Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for 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
Effective Date	:	17 January 2020

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol TAF113577
- This RAP is intended to describe the interim and final analyses required for the study.
- This version includes amendments to the originally approved RAP.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the RAP
Purpose	• The purpose of this Reporting and Analysis Plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol TAF113577. This document will be provided to the study team members to convey the content of the interim analyses and Statistical Analysis Complete (SAC) deliverables.
Protocol	• This RAP is based on the amended protocol [(Dated: 06-Nov-2018) of study TAF113577 [GSK Document Number 2014N207627_03, 2018] and eCRF Version 1.
Primary Objective	• To evaluate the pharmacokinetics (PK) of tafenoquine (TQ) 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.
Primary Endpoint	• AUC(0-∞) of TQ by weight band from a population PK model in pediatric subjects aged ≥2 years to <16 years (weighing ≥5 kg).
Study Design	• TAF113577 is a prospective, open-label, multicenter, non-comparative, single-arm study. All subjects will receive Chloroquine (CQ) and open-label TQ. • Potential subjects who are slide-positive for *P. vivax* will be started by the site on off-study CQ per local/national guidelines. Eligible subjects will also 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. • Approximately 240 subjects aged <16 years with *P. vivax* malaria will be screened to achieve 60 enrolled subjects. • A subject is considered to have completed the study if they attend all treatment and follow-up visits. • 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. • 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.
Planned Analyses	• Up to two interim analyses (at 16 and 32 subjects) have been planned so that the initially planned four PK samples per subject can be reduced to a minimum of two PK samples. • Recruitment will continue for safety data accumulation until 60 subjects are

Overview	Key Elements of the RAP
	enrolled. • All decisions regarding final analysis, as defined in this RAP document, will be made prior to Database Freeze of the study data.
Analysis Populations	• Safety Population: all subjects who received at least one dose of study medication. • Primary PK Population: all subjects with at least one PK sample taken at Days 3, 15, 29 or 60. This population will be used for the primary PK analysis to evaluate TQ exposure. • Microbiologic-Intent-To-Treat (mITT) population: All subjects who received a dose of study treatment (tafenoquine) and have microscopically-confirmed vivax parasitemia at baseline.
Hypothesis	• There are no hypotheses tested in this study
Primary Analyses	• The primary population PK model-based analysis to be performed may borrow some information from the adult model as appropriate. For example, the sparse sampling in a limited number of pediatric subjects may be insufficient to independently characterize all the population PK parameters e.g. the absorption phase. Consequently the information about absorption from the adult model may be used as prior information to feed into the pediatric PK model with the assumption that these 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]."
Secondary Analyses	• Relapse-free efficacy will be summarized descriptively. • Safety data, including data related to gastrointestinal tolerability, clinically relevant drops in hemoglobin and incidence and severity of AEs, will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

1.1. RAP Amendments

RAP Section	Amendment Details
Reporting and Analysis Plan_TAF113577_Final [11-APR-2017]	
Reporting and Analysis Plan_TAF113577_Amendment1_Final	
Section 2.3, Appendix 5.1 and Appendix	Dosing amended as per Protocol TAF113577 Amendment 2 (GSK Document number: 2014N207627_02)

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Section 4	Addition of Microbiological ITT population.
Appendix 2	Time and Events table amended as per Protocol TAF113577 Amendment 2 (GSK Document number: 2014N207627_02)
Appendix 3	Extended window for Study Day 1 to allow for screening procedures performed prior to Day 1.
Appendix 6.4	Updated censoring rule for subjects who demonstrated initial clearance to align with other studies in the project.
Appendix 10.12.7	Updated Pop PK file specification to align with current project standards.
Various	Minor typographical errors.
Reporting and Analysis Plan_TAF113577_Amendment2_Final	
Section 2.1 and Section 4	Addition of 2 analysis populations, the Screened and Enrolled populations.
Section 8.2.1, Section 10.6.3, Appendix 10.15.6 and Appendix 10.15.7	Amended definition for common AEs to those occurring in ≥10% subjects (previously ≥5%)
Various	Minor clarifications and amendments.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Three additional analysis populations have been defined in this RAP:

- Screened
- Enrolled
- Microbiological ITT (MITT)

The definitions are provided in Section 4.

The efficacy endpoint was called recurrence free efficacy in the protocol, to keep in line with other GSK studies in the project this will be referred to as relapse free efficacy throughout this document.

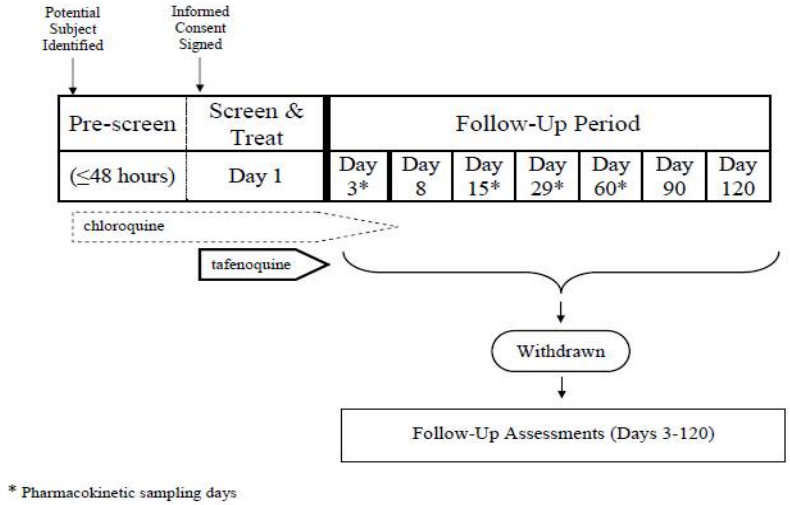
The window in which to confirm parasite clearance has been extended from the Day 8 visit to on or before the Day 29 visit to allow for missed and unscheduled visits which would represent clearance.

