finalised design should aim to balance sample size, sampling scheme and precision of estimation.

2. Methods

To conduct the trial simulation we begin from the adult population PK model incorporating allometry. We draw random samples from a distribution of bodyweight and categorise according to pre-established weight bands and corresponding doses. Full PK profiles, including residual, are generated for each subject. For each design scenario 1000 trial replicates are simulated. This superset of data forms the basis for analysis. A variety of sampling schemes can then be subsampled and a population PK model fitted to the data for each sampling scheme. Once a model is fitted, post-hoc individual estimates of exposure are calculated and compared with the true value for each subject. Deviation (Observed - Predicted) is calculated. Finally, the Root Mean Square Error (RMSE) is used to summarise the precision of each trial replicate. The overall outcome is a distribution of 1000 estimated of RMSEs for each trial design scenario, from which a sampling recommendation can be made.

In the Phase 2b analysis, the model used to describe the data was fully parameterised and all parameters were estimated with very good precision. In the paediatric trial we are concerned with estimation of exposure for the smallest number of subjects (as opposed to evaluation of efficacy). This means that the much smaller sample size, say 20 subjects compared with 200, may make estimation of all pharmacokinetic parameters challenging. Moreover, sparse sampling, particularly when there is no sampling during the absorption phase, makes estimation of a fully parametrised model impossible. A number of techniques are possible to overcome this challenge ranging from no parameter estimation (assume the adult model is a perfect description of paediatric subjects) to a Bayesian analysis with informative priors (using proc mcmc) and estimating posterior pharmacokinetic parameters after incorporating the paediatric data. For the purposes of this analysis, we will use full estimation for the full dataset and fix parameters as necessary for sparse sampled datasets. The final trial analysis may additionally make use of Bayesian techniques, but those will not be tested here.

3. Model Simulation

3.1. Pharmacokinetic Model

The Phase 2b adult data was described using a two-compartment model with first-order absorption and integral allometry that incorporated weight as a determinant of exposure. The model was parameterised in terms of macroconstants, A, B, Alpha and Beta and the full equation takes the form;

(t) = Dose*((BWT/60)**-pBWT)*(A*exp(-Alpha*t) + B*exp(-Beta*t) - (A+B)*exp(-KA*t)) + s2.

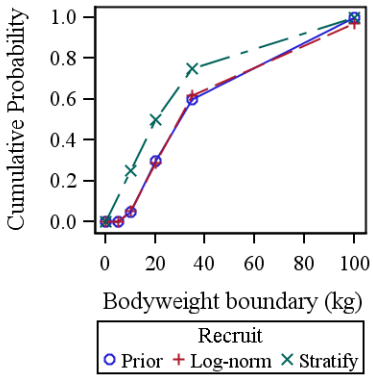
where s2 is the residual. Parameters A and B are random effects and share the same log-normal distribution with inter-subject variance s2b1. The terminal elimination rate, Beta, is also a random effect with variance s2b2 with no correlation to A and B. The final parameter estimates from the adult model are given in the table below. AUC(0-inf) was estimated from the macroconstant parameterisation as Dose*((BWT/60)**-pBWT)*(A/alpha + B/Beta - (A+B)/KA), and clearance calculated from AUC for both population and individual subjects.

Table 7 Pharmacokinetic Parameters for the Model (above)

Parameter	Value	Units	Notes
A	0.8586	ng/ml/mg	Macroconstant with V2/F
B	0.4813	ng/ml/mg	Macroconstant with V2/F
Alpha	0.4380	/day	Distribution half-life
Beta	0.0415	/day	Elimination half-life
KA	3.3073	/day	Absorption Rate
pBWT	0.5217	NA	Scaling power for BWT
s2b1	0.2766	NA	SDLOG(A,B) variability
s2b2	0.1695	NA	SDLOG(Beta) variability
s2	0.2657	NA	SDLOG(Resid) residual

A population of 1000 paediatric subjects is simulated for each of 1000 trials based on a log-normal weight distribution with mean 3.36 and log standard deviation 0.66. This gives a mean bodyweight of 28.9 kg and probabilities of <1%, 5%, 23%, 33% and 36% of being in weight bands 0-5, 5-10, 10-20, 20-35 and >35 kg respectively (see Figure 10 below). From this population subjects are then drawn with or without stratification. Since subjects of less than 5 kg will not be recruited, stratification only impacts the proportions in bands 2-5. Without stratification, bands 2 and 5 will be under-represented, which may have consequences for the estimation of allometric scaling and hence patient exposure at bodyweight extremes.

Figure 10 Cumulative Probability Distributions for Recruitment by Weight Band (above)



Having sampled a suitable population of subjects, the second trial design parameter is sampling times. A dense sampling scheme of twelve PK samples; 0.25, 0.5, 1, 2, 3, 4, 7, 15, 21, 29, 60 and 84 days forms the superset of all possible times. One of the aims of paediatric studies is to balance sampling of subjects with precision of exposure estimation. A number of sample schemes can be tested ranging from all twelve samples (the base case) down to as few as two or three samples (very sparse).

After simulating 1000 trials from the sampled population and PK sampling scheme, non-linear mixed-effects modelling can be used to estimate exposure. We use the same adult pharmacokinetic model; a two-compartment linear model with first-order absorption. Paediatric sparse sampling will typically mean that there are fewer subjects and sparser sampling than adult data. For example, sampling subjects from Day 3 means that there will be very limited information on absorption and distribution, hence estimation of the absorption and distribution rates, KA and Alpha, will not be possible. The low numbers of subjects means that estimation of the magnitude of any random effects may also prove difficult. Instead, we propose fixing these nuisance parameters to their adult reference values where necessary, whilst estimating other parameters of importance to the paediatric population; relative bioavailability compared with adults, allometric scaling power for bodyweight and terminal elimination rate, Beta.

Once the model is fitted and parameters estimated, individual estimates of exposure can be calculated and compared with the known value (i.e., known in the sense simulated from the true parameters for each subject in the trial); the square of the deviance from true AUC(0-inf) calculated and the trial summarised by root mean square error (RMSE). A distribution of RMSE values across all 1000 simulated trials is a summary measure of the precision of the trial design and allows direct comparison of designs.

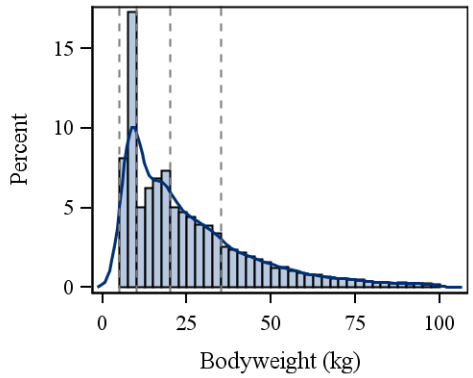
The primary objective of the paediatric study is to understand and predict the exposure for each weight band and compare with the desired target adult exposure of 96 ug.hr/ml for a 300 mg dose in a 60 kg adult. The final model can be used to predict exposure for the midpoint of each weight band, complete with propagated uncertainty in precision, using the Estimate statement in proc nlmixed. These prediction intervals for the final outcome for each trial and their properties can then be summarised over all simulated trials to give confidence that the trial design is capable of estimating exposure in a wider population of children.