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• 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 Objectives	**Secondary Endpoints**
• To assess the safety of tafenoquine when administered to pediatric subjects with *P. vivax* malaria.	• Key safety data (gastrointestinal tolerability, clinically relevant drops in hemoglobin, incidence and severity of adverse events and abnormal laboratory observations) 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.	• Relapse-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).

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• An open-label, multicentre, non-comparative, single-arm study. 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 study will recruit a target of 60 subjects. The duration of the study is 120 days; study treatment on Day 1, followed by seven follow-up visits on Days 3, 8, 15, 29, 60, 90 and 120. • 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. Furthermore, up to two interim analyses have been included in this study, so that full PK sampling can be reduced as soon as sufficient data have been collected.
Dosing	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. The doses prior to Protocol Amendment 1 are given which relate to the first interim analysis, together with the doses post Protocol Amendment 1 used in the second interim and final analyses.

Overview of Study Design and Key Features

Weights	Tafenoquine Dose[a] prior to Protocol Amendment 2	Tafenoquine Dose[a] post Protocol Amendment 2	Dosing Regimen post Protocol Amendment 2
>35 kg	300 mg	300 mg	2 × 150 mg or 6 x 50 mg
>20–≤35 kg	200 mg	200 mg	4 × 50 mg
>10–≤20 kg	150 mg	100 mg	2 × 50 mg
≥5–≤10 kg	100 mg	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.

Treatment Assignment	• This is an open label study. All subjects will receive TQ dose according to the baseline weight.
Interim Analysis	Up to two interim analyses have been planned so that serial but sparse PK sampling (i.e., 4 PK timepoints) may be reduced at the earliest opportunity.

2.4. Statistical Hypotheses

There are no hypotheses tested in this study.

3. PLANNED ANALYSES

3.1. Interim Analyses

Up to two main interim analyses have been planned so that serial but sparse PK sampling (i.e., 4 PK timepoints) may be reduced 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.

The interim analyses will be performed after the completion of the following sequential steps:

1. All required subjects (i.e. 16 or 32 subjects) have PK evaluable data as defined in the protocol (or 12/24 months post study initiation).
2. All required database cleaning activities have been completed and interim database release and database freeze has been declared by Data Management.

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 TQ PK for that weight band are adequately characterized and the 95% interval within the targeted 55-162 µg.hr/mL.

See Appendix 12 for details about the population pharmacokinetic analysis.

The correlation between TQ PK data from venous sampling and capillary microsampling will be evaluated. Based on the emerging data, if deemed appropriate, further PK sampling of TQ in pediatric subjects will be limited predominantly to capillary microsampling to reduce the PK sampling burden on this highly vulnerable population. Agreement will be evaluated based on correlation and Bland-Altman analyses. Further details will be documented in the TAF113577 Interim Analysis Charter.

The decision to enroll 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 and increases in key laboratory parameters. The review and decision-making process for inclusion of the ≥6 months - <2 years cohort will be outlined in detail in the TAF113577 Interim Analysis Charter.

At each interim analysis a review of all available outputs will be performed and decisions made regarding the continuation of the study as pre-planned. Potential changes to the study could include stopping the study based on safety concerns or adjusting dosing regimens. Further details will be documented in the TAF113577 Interim Analysis Charter.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.

4. ANALYSIS POPULATIONS

Table 1 Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	• Study Population
Enrolled	• All participants who passed screening and entered the study.	• Study Population
Safety	• All subjects who received the dose of study treatment (tafenoquine).	• Study Population • Safety
PK	• All subjects with at least one PK sample taken at Days 3, 15, 29 or 60, with accurate dosing and sample time histories.	• PK
MITT	• All subjects who received a dose of study treatment (tafenoquine) and have microscopically-confirmed vivax parasitemia at baseline.	• Efficacy

NOTES:

- Please refer to Appendix 15: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
    - This dataset will be the basis for the summaries and listings of protocol deviations.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 2 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 2 Overview of Appendices

Section	Component
10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
10.2	Appendix 2: Time & Events
10.3	Appendix 3: Assessment Windows
10.4	Appendix 4: Treatment States and Phases
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
10.8	Appendix 8: Values of Potential Clinical Importance
10.9	Appendix 9: Multicenter Studies
10.10	Appendix 10: Examination of Covariates, Subgroups & Other Strata
10.11	Appendix 11: Multiple Comparisons & Multiplicity
10.12	Appendix 12: Model Checking and Diagnostics for Statistical Analyses.
10.13	Appendix 13: Population Pharmacokinetic Analyses

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the Safety population, unless otherwise specified. All summaries will be presented by dose group.

The precise format and content of Study Population tables are shown in Appendix 15.

All data will be listed as presented in Appendix 15.

6.2. Subject Disposition

For screen failed subjects, a summary displaying the reasons for screen failure as number and percentage of subjects will be presented.

A summary of the number of subjects in the analysis populations will be provided.

For subjects in the safety population, the following summaries will be presented:

- The number and percentage of subjects who violated any inclusion or exclusion criteria along with the number and percentage for each criterion which was violated.
- Subject disposition, including the number of subjects who withdrew and the reasons for withdrawal will be presented.
- The number of subjects recruited into the study by country and centre.

6.3. Protocol Deviations

Important protocol deviations will be determined by the clinical investigators (and reviewed by the study team prior to DBF) and will be tabulated within the Clinical Study Report (CSR).

6.4. Demography and Baseline Characteristics

Demography and other baseline characteristics (age, gender, ethnicity, height, weight, methemoglobin (%), G6PD enzyme activity and enzyme activity as a percentage of the site's median) will be summarized for the safety population and the primary PK population.

Summaries of race and racial combinations and race and racial combination details will be produced.

Malaria signs and symptoms, splenomegaly status at baseline and previous episodes of malaria will be summarized.

No formal comparisons of baseline variables will be performed.

6.5. Prior and Concomitant Medications and Conditions

Summaries of prior medications (excluding prior chloroquine usage)and current (concomitant) medications will be produced. Additionally, a summary of the number (%) of subjects taking chloroquine prior to the start of study treatment will be produced.

Medical conditions by body system will be summarized separately for past medical conditions and current medical conditions. In addition, there will be summaries of past specific medical conditions and current specific medical conditions.

Subjects who take concomitant medications during the study will be listed. Concomitant medication text will be coded and classified by the Generic Term and the preferred term using the standardized GSK coding system (GSK DRUG).

6.6. Treatment Compliance and Exposure

A summary of the number and percentage of subjects who were successfully dosed with TQ will be produced, the summary will also display the number and percentage of subjects who had to be re-dosed.

7. PRIMARY PK AND STATISTICAL ANALYSES

7.1. PK Analyses

7.1.1. Overview of Planned PK Analyses

The primary efficacy analyses will be based on the primary PK population, unless otherwise specified.

The primary population PK model based analysis to be performed at the end of the study may borrow some information from the POP PK model developed from the systemic TQ PK data from the dose ranging Phase 2B study (TAF112582). For example, the sparse sampling scheme in pediatric subjects is likely to be insufficient to independently characterize all the population PK parameters e.g. 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). Additionally, any impact of formulation differences from Phase 2B study (TAF112582) and emerging data from the Part 2 of TAF112582 and TAF116564 may be utilized to inform model development. 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, 2009] (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 will be estimated using the population PK model. The details of the approach are described in Appendix 12 of this study reporting and analysis plan.

The final analysis of the data will include modelling 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.

Full details of data displays being presented are provided in Appendix 12.

7.1.2. Planned PK Statistical Analyses

A population pharmacokinetic (POP PK) model based approach will be utilized to analyse the TQ exposure data from this study. The POP PK model based on adult TQ systemic exposure data was utilized to predict pediatric doses with allometric scaling. Interim analyses will be conducted to estimate the systemic exposure in pediatric subjects across different weight bands. Based on that outcome, doses across weight bands may be modified or continued as is. The serial but sparse sampling may be further reduced post confirmation of exposure across weight groups as appropriate. The final analysis of all exposure data from this study will be conducted to formulate a final dosing recommendation for TQ in pediatric population. The technical details of the POP PK analysis are described in detail in Appendix 12.

8. SECONDARY STATISTICAL ANALYSES

8.1. Efficacy Analyses

8.1.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on the mITT population, unless otherwise specified.

Secondary Statistical Analyses
Endpoint(s)
• Relapse-free efficacy four months post-dosing. See Section 10.6.4 for derivations including censoring.
Specification
• mITT population • Kaplan-Meier estimates
Results Presentation

• Summary of the proportion of subjects with relapse-free efficacy at four months as n (%) (Table 2.2) by dose group and overall.
• Analysis table will show:
  ◦ Number of subjects with an observed relapse and numbers of subjects censored (censored prior to 4 months, and censored relapse-free at 4 months, see Section 10.6.4 for censoring derivations)
  ◦ Point estimate and 95% confidence interval of the relapse-free efficacy rate across all the dose groups combined.
• A Kaplan-Meier survival curve will also be produced).

Additional Efficacy Summaries
• Summary of parasite presence (parasitological assessment, to include *P.vivax and P.falciparum asexual parasites*), mITT population. • Summary of subjects with *P. falciparum* asexual parasite emergence post baseline (n, %)

Efficacy Listings
• Efficacy data will be listed as presented in Appendix 15: List of Data Displays

8.2. Safety Analyses

8.2.1. Overview of Planned Analyses

The safety analyses will be based on the Safety population, unless otherwise specified.

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

Details of the mock-ups that describe the precise format and content of Safety figures, tables and listings are shown in Appendix 16.

8.2.1.1. Adverse Events

Counting of Adverse Events (AEs) will be based on the number of subjects – not the number of AEs. For example, if a subject reports the same AE on three occasions within the relevant time interval, that AE will only be counted once. If a subject experiences the same AE (i.e. same preferred term (PT)) more than once, they are counted only once under the count for the preferred term. If a subject experiences more than one AE in a particular System Organ Class (SOC), they will only be included once in the count for the SOC, but will appear in the count for each appropriate preferred term within the SOC. Therefore, the sum of the numbers of subjects with each preferred term event within a SOC may exceed the total number of subjects with at least one event. For the summary of AEs by maximum intensity, subjects who experience the same event several times with different intensity will only be counted once with the maximum intensity.

Only treatment emergent AEs (TEAEs) will be presented as all subjects receive study medication on Study Day 1. TEAEs are defined as AEs with an onset date and time on or after that of the start of first dose of study medication (including CQ).

The recurrence of *P. vivax* malaria and any associated signs and symptoms are recorded as Disease Related Events (DREs) and will not be included in the AE data displays, but will be listed separately.

Adverse Events will be summarized by dose group and overall as specified below and in Appendix 15: List of Data Displays, and presented in order of descending frequency. Table 3 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 15: List of Data Displays.