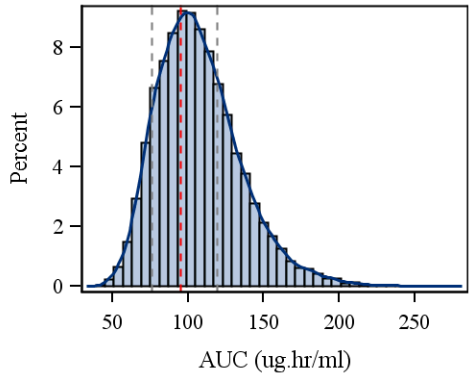
3.2. A Sample Trial Design

3.2.1. Simulated Data

As an example, we consider a sample trial design of 20 subjects with stratification based on weight and five subjects per weight band. The simulated weight distribution, including weight bands, coupled with exposures for all 20000 subjects are shown in Figure 11. Note that weight stratification distorts the expected log-normal weight distribution and that the proportion in each weight band is a constant 25%.

Figure 11 Summary Weight and Exposure Distributions for the Simulated Population (above)

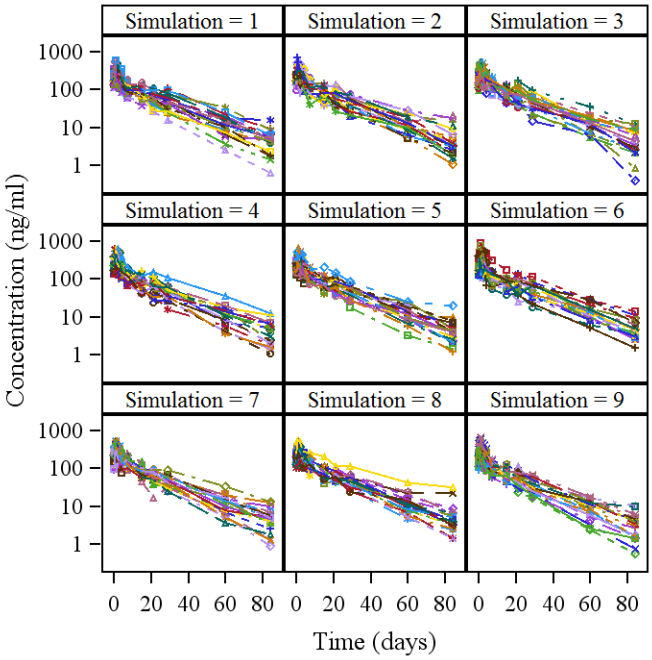




3.2.2. Simulated Pharmacokinetic Profiles

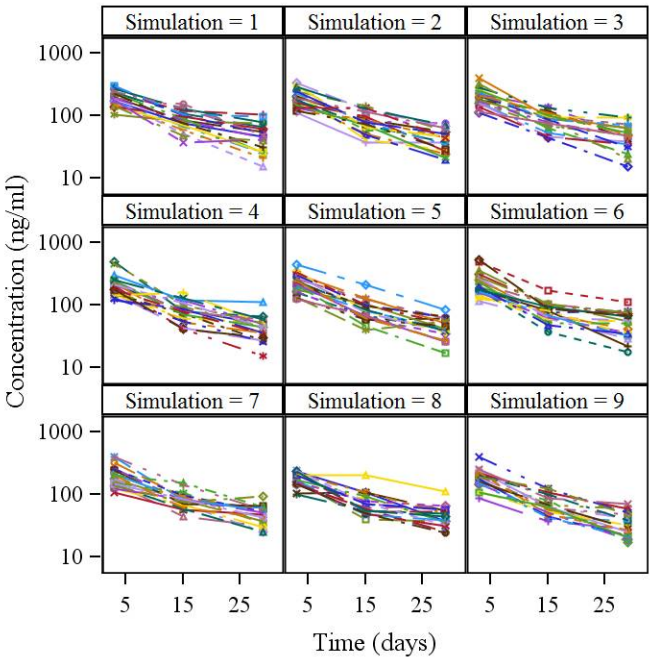
We now consider a sparse sampling scheme with pharmacokinetic samples taken on Days 3, 15, 29. For illustration, we plot data and analysis results from the first nine simulated trials to show trial-to-trial variability. Final results and conclusions are drawn from all 1000 simulated clinical trials. The full pharmacokinetic profiles for the first nine trials are shown below with sampling from 0.5 to 84 days:

Figure 12 Simulated Full Pharmacokinetic Profiles (Trials 1-9) (above)



By way of contrast, with a sampling scheme of only three time points, the analysis dataset for this specific trial design looks much less promising, with no data during the absorption and distribution phases whatsoever, and a relatively short observation of terminal elimination compared with the half-life:

Figure 13 Simulated Sparse Pharmacokinetic Profiles (Trials 1-9) (above)



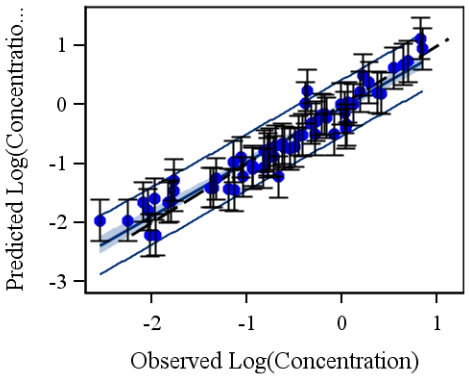
Since the inter-subject variability for the elimination of tafenoquine is low, the half-life, beta looks well-defined on a population basis, despite a truncation of sampling at Day 29. This means that sampling beyond one month may not be necessary and this analysis is designed to test that hypothesis. Multiple sampling scenarios can be tested, but without data during the absorption process, estimation of absorption and distribution rates, KA and Alpha, will not be possible.

3.2.3.Non-linear Mixed-Effects Modelling

We know from the adult data with full pharmacokinetic profiles that tafenoquine concentrations are well-described by a two-compartment model with first-order absorption. The sparse sampling in this example means that estimation of absorption, distribution and possibly inter-subject variability will be challenging. Instead, we fix certain parameters to those of adults, whilst allowing the model to estimate others. For this example we estimate parameters; A (equivalent to an intercept in a linear model), Beta, allometric power pBWT and the residual s2. We fix Alpha and the ratio A/B (equivalent to the overall shape of the two-compartment profile), and the inter-subject variability s2b1. For simplicity, only a single random effect is used in the model to describe variability on A and B equally (as would be expected for volume of distribution, V/F). In this model all subjects will have the same terminal-phase elimination rate, Beta, despite the data being simulated with variability in this parameter, but each subject will have an individual clearance, CL/F and AUC(0-inf) due to the random effect. Starting values for estimated parameters are the adult values.

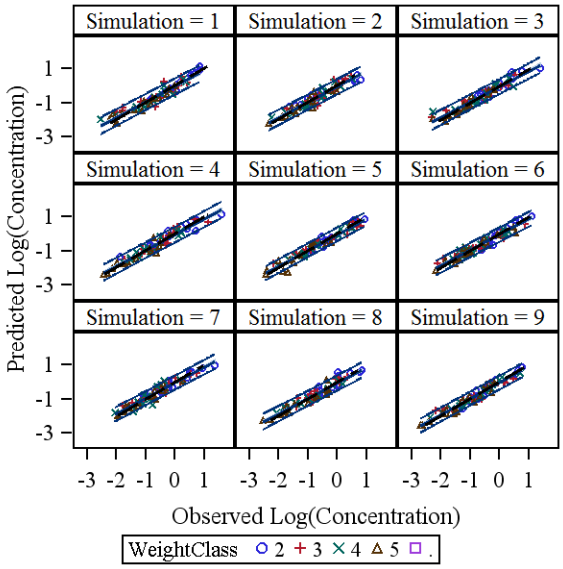
A conventional model diagnostic plot of observed vs. individual predicted (Log) concentration (DV vs. iPRED in NONMEM) is shown in the plots below. The first plot shows a representative trial, with prediction intervals from proc nlmixed for each data point. The dashed line is the line of equality, the solid line a regression of DV vs. iPRED and the shaded region the prediction interval for the linear regression. Notice the prediction interval for almost every data point includes the line of unity (this interval diagnostoc is not available in NONMEM).