Table 3 Overview of Planned Adverse Event Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
All AEs			Y[1]
All TEAEs by SOC	Y		
All TEAEs by PT	Y		
Drug-related TEAE by PT	Y		
TEAEs by maximum grade or intensity	Y		
Common (≥10% in any treatment group) TEAEs by PT	Y	Y[2]	
Common (≥10% in any treatment group) Non-serious TEAEs by SOC and PT – number of subjects and occurrences	Y		
TEAEs by week and month of onset	Y		
Subject numbers for individual AEs			Y
Relationship between AE SOCs, PTs and verbatim text			Y
All drug-related TEAEs by SOC and maximum grade or intensity[4]	Y		
Serious and Other Significant AEs			
Fatal TEAEs by PT	Y		Y
Serious TEAEs[3]	Y		Y
Drug related serious TEAEs by PT	Y		
Drug related fatal serious TEAEs by PT	Y		
TEAEs leading to withdrawal from the study	Y		Y
AEs that are considered to be potentially hematologically-related (i.e. clinically relevant drops in Hb or Hct or other complications)	Y		
Grade 3 and Grade 4 AEs by PT	Y		
Disease Related Events			Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, SOC = System Organ Class, PT = Preferred Term.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- TEAEs (SAEs) are defined as AEs (SAEs) with an onset date and time on or after that of the start of first dose of study medication (including CQ).
- AEs which have missing onset dates and any with an onset date equal to that of medication, but where onset time is unknown, will be considered to be treatment emergent.
- For each preferred term counting will be done by subject and not event.
- AEs related to drug will be selected based on where the 'Relationship to Investigational Product' flag on the eCRF has been marked 'Yes'.
- See Section 10.6.3 for additional information on the derivations and definitions of AEs
- Additional information on any deaths will be provided by Global Clinical Safety and Pharmacovigilance (GCSP) as part of the SAE reconciliation process.
- Events will be sorted based on Total incidence unless otherwise noted in Section 10.15.6
- [1] TEAEs will be flagged
- [2] Plot of common AEs will be generated. Note that since there is no control arm, relative risks won't be calculated
- [3] By SOC, by PT, by overall frequency and by SOC – number of subjects and occurrences
- [4] Interim analyses only

8.3. Vital Signs

Vital sign measurements include systolic and diastolic blood pressure, temperature, heart rate and respiratory rate. Vital signs are to be performed on Day 1, and prior to all PK sampling.

These measurements are summarised and summary statistics of the measurements by visit and change from baseline will be presented by dose group and overall.

8.4. Clinical Laboratory Parameters

8.4.1. Overview of Planned Clinical Laboratory Analyses

Clinical safety laboratory assessments including hematology, clinical chemistry, methemoglobin and additional parameters and screening tests are reported before the first dose of study drug and at Day 8 (and additionally at Day 3 for hematology).

Summaries of laboratory results and changes from baseline will be provided by visit. A listing displaying clinically relevant drops in hemoglobin by dose group will also be provided.

Table 4 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 15: List of Data Displays.

Table 4 Overview of Planned Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Chemistry						
Chemistry Data by Time	Y	Y[3]				
Chemistry Changes from Baseline				Y		
Chemistry Laboratory Abnormalities[1]	Y		Y			
Clinical Chemistry Profile Plots		Y[2]				
Hematology						
Hematology Data by Time and Sex	Y	Y[3]				
Hematology Changes from Baseline by Time and Sex				Y	Y[3]	
Hematology Laboratory Abnormalities[1]	Y		Y			
Hemoglobin Categories[4] of Change from Baseline by Time				Y		
Hemoglobin Categories[4] of Change from Baseline by Time and Sex				Y		
Maximum Fall in Hemoglobin Over First 10 Days					Y	
Mean Change in Hemoglobin Over First 10 Days[4]				Y		
Hematology Profile Plots[5]		Y				
Hepatobiliary (Liver)						
Liver Monitoring/Stopping Event Reporting	Y		Y			
Liver Biopsy Details	Y					
Liver Imaging Details	Y		Y			
Medical Conditions for Subjects with Liver Stopping Events			Y			
LFT Profile Plots[6]		Y				
LFT Abnormalities		Y				
Maximum LFTs		Y				
LFT Changes from Baseline		Y				

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- [1] Abnormalities refer to values outside of the clinical concern range (F3) for the tables, and either outside of the clinical concern range (F3) or with a change from baseline of clinical concern (F2) for the listings, as defined in Section 10.8.1.
- [2] Only for subjects with >3 ULN in ALT or AST or change from baseline in urea or creatinine >50%.
- [3] Boxplots for Hemoglobin, WCC, Platelets, ALT, AST and Creatinine. Change from baseline boxplot for Hemoglobin only.
- [4] Categories defined as <=20 g/L, >20 g/L to <=30 g/L, > 30 g/L [5] See Section 8.4.2
- [5] Individual plots for all subjects at each interim analysis. At SAC, only for subjects with a >30g/L decline from baseline hemoglobin or and found to be G6PD deficient; see Section 8.4.2.
- [6] Individual plots for all subjects at each interim analysis. At SAC, only for subjects with >3 ULN in ALT or AST
- All scheduled visits should be included in the tables and figures.
- Data recorded at unscheduled assessments will not be included in tables and figures (with the exception of being used in establishing maximum/minimum changes post baseline) but will be listed.

- Change from baseline is defined in Section 10.5.2.

8.4.2. Hemoglobin Declines and Related Laboratory Parameters

For all subjects with a drop in hemoglobin >30 g/L or ≥30%, G6PD enzyme activity will be plotted against maximum drop in hemoglobin up to and including the Day 8 visit, with separate pages for each dose group. Within the plot, different symbols will be used for the following categories:

- subjects who were G6PD genotyped and had a mutation classified as World Health Organization (WHO) class 1
- subjects who were G6PD genotyped and had a mutation classified as WHO class 2 or 3
- subjects who were G6PD genotyped and had a mutation of unknown significance
- subjects who were G6PD genotypically normal or had a mutation classified as a normal variant (WHO class 4)
- subjects who were not G6PD genotyped or did not have an evaluable genotyping result

Individual profile plots for all subjects at each interim analysis. For SAC, if a subject has a >30g/L or ≥30% decline from baseline hemoglobin or is found to be G6PD deficient, a hematological profile plot will be produced for the subject. This will display their hemoglobin, absolute reticulocyte, methemoglobin and bilirubin results (total and indirect bilirubin on same plot) at each visit. The subject ID, treatment group, sex, age, weight and G6PD status should be included as a header for each subject's plot.

8.5. Pharmacokinetic Analyses

8.5.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses will be based on the Pharmacokinetic population, unless otherwise specified.

8.5.2. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 10.5.3 Reporting Process & Standards).

8.5.3. Pharmacokinetic Parameters

PK parameters will be estimated based on POP PK model. See Appendix 12 for more details.

8.5.4. Population Pharmacokinetic (PopPK) Analyses

- The primary goal of this analysis is to characterize the population pharmacokinetics of tafenoquine (TQ) administered orally in subjects with *P. vivax* malaria.

- The influence of subject demographics, baseline characteristics, including disease activity, and co-medication on the pharmacokinetics of TQ in this population will be investigated.

- A summary of the planned population pharmacokinetic analyses are outlined below:
  - Drug plasma concentration-time data will be subjected to nonlinear mixed effects modelling using the program NONMEM to develop a population PK model.
  - Individual post-hoc estimated PK parameters will be summarised descriptively.
  - To support this analysis a NONMEM data file will be generated.
  - The details for the dataset specifications are provided in Appendix 13: Population Pharmacokinetic Analyses with detailed methodology for the analysis.

8.6. Pharmacodynamic Analyses

Not applicable

8.7. Pharmacokinetic / Pharmacodynamic Analyses

Not applicable

8.8. Evaluation of Microsampling

The relationship between venous blood sampling concentrations and capillary microsampling concentrations will be explored using the PK population.

A scatterplot comparing the venous blood plasma concentrations and the microsampling blood concentrations for all subjects, at all timepoints will be produced. In addition, the correlation between the methods will be calculated and presented in the same plot. The correlation will be calculated separately for each quartile, according to the concentration range observed.

To quantify the level of agreement between the blood sampling methods, a Bland-Altman plot will be produced [Bland, 1999]. The plot will display average concentration (x-axis) versus the concentration ratio (microsampling concentration/venous concentration) (y-axis). The following reference lines will be included in the plot

- Mean concentration ratio (bias)
- Mean concentration ratio ± 5% (interim analysis 1 only)
- Mean concentration ratio ± 15% (interim analysis 2 and SAC only)
- Limits of agreement calculated as: mean concentration ratio ± 1.96 x SD

9. REFERENCES

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Supportive Templates (for RAP), IMMS Example: Reporting and Analysis Plan (RAP) Template_Core Safety Reporting Standards

10. APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
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Section 10.3	Appendix 3: Assessment Windows
Section 10.4	Appendix 4: Treatment States & Phases
Section 10.5	Appendix 5: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.6	Appendix 6: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Pharmacokinetic • Pharmacodynamic and or Biomarkers
Section 10.7	Appendix 7 Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 10.8	Appendix 8: Values of Potential Clinical Importance
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Other RAP Appendices	
Section 10.14	Appendix 14: Abbreviations & Trade Marks
Section 10.15	Appendix 15: List of Data Displays
Section 10.16	Appendix 16: Example Mock Shells for Data Displays

10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

10.1.1. Exclusions from Per Protocol Population

No per protocol population has been defined for this study.

10.2. Appendix 2: Time & Events

10.2.1. Protocol Defined Time & Events

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									

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 (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.
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.

10.3. Appendix 3: Assessment Windows

10.3.1. Definitions of Assessment Windows for Analyses

Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
Safety, PK, Efficacy	All	Day 1	Day -2	Day 1	Day 1
Safety, Efficacy	All except PK	Day 3	Day 3	Day 5	Day 3
Safety, PK, Efficacy	All	Day 8	Day 6	Day 10	Day 8
Safety, PK, Efficacy	All	Day 15	Day 12	Day 18	Day 15
Safety, PK, Efficacy	All	Day 29	Day 24	Day 34	Day 29
Safety, PK, Efficacy	All	Day 60	Day 50	Day 70	Day 60
Safety, PK, Efficacy	All	Day 90	Day 80	Day 100	Day 90
Safety, PK, Efficacy	All	Day 120	Day 110	Day 130	Day 120

For all data summarised by visit, the nominal visit description will be used. Unscheduled and withdrawal visit data will be slotted into a scheduled visit window, but the data will only be included in summaries and figures if no scheduled visit exists within the window. If there are multiple assessments within the same window which are not unscheduled visits, the earliest results will be used in the summaries. If only unscheduled visits are included in the same window, the earliest of these results will be used in summaries and figures.

For derivations of the maximum/minimum value/change post-baseline, then all data will be considered, regardless of whether or not it slotted to a scheduled window.

10.4. Appendix 4: Treatment States and Phases

10.4.1. Treatment States

Adverse events will be classified according to time of occurrence relative to the start of the study treatment. No other treatment states are required for this study.