Figure 14 Diagnostic Plot of DV vs. iPRED With Prediction Interval Bars (Trial 1) (above)



Removing the prediction interval error bars for clarity, we can show the same diagnostic plot for the first nine trials. By fixing some of the parameters, the model is able to provide excellent predictions in spite of the sparse sampling scheme.

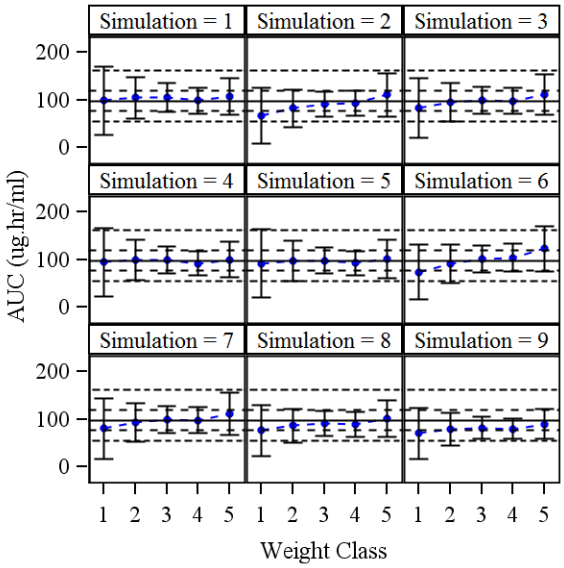
Figure 15 Diagnostic Plot of DV vs. iPRED (Trials 1-9) (above)



3.2.4. Predicted Exposures

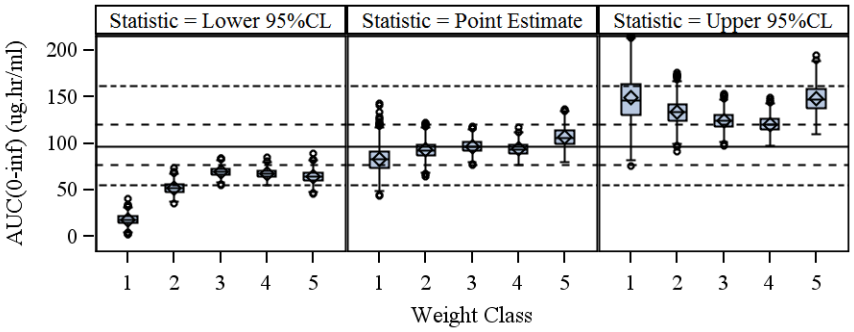
Having estimated the model parameters, proc nlmixed can provide population estimates of exposure calculated from the fixed effects. Using the mid-points for each weight band; 2.5, 7.5, 15, 27.5 and 47.5 kg, and the closed-form expression for AUC(0-inf) given earlier, the predicted population mean AUC(0-inf) for the first nine trials by weight class are shown below, complete with target 96 ug.hr/ml and the interval 77-120 which represents traditional bounds for bioequivalence, complete with 55-162 which is the prediction interval for a 60 kg adult.

Figure 16 Predicted AUC (0-inf) by Weight Class (Trials 1-9) (above)



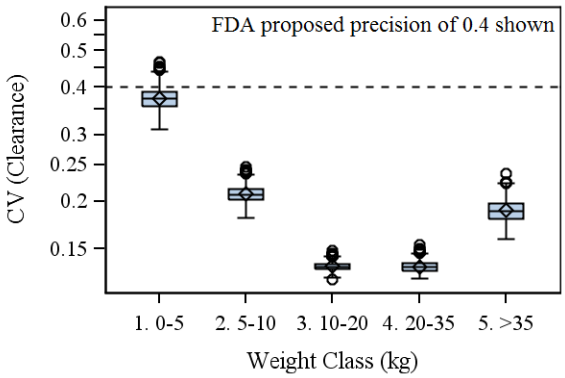
Summarising all 1000 simulated trials, shows that the point estimate AUC by weight class for all weight bands falls within the 80-125 conventional bounds for bioequivalence. Confidence limits for weight bands 10-20 and 20-35 kg may additionally fall within the same bands for some trial replicates, which means that formal bioequivalence could be declared (Figure 17) based on model predicted exposure. For other weight bands, formal bioequivalence is unlikely without a larger sample size.

Figure 17 Predicted AUC (0-inf) Mean and 95% CLs by Weight Class (All Trials) (above)



One measure of precision is the coefficient of variation (CV) of a predicted parameter. The parameterisation used in this modelling requires clearance to be calculated from the macroconstants. The CV can however be calculated and summarised over all clinical trials to measure trial design performance. The FDA have proposed a target CV of 0.4 as a guide to sample size in paediatric trials. This target does not, however, factor in the effects of bodyweight on clearance, nor does it take into account the fact that the actual trial replicate will have a trial-specific distribution of bodyweights and the model predicted clearance will be a function of bodyweight; hence predictions of clearance (but not AUC) are required across the weight range of a wider population. In the plot below we present the CV distribution by weight class. Although this example uses stratifcation by bodyweight, even in the weight class 0-5 kg, who were explicitly excluded from the trial, the sample trial design provides acceptable precision.

Figure 18 Predicted Coefficient of Variation for Clearance by Weight Class (All Trials) (above)



A further method of evaluating the performance of a trial, and one that is much less arbitrary than a nominal target CV of 0.4, is to consider how well the post-hoc individual exposure estimates compare with the (true) exposure for each subject. The root mean square error for AUC(0-inf) provides an objective measure of the precision of any trial design, independent of bodyweight.

Figure 19 Histogram of RMSE for Predicted AUC (0-inf) (above)

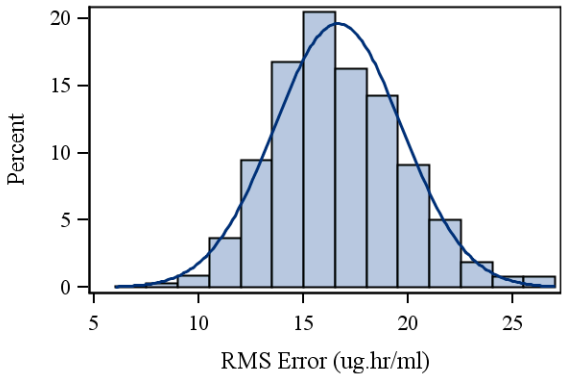


Table 8 RMSE (ug.hr/ml) for Sample Trial (above)

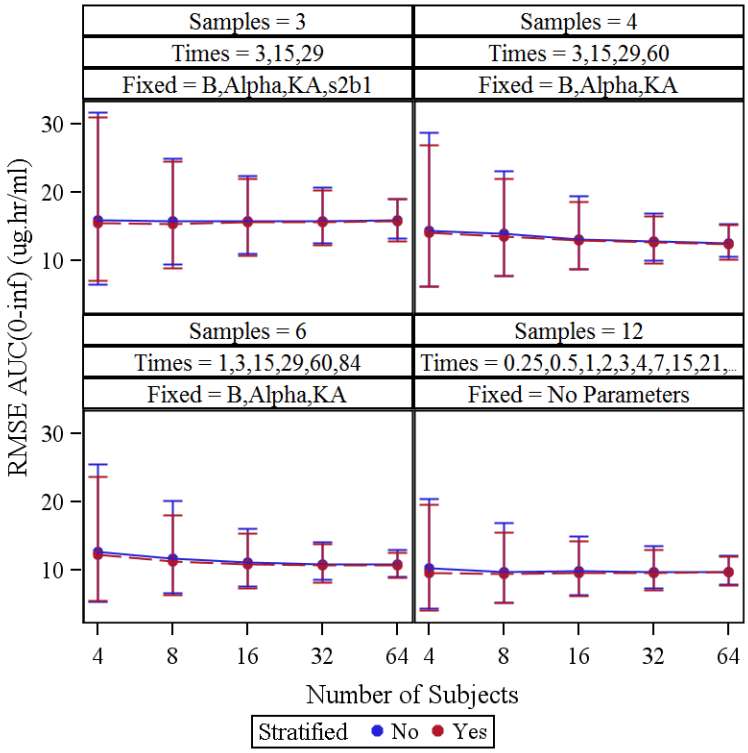
Scenario	Subjects	Stratified	Times	Fixed	Median	Lower	Upper
Sample Trial	20	Yes	3,15,29	B,Alpha,KA,s2b2	16.4	12.0	21.9