10.4.1.1. Treatment States for AE Data

Treatment State	Definition
Onset Time Since 1st Dose (Days)	If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on eCRF OR value is missing.
Onset before Day 7	AE Start Date ≤ Study Day 7
Onset on days 8-15	Study Day 8 ≤ AE Start Date < Study Day 16
Onset on days 16-29	Study Day 16 ≤ AE Start Date < Study Day 30
Onset in Months 2 or 3	Study Day 30 ≤ AE Start Date < Study Day 91
Onset after Month 3	AE Start Date ≥ Study Day 91

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
	Data Displays for Reporting		
Description	**Description – Interim 1**	**Description – Interim 2 and Final**	**Order [1]**
≥ 5 kg to ≤ 10 kg		TQ 50mg	1
> 10 kg to ≤ 20 kg[2]		TQ 100mg	2
> 10 kg to ≤ 20 kg[3]	TQ 150mg	TQ 150mg	3
> 20 kg to ≤ 35 kg	TQ 200mg	TQ 200mg	4
> 35 kg	TQ 300mg	TQ 300mg	5
Tafenoquine	Total	Total	6

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.
2. Subjects from Cohorts 2 and 3
3. Subjects from Cohort 1

10.5.2. Baseline Definition & Derivations

10.5.2.1. Baseline Definitions

For all endpoints the baseline value will be the latest pre-Tafenoquine dose assessment on Day 1.

Asexual parasite and gametocyte counts

If there are multiple pre-treatment assessments, a subject will be considered to have a positive (non-zero) baseline assessment if *any* of the assessments are positive. They will only be considered to have a zero baseline count if all of the pre-treatment assessments are slide negative.

10.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.5.2 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

10.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Area	: /arenv/arprod/sb252263/taf113577/internal_01 : /arenv/arprod/sb252263/taf113577/internal_02 /arenv/arprod/sb252263/taf113577/final_01
QC Spreadsheet	: /arenv/arprod/sb252263/taf113577/final_01/qc
Analysis Datasets	
• Interim analysis datasets will be created according to legacy GSK IDSL A&R dataset standards. Final analysis datasets will be created according to CDISC standards (SDTM IG Version 3.1.3 & AdaM IG Version 1.0. • For creation of ADaM datasets (ADCM, ADC1 and ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for interim and final analyses.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses: • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.

Reporting Standards	

• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.
  • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings.	

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables, unless slotted to a scheduled visit (Section 10.3.1). The exception is when maximum/minimum values/changes post baseline are summarised, in which case, all data will be considered. • Unscheduled visits will not be included in figures, unless slotted to a scheduled visit (Section 10.3.1). The exception is when maximum/minimum values/changes post baseline are plotted, in which case, all data will be considered. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Multiple Measurements at One Time Point

- If there are multiple assessments within the same window which are not unscheduled visits, the earliest results will be used in the summaries. All values will be listed.
- Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.

Study Day

- Study Day 1 is defined as the day the dose of study medication was taken.
- Study Day >1 calculated as the number of days from study Day 1 date:
  - Ref Date = Missing → Study Day = Missing
  - Ref Date < Study Day 1 date → Study Day = Ref Date – study Day 1 date
  - Ref Data ≥ Study Day 1 date → Study Day = Ref Date – (study Day 1 date) + 1

Cohort

- A subject's cohort can be determined based on the date of study medication as follows:
  - Cohort 1 – Date of study medication <05-Jan-2018
  - Cohort 2 – Date of study medication ≥05-Jan-2018 and <26-Feb-2019
  - Cohort 3 – Date of study medication ≥26-Feb-2019

10.6.2. Study Population

Demographics

Body Mass Index (BMI)

- Calculated as **Weight (kg) / [Height (m)]^2**

Prior and Concomitant Medications

- Medications will be coded using the latest version of GSK Drug.
- Prior medications = medications taken up to 30 days before the date and time of the first dose of study medication.
- Any medications with stop dates earlier than 30 days will not be reported in tables and listings.
- Concomitant medications = medications with start date and time on or after the start date and time of the dose of study medication (Study Day 1). Medications, with the exception of chloroquine, taken prior to the study and continuing during the study will be summarised as both prior medications and concomitant medications.
- All subjects were expected to take chloroquine prior to the start of study medication, and often continuing after the start date of study medication. The number and percent of subjects taking prior chloroquine will be summarised separately to other prior medications. If chloroquine treatment is started after the start of study medication, e.g. to treat a relapse, this should be reported in the same way as other concomitant medications. All chloroquine data (prior and

Prior and Concomitant Medications

concomitant) will be included in the listing of prior and concomitant medications.

- See Section 10.7.2 for the handling of missing and partial dates.

Treatment Compliance and Exposure

- All study medication will be administered at the investigator centre in the presence of the Investigator or study nurse, and ingestion confirmed.
- On the day of dosing, a subject will be classified as compliant with daily administered dose if they do not vomit the initial dose or if they are successfully re-dosed.
- A subject is considered to be compliant in clinic if they retain all study medication given to them.
- Subjects who were entered but did not report a treatment start date will be categorised as having zero doses.
- Study treatment consists of a single dose so duration of exposure will not be calculated.

G6PD enzyme activity as a percentage of site median

- Each site has a median G6PD enzyme value for healthy G6PD-normal subjects, determined from G6PD-normal males in study TAF115226:

Region	Country	Site	Investigator	Centre ID	G6PD median value (IU/g Hb)
South America	Brazil	Fundação de Medicina Tropical do Amazonas, Amazonas	De Lacerda	PPD	7.92
	Colombia	Oncomedica SA, Monteria	Velez	PPD	8.32
	Peru	Asociacion Civil Selva Amazonica, Iquitos	Llanos	PPD	9.01
Asia	Thailand	Mea Sot General Hospital, Tak	Kluabwang	PPD	7.79
	Thailand	Hospital for Tropical Disease, Bangkok	Chokejindachai	PPD	7.40
	Vietnam	National Institute of Malariology, parasitology and entomology (NIMPE), Hanoi	Bui	PPD	10.51
	Vietnam	Oxford University Clinical Research Unit, Ho Chi Minh City	Tran	PPD	8.38

G6PD enzyme activity as a percentage of site median

	Vietnam	OUCRU-Phuoc Long Medical Center, Ho Chi Minh City	Tran	PPD	8.38

- Enzyme activity as percentage of site median = (absolute enzyme activity / site median) x 100%
- G6PD deficient subjects are defined as those with a G6PD enzyme activity <70% of the site median.

10.6.3. Safety

Adverse Events

- All AEs reported up to and including the Day 120 visit following enrolment of a subject into the study will be documented.
- These will be recorded and coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). All terms applied will be reviewed by a GSK physician prior to database freeze. If any malaria related coded terms are considered to have lost useful information in the coding step (e.g., if a verbatim term of '*Plasmodium vivax* malaria' is mapped to 'malaria'), he/she will recommend a study-specific code, which will be documented.
- Treatment emergent AEs are defined as AEs with an onset date and time on or after that of the start of first dose of study medication (including CQ).
- AEs with entirely missing or unknown start dates will be assumed to be treatment emergent for reporting. AEs where the start date is equal to that of study medication, but where the start time is unknown will also be assumed to be treatment emergent. AEs with missing end dates are not anticipated to affect reporting.
- If the grade/intensity is missing for an AE, it will be considered severe/Grade 3 if an AE, or Grade 4 if an SAE and the subject is alive, or Grade 5 if an SAE and the subject dies (i.e. the highest intensity possible) for the summary of AEs by maximum intensity.
- See Section 10.7.2 for more information on missing and partial dates.
- Common AEs are those occurring in ≥10% of subjects in any treatment group.
- The recurrence of malaria and any associated signs and symptoms are recorded as Disease Related Events (DREs) and will not be classified as AEs.
- The GSK clinical team will review terms that qualify as potentially hematologically related.

Laboratory Parameters

- If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' is present, the number of decimal places of x will be used to determine how much to add or subtract in order to impute the corresponding numeric

Laboratory Parameters
value. • Example 1: 2 decimal place = '< x ' becomes x – 0.01 • Example 2: 1 decimal place = '> x' becomes x + 0.1 • Example 3: 0 decimal places = '< x' becomes x – 1

Vital Signs – Mean Arterial Blood Pressure
• To be calculated (to 1 decimal place) where systolic and diastolic blood pressure are both present at the same timepoint: $$mean\ arterial\ blood\ pressure = \frac{(systolic\ blood\ pressure + 2(diastolic\ blood\ pressure)}{3}$$