These results show that for the sample trial design the median RMSE for AUC(0-inf) is only 16 ug.hr/ml (18%), with 90% (5-95th percentiles) of all trials falling in the range 12.1-21.9 ug.hr/ml. By fixing suitable parameters to their adult values, even 20 subjects with only three samples per subject can give a reasonable estimate of individual and population exposure with less that 20% error.

4. Results

We consider the following scenarios; fixed or weight-based stratification; full, sparse or very sparse pharmacokinetic sampling; and sample sizes ranging from 4 to 64 subjects in doubling steps. The trial design space therefore has multiple dimensions than can be explored. The measure of trial performance is RMSE AUC(0-inf), with a lower value being a higher performing trial. The goal is not, however, one of optimisation, but evaluation of adequacy. The full trial design without stratification, all twelve samples and 64 subjects can be thought of as the reference, and all other trial designs considered in this context. In each sampling scenario, the number of parameters estimated is set depending on sampling scheme (but not sample size).

Figure 20 Summary Plot of RMSE for All Trial Scenarios (above)



Looking at the plot of RMSE for AUC(0-inf) and the listing of trial results (Table 9), we note the effects of sample size are relatively modest, provided we are prepared to fix parameters from the adult model. Increasing sample size reduces the trial-to-trial variability, but the median RMSE is relatively constant for any given sampling and parameter estimation scheme. Weight stratification was tested for all scenarios and has a smaller effect than might be anticipated unless the sample size is very small (4-8 subjects), largely because the weight range included is still wide and able to demonstrate allometry (estimation of pBWT). Prediction of AUC(0-inf) at the lowest weight class 0-5 kg may, however, be improved. Number of PK samples and durations of sampling is not significant provided that the terminal phase elimination is sampled appropriately. The low variability in terminal half-life means that no random effect is needed to describe this data (despite it being simulated with variability).

5.Conclusions

Any paediatric clinical trial with a primary objective of characterising pharmacokinetics should aim to balance sample size, precision and extrapolation from adult data. Tafenoquine pharmacokinetics in adults are well-characterised which means that extrapolation to children should focus on the allometric aspects of bodyweight and relative bioavailability, rather than assuming nothing is known. From an estimation perspective, this means that any sampling can borrow information from adults effectively, the question being what information to borrow. In this analysis we have shown using simulated paediatric clinical trials, that a relatively small sample size is sufficient to characterise the exposure of tafenoquine in children provided some parameters are fixed to adult values. Moreover, stratification by previously defined weight bands during the clinical trial does not appear to offer additional precision, except for very small sample sizes.

Fixing some aspects of the model from adults; namely absorption and distribution, allows the trial to focus on clearance and exposure. We find that even very sparse sampling with three or four plasma samples will be sufficient to estimate exposure in paediatric subjects. In all events, this trial simulation exercise shows that the expected precision for reasonable designs will give an estimate of paediatric exposure within 15% of the true value, and well below the 40% proposed by the FDA. Once approximately 20 subjects have been recruited, an interim analysis can be used to make predictions of AUC(0-inf) by weight class and the need for re-estimation of the dosing nomogram considered.

6. Appendix

Table 9 RMSE (ug.hr/ml) for All Trial Scenarios

Subjects	Stratified	Times	Fixed	Median	Lower	Upper
64	No	0.25,0.5,1,2,3,4,7,15,21,29,60,84	No Parameters	9.8	8.0	12.2
32	No	0.25,0.5,1,2,3,4,7,15,21,29,60,84	No Parameters	9.8	7.5	13.6
16	No	0.25,0.5,1,2,3,4,7,15,21,29,60,84	No Parameters	9.9	6.4	15.0
8	No	0.25,0.5,1,2,3,4,7,15,21,29,60,84	No Parameters	9.8	5.3	16.9
4	No	0.25,0.5,1,2,3,4,7,15,21,29,60,84	No Parameters	10.4	4.4	20.4
64	No	1,3,15,29,60,84	B,Alpha,KA	10.9	9.1	13.0
32	No	1,3,15,29,60,84	B,Alpha,KA	11.0	8.6	14.2
16	No	1,3,15,29,60,84	B,Alpha,KA	11.2	7.7	16.1
8	No	1,3,15,29,60,84	B,Alpha,KA	11.8	6.6	20.2
4	No	1,3,15,29,60,84	B,Alpha,KA	12.7	5.5	25.5
64	No	3,15,29,60	B,Alpha,KA	12.7	10.6	15.4
32	No	3,15,29,60	B,Alpha,KA	12.9	10.0	17.0
16	No	3,15,29,60	B,Alpha,KA	13.2	8.8	19.5
8	No	3,15,29,60	B,Alpha,KA	13.9	7.9	23.1
4	No	3,15,29,60	B,Alpha,KA	14.4	6.3	28.8
64	No	3,15,29	B,Alpha,KA,s2b1	16.0	13.3	19.1
32	No	3,15,29	B,Alpha,KA,s2b1	15.9	12.6	20.7
16	No	3,15,29	B,Alpha,KA,s2b1	15.8	11.1	22.5
8	No	3,15,29	B,Alpha,KA,s2b1	15.8	9.4	25.0
4	No	3,15,29	B,Alpha,KA,s2b1	16.0	6.5	31.8
64	Yes	0.25,0.5,1,2,3,4,7,15,21,29,60,84	No Parameters	9.7	7.9	12.0

Subjects	Stratified	Times	Fixed	Median	Lower	Upper
32	Yes	0.25,0.5,1,2,3,4,7,15,21,29,60,84	No Parameters	9.7	7.2	13.1
16	Yes	0.25,0.5,1,2,3,4,7,15,21,29,60,84	No Parameters	9.7	6.3	14.2
8	Yes	0.25,0.5,1,2,3,4,7,15,21,29,60,84	No Parameters	9.5	5.3	15.5
4	Yes	0.25,0.5,1,2,3,4,7,15,21,29,60,84	No Parameters	9.7	4.1	19.6
64	Yes	1,3,15,29,60,84	B,Alpha,KA	10.7	9.0	12.6
32	Yes	1,3,15,29,60,84	B,Alpha,KA	10.7	8.3	13.9
16	Yes	1,3,15,29,60,84	B,Alpha,KA	10.9	7.4	15.4
8	Yes	1,3,15,29,60,84	B,Alpha,KA	11.3	6.4	18.1
4	Yes	1,3,15,29,60,84	B,Alpha,KA	12.3	5.5	23.7
64	Yes	3,15,29,60	B,Alpha,KA	12.4	10.2	15.2
32	Yes	3,15,29,60	B,Alpha,KA	12.7	9.6	16.5
16	Yes	3,15,29,60	B,Alpha,KA	13.0	8.7	18.7
8	Yes	3,15,29,60	B,Alpha,KA	13.6	7.8	22.0
4	Yes	3,15,29,60	B,Alpha,KA	14.1	6.2	27.0
64	Yes	3,15,29	B,Alpha,KA,s2b1	15.8	12.9	19.1
32	Yes	3,15,29	B,Alpha,KA,s2b1	15.7	12.3	20.4
16	Yes	3,15,29	B,Alpha,KA,s2b1	15.7	10.8	22.0
8	Yes	3,15,29	B,Alpha,KA,s2b1	15.5	8.9	24.6
4	Yes	3,15,29	B,Alpha,KA,s2b1	15.6	7.1	31.0

12.10. Appendix 10: Protocol Amendment Changes

Amendment 1

This amendment is site-specific and applies to one center in Thailand (center PPD). The primary reason for this amendment is to add an inclusion criterion stating that only subjects of Thai nationality can be enrolled in the study. In addition, vital signs and the physical examination will be conducted at all visits of the study.

5.1 Inclusion Criteria

PREVIOUS TEXT

Not applicable.

ADDED TEXT

2. The subject is of Thai nationality.

7.1 Time and Events Table

PREVIOUS TEXT

Protocol Activity	Visit Day									
	Screen & Treat	Follow-Up Period							Recurrence Visit[a]	Withdrawal Visit[b]
	Day 1[c]	Day 3	day 8	Day 15	Day 29	Day 60	Day 90	Day 120	Recurrence	Withdrawal
Window		+2d	-/+2d	-/+3d	-/+5d	-/+10d	-/+10d	-/+10d		
Informed Consent Process	X									
Demographic Information	X									
Initial History Only [d]	X									
Physician Assess. Malaria Signs & Symptoms	X									
Inclusion/Exclusion Criteria	X									
Efficacy Assessments										
Parasitological Assessment (blood smear)	X		X		X	X	X	X	X	X
Plasmodium PCR genotyping	X								X	
Safety Assessments										
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Vital Signs [e]	X	X		X	X	X			X	X
Brief Physical Examination	X	X	X		X	X	X	X	X	X
Adverse Events Assessment [f]	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events [g]	X	X	X	X	X	X	X	X	X	X
G6PD (phenotyping) [h]	X									
G6PD (genotyping)	X [i]									
Laboratory Assessments										
Hematology [j]	X	X	X							
Clinical Chemistry [k]	X		X							
Methemoglobin	X		X							
Pregnancy Test [l]	X				X	X	X		X	X
Pharmacokinetic Assessments										
Pharmacokinetic Sampling		X[m]		X[n]	X[n]	X			X	
Investigational Product										
Dispense Open Label tafenoquine	X									

Protocol Activity	Visit Day									
	Screen & Treat	Follow-Up Period							Recurrence Visit[a]	Withdrawal Visit[b]
	Day 1[c]	Day 3	day 8	Day 15	Day 29	Day 60	Day 90	Day 120	Recurrence	Withdrawal
Window		+2d	-/+2d	-/+3d	-/+5d	-/+10d	-/+10d	-/+10d		
Treatment Compliance Int. - Invest.	X									
IVRS Registration	X									

a. Subjects who have a recurrence will continue to be monitored for safety and efficacy at all scheduled visits through day 120. Recurrence is defined by a positive blood smear with or without vivax malaria symptoms.
b. If a subject withdraws, the site should offer to conduct safety assessments through Day 120.
c. Visit Day 1 includes all screening procedures and treatment with tafenoquine.
d. Includes medical, disease and therapy histories.
e. Vital signs include height and weight (screening only), blood pressure, temperature, heart rate and respiratory rate. Vital signs are to be performed on Day 1, and immediately prior to all pharmacokinetic sampling.
f. Adverse events are recorded from the time of the first dose of study medication.
g. Serious adverse events are recorded from the time of consent in order to fulfil international regulatory requirements.
h. G6PD phenotyping to be performed by quantitative spectrophotometric analysis. One or more G6PD rapid point of care tests may be performed at baseline (Day 1) only.
i. A blood sample for G6PD genotyping will be collected only from subjects who experience a SAE due to hemoglobin decline. Subjects with hemoglobin decline should continue to attend all visits through Day 120 to monitor Hb status.
j. Hematology includes hemoglobin, hematocrit, red blood cell/white blood cell/platelet counts, mean cell volume, white blood cell differential and reticulocyte count.
k. Clinical Chemistry includes CPK, BUN, serum creatinine, total and indirect bilirubin and liver clinical chemistry.
l. Pregnancy testing is only for females of child-bearing potential. Use a urine pregnancy test that is routinely used at the site with a test sensitivity for human chorionic gonadotropin (hCG) level ≤ 25 mIU/mL.
m. Day 3 PK sample must be taken 24-96 hours post TQ dose.
n. Once full PK sampling has completed, remaining enrolled subjects will provide two PK samples at Day 15 and Day 29.

REVISED TEXT

Protocol Activity	Visit Day									
	Screen & Treat	Follow-Up Period							Recurrence Visit[a]	Withdrawal Visit[b]
	Day 1[c]	Day 3	day 8	Day 15	Day 29	Day 60	Day 90	Day 120	Recurrence	Withdrawal
Window		+2d	-/+2d	-/+3d	-/+5d	-/+10d	-/+10d	-/+10d		
Informed Consent Process	X									
Demographic Information	X									
Initial History Only [d]	X									
Physician Assess. Malaria Signs & Symptoms	X									
Inclusion/Exclusion Criteria	X									

Protocol Activity	Visit Day									
	Screen & Treat	Follow-Up Period							Recurrence Visit[a]	Withdrawal Visit[b]
	Day 1[c]	Day 3	day 8	Day 15	Day 29	Day 60	Day 90	Day 120	Recurrence	Withdrawal
Window		+2d	-/+2d	-/+3d	-/+5d	-/+10d	-/+10d	-/+10d		
Efficacy Assessments										
Parasitological Assessment (blood smear)	X		X		X	X	X	X	X	X
Plasmodium PCR genotyping	X								X	
Safety Assessments										
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Vital Signs [e]	X	X	X	X	X	X	X	X	X	X
Brief Physical Examination	X	X	X	X	X	X	X	X	X	X
Adverse Events Assessment [f]	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events [g]	X	X	X	X	X	X	X	X	X	X
G6PD (phenotyping) [h]	X									
G6PD (genotyping)	X [i]									
Laboratory Assessments										
Hematology [j]	X	X	X							
Clinical Chemistry [k]	X		X							
Methemoglobin	X		X							
Pregnancy Test [l]	X				X	X	X		X	X
Pharmacokinetic Assessments										
Pharmacokinetic Sampling		X[m]		X[n]	X[n]	X			X	
Investigational Product										
Dispense Open Label tafenoquine	X									
Treatment Compliance Int. - Invest.	X									
IVRS Registration	X									

a. Subjects who have a recurrence will continue to be monitored for safety and efficacy at all scheduled visits through day 120. Recurrence is defined by a positive blood smear with or without vivax malaria symptoms.
b. If a subject withdraws, the site should offer to conduct safety assessments through Day 120.
c. Visit Day 1 includes all screening procedures and treatment with tafenoquine.
d. Includes medical, disease and therapy histories.
e. Vital signs include height and weight (screening only), blood pressure, temperature, heart rate and respiratory rate. Refer to Section 7.5.4 for additional details.
f. Adverse events are recorded from the time of the first dose of study medication.
g. Serious adverse events are recorded from the time of consent in order to fulfil international regulatory requirements.

h. G6PD phenotyping to be performed by quantitative spectrophotometric analysis. One or more G6PD rapid point of care tests may be performed at baseline (Day 1) only.
i. A blood sample for G6PD genotyping will be collected only from subjects who experience a SAE due to hemoglobin decline. Subjects with hemoglobin decline should continue to attend all visits through Day 120 to monitor Hb status.
j. Hematology includes hemoglobin, hematocrit, red blood cell/white blood cell/platelet counts, mean cell volume, white blood cell differential and reticulocyte count.
k. Clinical Chemistry includes CPK, BUN, serum creatinine, total and indirect bilirubin and liver clinical chemistry.
l. Pregnancy testing is only for females of child-bearing potential. Use a urine pregnancy test that is routinely used at the site with a test sensitivity for human chorionic gonadotropin (hCG) level ≤ 25 mIU/mL.
m. Day 3 PK sample must be taken 24-96 hours post TQ dose.
n. Once full PK sampling has completed, remaining enrolled subjects will provide two PK samples at Day 15 and Day 29.

Amendment 2

This amendment is global and applies to all centers. In this amendment a newly-described risk was added to the Risk Assessment Table, a typographical error was corrected in the inclusion criteria regarding approved methods of contraception, and, based on results from cohort 1, changes were made to the tafenoquine dose banding scheme. A change was made to the secondary medical monitor.

In addition, the site-specific information in the previous amendment will be carried over into this amendment, thus superseding Amendment No. 1.

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

PREVIOUS TEXT

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

REVISED TEXT

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

4.6.1. Risk Assessment

PREVIOUS TEXT

Not applicable.

ADDED TEXT (to Risk Assessment Table)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Nervous system & psychiatric disorders	Phase 3 results in adult patients showed mild to moderate self-limiting nervous system & psychiatric disorders including dizziness, anxiety & insomnia. See Investigator Brochure addendum for more details.	• Consider excluding patients with a history of serious psychiatric disorders such as psychosis, depression and suicidal ideation.

5.1. Inclusion Criteria

PREVIOUS TEXT

2. The subject is of Thai nationality.

REVISED TEXT

2. The subject is of Thai nationality **(applicable only to subjects at center** PPD .

PREVIOUS TEXT

[4] SEX
• Males and females are eligible to enter the study. A female is eligible to enter and participate in this study if she is non-pregnant, non-lactating and if she is of: a. Non-childbearing potential (i.e., premenstrual); 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: i. 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. ii. Use of combined oral contraceptive consisting of spermicide with either condom or diaphragm iii. Use of intrauterine device with a documented failure rate of <1% per year iv. Use of depo provera injection v. Male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female.

REVISED TEXT

[4] SEX
8. Males and females are eligible to enter the study. A female is eligible to enter and participate in this study if she is non-pregnant, non-lactating and if she is of: a. Non-childbearing potential (i.e., premenstrual); 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: i. Use of oral contraceptive, either combined or progestogen alone used in conjunction with double barrier method as defined below. ii. Use of an intrauterine device with a documented failure rate of <1% per year. iii. Use of depo provera injection iv. Double barrier method consisting of spermicide with either condom or diaphragm v. Male partner who is sterile prior to the female subject’s entry into the study and is the sole sexual partner for that female. vi. 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.

6.1. Treatment Assignment

PREVIOUS TEXT

Table 10 Tafenoquine Dosing

Weights	Tafenoquine Dose[a]	Dosing Regimen
>45 kg	300 mg	2 × 150 mg
>40–≤45 kg	300 mg	2 × 150 mg
>35–≤40kg	300 mg	2 × 150 mg
>30–≤35kg	200 mg	4 × 50 mg
>25–≤30 kg	200 mg	4 × 50 mg
>20–≤25 kg	200 mg	4 × 50 mg
>15–≤20 kg	150 mg	3 × 50 mg
>10–≤15 kg	150 mg	3 × 50 mg
≥5–≤10 kg	100 mg	2 × 50 mg

a. The TQ dose is based on achieving a target AUC(0–∞) of 96 µg.h/ml.

The single dose of TQ will be administered at the investigator site. Subjects >35 kg will take the TQ adult tablet. All 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 6.9.1.2.

REVISED TEXT

Table 11 Tafenoquine Dosing

Weights	Tafenoquine Dose[a]	Dosing Regimen
>45 kg	300 mg	2 × 150 mg or 6 × 50 mg
>40–≤45 kg	300 mg	2 × 150 mg or 6 × 50 mg
>35–≤40kg	300 mg	2 × 150 mg or 6 × 50 mg
>30–≤35kg	200 mg	4 × 50 mg
>25–≤30 kg	200 mg	4 × 50 mg
>20–≤25 kg	200 mg	4 × 50 mg
>15–≤20 kg	100 mg	2 × 50 mg
>10–≤15 kg	100 mg	2 × 50 mg
≥5–≤10 kg	50 mg	1 × 50 mg

a. The TQ dose is based on achieving a target AUC(0–∞) of 96 µg.h/ml.

The single dose of TQ will be administered at the investigator site. Subjects >35 kg have the choice of taking the TQ adult tablet or the TQ pediatric tablet. All 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 6.9.1.2.

7.1. Time and Events Table

PREVIOUS TEXT

Protocol Activity	Visit Day									
	Screen & Treat	Follow-Up Period							Recurrence Visit[a]	Withdrawal Visit[b]
	Day 1[c]	Day 3	day 8	Day 15	Day 29	Day 60	Day 90	Day 120	Recurrence	Withdrawal
Window		+2d	-/+2d	-/+3d	-/+5d	-/+10d	-/+10d	-/+10d		
Informed Consent Process	X									
Demographic Information	X									

Protocol Activity	Visit Day									
	Screen & Treat	Follow-Up Period							Recurrence Visit[a]	Withdrawal Visit[b]
	Day 1[c]	Day 3	day 8	Day 15	Day 29	Day 60	Day 90	Day 120	Recurrence	Withdrawal
Window		+2d	-/+2d	-/+3d	-/+5d	-/+10d	-/+10d	-/+10d		
Initial History Only [d]	X									
Physician Assess. Malaria Signs & Symptoms	X									
Inclusion/Exclusion Criteria	X									
Efficacy Assessments										
Parasitological Assessment (blood smear)	X		X		X	X	X	X	X	X
Plasmodium PCR genotyping	X								X	
Safety Assessments										
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Vital Signs [e]	X	X	X	X	X	X	X	X	X	X
Brief Physical Examination	X	X	X	X	X	X	X	X	X	X
Adverse Events Assessment [f]	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events [g]	X	X	X	X	X	X	X	X	X	X
G6PD (phenotyping) [h]	X									
G6PD (genotyping)	X [i]									
Laboratory Assessments										
Hematology [j]	X	X	X							
Clinical Chemistry [k]	X		X							
Methemoglobin	X		X							
Pregnancy Test [l]	X				X	X	X		X	X
Pharmacokinetic Assessments										
Pharmacokinetic Sampling		X[m]		X[n]	X[n]	X			X	
Investigational Product										
Dispense Open Label tafenoquine	X									
Treatment Compliance Int. - Invest.	X									
IVRS Registration	X									

a. Subjects who have a recurrence will continue to be monitored for safety and efficacy at all scheduled visits through day 120. Recurrence is defined by a positive blood smear with or without vivax malaria symptoms.
b. If a subject withdraws, the site should offer to conduct safety assessments through Day 120.
c. Visit Day 1 includes all screening procedures and treatment with tafenoquine.

d. Includes medical, disease and therapy histories.
e. Vital signs include height and weight (screening only), blood pressure, temperature, heart rate and respiratory rate. Refer to Section 7.5.4 for additional details.
f. Adverse events are recorded from the time of the first dose of study medication.
g. Serious adverse events are recorded from the time of consent in order to fulfil international regulatory requirements.
h. G6PD phenotyping to be performed by quantitative spectrophotometric analysis. One or more G6PD rapid point of care tests may be performed at baseline (Day 1) only.
i. A blood sample for G6PD genotyping will be collected only from subjects who experience a SAE due to hemoglobin decline. Subjects with hemoglobin decline should continue to attend all visits through Day 120 to monitor Hb status.
j. Hematology includes hemoglobin, hematocrit, red blood cell/white blood cell/platelet counts, mean cell volume, white blood cell differential and reticulocyte count.
k. Clinical Chemistry includes CPK, BUN, serum creatinine, total and indirect bilirubin and liver clinical chemistry.
l. Pregnancy testing is only for females of child-bearing potential. Use a urine pregnancy test that is routinely used at the site with a test sensitivity for human chorionic gonadotropin (hCG) level ≤ 25 mIU/mL.
m. Day 3 PK sample must be taken 24-96 hours post TQ dose.
n. Once full PK sampling has completed, remaining enrolled subjects will provide two PK samples at Day 15 and Day 29.

REVISED TEXT

Protocol Activity	**Visit Day**									
	Screen & Treat	**Follow-Up Period**							**Recurrence Visit[a]**	**Withdrawal Visit[b]**
	Day 1[c]	**Day 3**	**day 8**	**Day 15**	**Day 29**	**Day 60**	**Day 90**	**Day 120**	**Recurrence**	**Withdrawal**
Window		**+2d**	**-/+2d**	**-/+3d**	**-/+5d**	**-/+10d**	**-/+10d**	**-/+10d**		
Informed Consent Process	X									
Demographic Information	X									
Initial History Only [d]	X									
Physician Assess. Malaria Signs & Symptoms	X									
Inclusion/Exclusion Criteria	X									
Efficacy Assessments										
Parasitological Assessment (blood smear)	X		X		X	X	X	X	X	X
Plasmodium PCR genotyping	X								X	
Safety Assessments										
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Vital Signs [e,f]	X	X		X	X	X			X	X
Brief Physical Examination [f]	X	X	X		X	X	X	X	X	X

Protocol Activity	Visit Day									
	Screen & Treat	Follow-Up Period							Recurrence Visit[a]	Withdrawal Visit[b]
	Day 1[c]	Day 3	day 8	Day 15	Day 29	Day 60	Day 90	Day 120	Recurrence	Withdrawal
Window		+2d	-/+2d	-/+3d	-/+5d	-/+10d	-/+10d	-/+10d		
Adverse Events Assessment [g]	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events [h]	X	X	X	X	X	X	X	X	X	X
G6PD (phenotyping) [i]	X									
G6PD (genotyping)	X [j]									
Laboratory Assessments										
Hematology [k]	X	X	X							
Clinical Chemistry [l]	X		X							
Methemoglobin	X		X							
Pregnancy Test [m]	X				X	X	X		X	X
Pharmacokinetic Assessments										
Pharmacokinetic Sampling		X[n]		X[o]	X[o]	X			X	
Investigational Product										
Dispense Open Label tafenoquine	X									
Treatment Compliance Int. - Invest.	X									
IVRS Registration	X									

a. Subjects who have a recurrence will continue to be monitored for safety and efficacy at all scheduled visits through day 120. Recurrence is defined by a positive blood smear with or without vivax malaria symptoms.
b. If a subject withdraws, the site should offer to conduct safety assessments through Day 120.
c. Visit Day 1 includes all screening procedures and treatment with tafenoquine.
d. Includes medical, disease and therapy histories.
e. Vital signs include height and weight (screening only), blood pressure, temperature, heart rate and respiratory rate. Refer to Section 7.5.4 for additional details.
f. At Center PPD Vital Signs and Brief Physical Examination will be performed at every visit.
g. Adverse events are recorded from the time of the first dose of study medication.
h. Serious adverse events are recorded from the time of consent in order to fulfil international regulatory requirements.
i. 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.
j. A blood sample for G6PD genotyping will be collected only from subjects who experience a SAE due to hemoglobin decline. Subjects with hemoglobin decline should continue to attend all visits through Day 120 to monitor Hb status.
k. Hematology includes hemoglobin, hematocrit, red blood cell/white blood cell/platelet counts, mean cell volume, white blood cell differential and reticulocyte count.
l. Clinical Chemistry includes CPK, BUN, serum creatinine, total and indirect bilirubin and liver clinical chemistry.
m. Pregnancy testing is only for females of child-bearing potential. Use a urine pregnancy test that is routinely used at the site with a test sensitivity for human chorionic gonadotropin (hCG) level ≤ 25 mIU/mL.
n. Day 3 PK sample must be taken 24-96 hours post TQ dose.
o. Once full PK sampling has completed, remaining enrolled subjects will provide two PK samples at Day 15 and Day 29.

7.5.3. Physical Exams

PREVIOUS TEXT

Physical examinations will be performed during the treatment period (Day 1), at all follow-up visits, and if there is a relapse or premature withdrawal visit.

REVISED TEXT

Physical examinations will be performed during the treatment period (Day 1), the follow-up period on Days 3, 8, 29, 60, 90 and 120 and if there is a relapse or premature withdrawal visit. (At center PPD physical examinations are required at all follow-up visits.)

7.5.4. Vital Signs

PREVIOUS TEXT

Vital signs will be performed on the day of TQ treatment (Day 1), at all follow-up visits, and if there is a recurrence or premature withdrawal visit. At visits where a pharmacokinetic (PK) sample is taken, vital signs should be conducted immediately prior to the PK sample collection.

REVISED TEXT

Vital signs will be performed on the day of TQ treatment (Day 1), immediately prior to pharmacokinetic (PK) measurements, and if there is a recurrence or premature withdrawal visit. (At center PPD vital signs are to be performed at all follow-up visits.)

Amendment 3

Amendment No. 3 is a site-specific amendment, and applies to one center in Brazil (Center PPD; Manaus, Brazil). Revisions to the protocol were made for this center to conduct ophthalmic assessments of subjects at screening and prior to randomization, at the Day 120 visit, and at withdrawal as applicable.

4. STUDY DESIGN

PREVIOUS TEXT

Not applicable.

ADDED TEXT

- A single center (PPD; Manaus, Brazil) will perform ophthalmic safety assessments at selected visits to monitor subjects for changes in the eye.

5.2. Exclusion Criteria

PREVIOUS TEXT

Not applicable.

ADDED TEXT

13. The subject has any retinal abnormality in the macular region, either pre-existing or identified at the baseline visit (Center PPD only).

7.1 Time and Events Table

PREVIOUS TEXT

Protocol Activity	Visit Day									
	Screen & Treat	Follow-Up Period							Recurrence Visit[a]	Withdrawal Visit[b]
	Day 1[c]	Day 3	day 8	Day 15	Day 29	Day 60	Day 90	Day 120	Recurrence	Withdrawal
Window		+2d	-/+2d	-/+3d	-/+5d	-/+10d	-/+10d	-/+10d		
Informed Consent Process	X									
Demographic Information	X									
Initial History Only [d]	X									
Physician Assess. Malaria Signs & Symptoms	X									
Inclusion/Exclusion Criteria	X									
Efficacy Assessments										
Parasitological Assessment (blood smear)	X		X		X	X	X	X	X	X
Plasmodium PCR genotyping	X								X	
Safety Assessments										
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Vital Signs [e,f]	X	X		X	X	X			X	X
Brief Physical Examination [f]	X	X	X		X	X	X	X	X	X
Adverse Events Assessment [g]	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events [h]	X	X	X	X	X	X	X	X	X	X

Protocol Activity	Visit Day									
	Screen & Treat	Follow-Up Period							Recurrence Visit[a]	Withdrawal Visit[b]
	Day 1[c]	Day 3	day 8	Day 15	Day 29	Day 60	Day 90	Day 120	Recurrence	Withdrawal
Window		+2d	-/+2d	-/+3d	-/+5d	-/+10d	-/+10d	-/+10d		
G6PD (phenotyping) [i]	X									
G6PD (genotyping)	X [j]									
Laboratory Assessments										
Hematology [k]	X	X	X							
Clinical Chemistry [l]	X		X							
Methemoglobin	X		X							
Pregnancy Test [m]	X				X	X	X		X	X
Pharmacokinetic Assessments										
Pharmacokinetic Sampling		X[n]		X[o]	X[o]	X			X	
Investigational Product										
Dispense Open Label tafenoquine	X									
Treatment Compliance Int. - Invest.	X									
IVRS Registration	X									

a. Subjects who have a recurrence will continue to be monitored for safety and efficacy at all scheduled visits through day 120. Recurrence is defined by a positive blood smear with or without vivax malaria symptoms.
b. If a subject withdraws, the site should offer to conduct safety assessments through Day 120.
c. Visit Day 1 includes all screening procedures and treatment with tafenoquine.
d. Includes medical, disease and therapy histories.
e. Vital signs include height and weight (screening only), blood pressure, temperature, heart rate and respiratory rate. Refer to Section 7.5.4 for additional details.
f. At Center PPD, Vital Signs and Brief Physical Examination will be performed at every visit.
g. Adverse events are recorded from the time of the first dose of study medication.
h. Serious adverse events are recorded from the time of consent in order to fulfil international regulatory requirements.
i. 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.
j. A blood sample for G6PD genotyping will be collected only from subjects who experience a SAE due to hemoglobin decline. Subjects with hemoglobin decline should continue to attend all visits through Day 120 to monitor Hb status.
k. Hematology includes hemoglobin, hematocrit, red blood cell/white blood cell/platelet counts, mean cell volume, white blood cell differential and reticulocyte count.
l. Clinical Chemistry includes CPK, BUN, serum creatinine, total and indirect bilirubin and liver clinical chemistry.
m. Pregnancy testing is only for females of child-bearing potential. Use a urine pregnancy test that is routinely used at the site with a test sensitivity for human chorionic gonadotropin (hCG) level ≤ 25 mIU/mL.
n. Day 3 PK sample must be taken 24-96 hours post TQ dose.
o. Once full PK sampling has completed, remaining enrolled subjects will provide two PK samples at Day 15 and Day 29.

REVISED TEXT

Protocol Activity	Visit Day									
	Screen & Treat	Follow-Up Period							Recurrence Visit[a]	Withdrawal Visit[b]
	Day 1[c]	Day 3	day 8	Day 15	Day 29	Day 60	Day 90	Day 120	Recurrence	Withdrawal
Window		+2d	-/+2d	-/+3d	-/+5d	-/+10d	-/+10d	-/+10d		
Informed Consent Process	X									
Demographic Information	X									
Initial History Only [d]	X									
Physician Assess. Malaria Signs & Symptoms	X									
Inclusion/Exclusion Criteria	X									
Efficacy Assessments										
Parasitological Assessment (blood smear)	X		X		X	X	X	X	X	X
Plasmodium PCR genotyping	X								X	
Safety Assessments										
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Vital Signs [e,f]	X	X		X	X	X			X	X
Brief Physical Examination [f]	X	X	X		X	X	X	X	X	X
Adverse Events Assessment [g]	X	X	X	X	X	X	X	X	X	X
Serious Adverse Events [h]	X	X	X	X	X	X	X	X	X	X
G6PD (phenotyping) [i]	X									
G6PD (genotyping)	X [j]									
Ophthalmological Exam (qualified site only)	X							X		X
Laboratory Assessments										
Hematology [k]	X	X	X							
Clinical Chemistry [l]	X		X							
Methemoglobin	X		X							
Pregnancy Test [m]	X				X	X	X		X	X
Pharmacokinetic Assessments										
Pharmacokinetic Sampling		X[n]		X[o]	X[o]	X			X	
Investigational Product										
Dispense Open Label tafenoquine	X									
Treatment Compliance Int. - Invest.	X									

Protocol Activity	Visit Day									
	Screen & Treat	Follow-Up Period							Recurrence Visit[a]	Withdrawal Visit[b]
	Day 1[c]	Day 3	day 8	Day 15	Day 29	Day 60	Day 90	Day 120	Recurrence	Withdrawal
Window		+2d	-/+2d	-/+3d	-/+5d	-/+10d	-/+10d	-/+10d		
IVRS Registration	X									

a. Subjects who have a recurrence will continue to be monitored for safety and efficacy at all scheduled visits through day 120. Recurrence is defined by a positive blood smear with or without vivax malaria symptoms.
b. If a subject withdraws, the site should offer to conduct safety assessments through Day 120.
c. Visit Day 1 includes all screening procedures and treatment with tafenoquine.
d. Includes medical, disease and therapy histories.
e. Vital signs include height and weight (screening only), blood pressure, temperature, heart rate and respiratory rate. Refer to Section 7.5.4 for additional details.
f. At Center PPD Vital Signs and Brief Physical Examination will be performed at every visit.
g. Adverse events are recorded from the time of the first dose of study medication.
h. Serious adverse events are recorded from the time of consent in order to fulfil international regulatory requirements.
i. 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.
j. A blood sample for G6PD genotyping will be collected only from subjects who experience a SAE due to hemoglobin decline. Subjects with hemoglobin decline should continue to attend all visits through Day 120 to monitor Hb status.
k. Hematology includes hemoglobin, hematocrit, red blood cell/white blood cell/platelet counts, mean cell volume, white blood cell differential and reticulocyte count.
l. Clinical Chemistry includes CPK, BUN, serum creatinine, total and indirect bilirubin and liver clinical chemistry.
m. Pregnancy testing is only for females of child-bearing potential. Use a urine pregnancy test that is routinely used at the site with a test sensitivity for human chorionic gonadotropin (hCG) level ≤ 25 mIU/mL.
n. Day 3 PK sample must be taken 24-96 hours post TQ dose.
o. Once full PK sampling has completed, remaining enrolled subjects will provide two PK samples at Day 15 and Day 29.

7.2. Screening and Critical Baseline Assessments

PREVIOUS TEXT

Not applicable.

ADDED TEXT

- Center PPD (Manuas, Brazil) only will perform the following ophthalmic assessments prior to randomization:
    - Visual acuity will be assessed by standard methods
    - Slit lamp examination of the cornea to evaluate for vortex keratopathy
    - Retinal digital imaging (color photographs, fundus autofluorescence and OCT)

7.5.7. Ophthalmic Assessments (Center PPD Only)

PREVIOUS TEXT

Not applicable.

ADDED TEXT

Ophthalmic assessments will be performed at Center PPD (Manaus, Brazil) at screening and prior to randomization, at Day 120 and at the withdrawal visit, if applicable. The Principal Investigator and site ophthalmologist will determine if the child is able to comply with the assessments, based on their malaria status and ability to reasonably cooperate with the assessments. Subjects who do not complete the ophthalmic examination at baseline, including interpretable retinal imaging, should not complete ophthalmic exams at follow-up or withdrawal. If a subject completes a portion of the ophthalmic exams at baseline, only those same exams should be completed at follow-up.

9.4.2. Secondary Analyses

PREVIOUS TEXT

The overall safety and particularly of key endpoints such as gastrointestinal tolerability, clinically relevant drops in hemoglobin and incidence of AEs will be assessed.

REVISED TEXT

The overall safety and particularly of key endpoints such as gastrointestinal tolerability, clinically relevant drops in hemoglobin and incidence of AEs will be assessed. The ophthalmic assessments of visual acuity, keratopathy and retinopathy will be summarized.