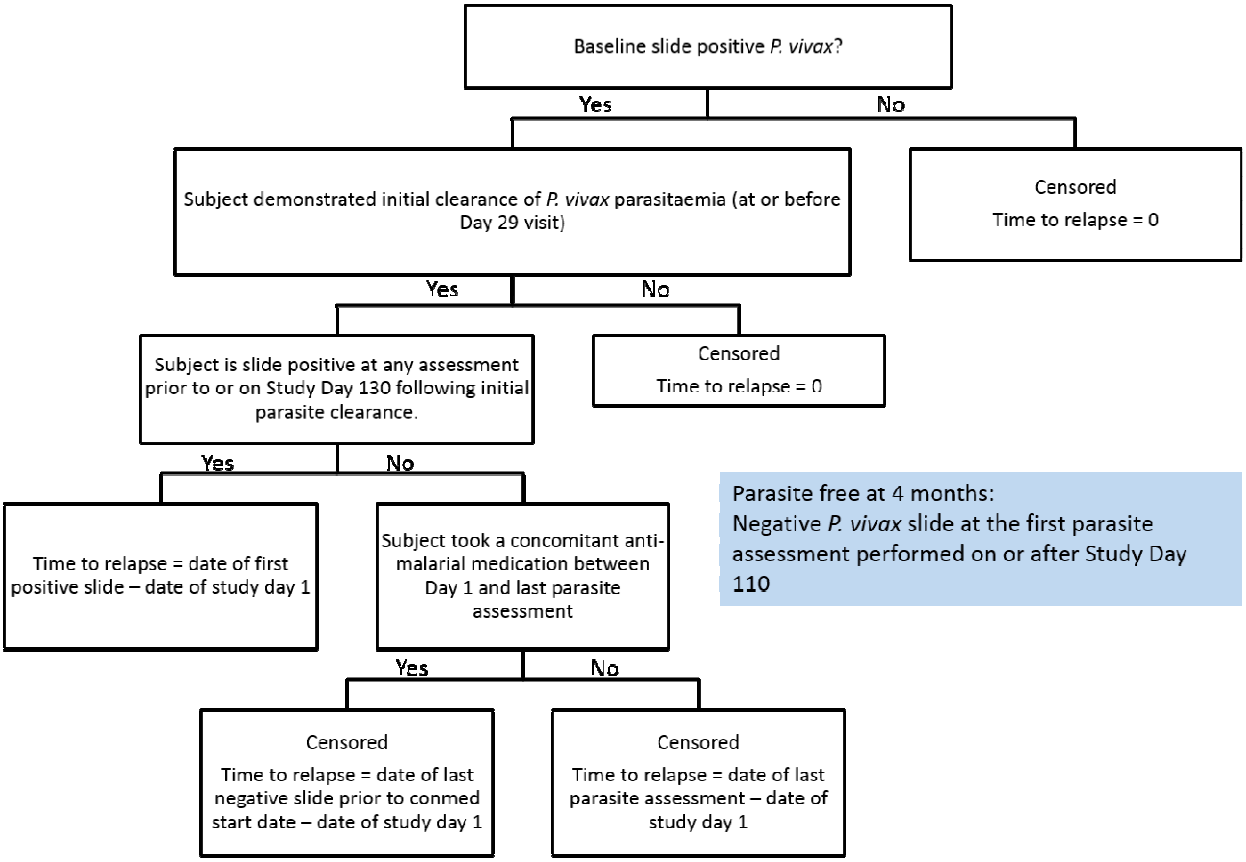
10.6.4. Efficacy

Relapse free efficacy at 4 months

- Relapse is defined below based on a positive blood smear with or without vivax malaria symptoms.

- A subject will be considered to have demonstrated relapse free efficacy for the purpose of the efficacy analysis if all of the following are true (also described in Figure 1):
  - Subject is slide positive for P. *vivax* (per slide or source documents) at baseline.
  - Subject demonstrated initial clearance of *P. vivax* parasitemia. This is defined as a negative slide at or before the Day 29 visit. Subjects who do not meet this criteria will be censored, with time to relapse = 0 days.
  - Subject is not slide-positive for P. *vivax* at any assessment prior to or on Study Day 130 following initial parasite clearance. Subjects who are slide-positive for P. *vivax* will be classified as relapses, with time to relapse = (date of first positive slide) – (date of Study Day 1) days.
  - Subject did not take a concomitant medication with anti-malarial activity at any point between Study Day 1 and their last parasite assessment (up to and including Study Day 130). A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified accordingly. Subjects who did take a drug with anti-malarial activity but never had a positive asexual *P. vivax* parasite slide after initial clearance will be censored, with time to relapse censored at (date of last negative parasite assessment prior to concomitant medication start) – (date of Study Day 1). If a subject has not had a negative assessment prior to the concomitant medication start date, they will be censored at 0 days.
  - Subject is parasite-free at 4 months. This is defined as a negative asexual *P. vivax* parasite slide at the first parasite assessment performed on or after Study Day 110 (up to and including Study Day 130).
- Subjects who do not have a positive asexual *P. vivax* parasite slide following initial clearance but where the final parasite assessment occurred before Study Day 110 will not have been classified by the preceding rules. These subjects will be considered to be censored, with time to relapse censored at (Date of final parasite assessment) – (date of Study Day 1).
- If a subject has a relapse outcome and a censored outcome, they will be considered to be a relapse, even if the time point of the relapse is later than the time point of censoring. For example, a subject who took a medication with anti-malarial activity at Study Day 32, but remained parasite-free after initial clearance until Study Day 68 will be treated as a relapse at Study Day 68.

Figure 1 Flowchart of algorithm for relapse-free efficacy at 4 months



10.6.5. Pharmacokinetic

See Appendix 13.

10.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) is defined as a subject who attends all treatment and follow-up visits. • Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument : o These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses due to outlying data will be documented along with the reason for exclusion in the clinical study report.

10.7.2.1. Handling of Missing Dates

Element	Reporting Detail
Adverse Events	• It is not possible to record partial dates in the eCRF for AEs. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • AEs with entirely missing or unknown start dates will be assumed to be treatment emergent for reporting. • AEs with missing end dates are not anticipated to affect reporting.
Concomitant medications	• Where the start or stop date of a concomitant medication record is entirely missing or unknown, the eCRF flags 'Taken prior to study?' and 'Ongoing medication?' will be used in order to derive whether it is prior or concurrent. • If these flags are also missing, then it will be assumed that it is concurrent. • In the event that use of the same medication is recorded at more than one visit (and if this has not been collapsed to one record), the eCRF flags will be cross-checked for both records.

10.7.2.2. Handling of Partial Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.

Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
	• The recorded partial date will be displayed in listings.

Adverse Events	• It is not possible to record partial dates in the eCRF for AEs.

10.8. Appendix 8: Values of Potential Clinical Importance

10.8.1. Laboratory Values

Element	Reporting Detail
F1 flag	• Denotes a value that falls outside the normal range. • Used by the laboratory and provided directly by the site for inclusion on the database.
F2 flag	• Denotes a value that has increased or decreased from baseline by more than a specified amount. • Defined below

F3 flag	• Denotes a value that falls outside an extended normal range.
	• This range is independent of any change from baseline or other values.
	• F3 range is calculated as:
	  • Absolute: pre-specified limits.
	  • Proportional: upper and lower limits are defined by multiplying the normal range limits by different factors
	• Defined below

General	• If a subject has both 'high' and 'low' values flagged for a parameter during the study, they will be reported once under each category.

Hematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hemoglobin	G/L	F2	Max(baseline – >30 g/L, ≥30% decline from baseline)	
Platelet count	10^9/L	F3	50	
Lymphocytes	10^9/L	F3	0.5	4
Eosinophils	10^9/L	F3		1.5
Reticulocytes count	10^12/L	F3		1xULN

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Creatine kinase (CPK) [a]	IU/L	F3		5x ULN
Creatinine[a]	μmol/L	F2		3x baseline
		F3		3x ULN

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Urea (BUN) [b]	mmol/L	F3		11.067
Alanine aminotransferase	IU/L	F3		3x ULN
Aspartate aminotransferase	IU/L	F3		3x ULN
Total bilirubin	μmol/L	F3		1.5x ULN
Indirect bilirubin	μmol/L	F3		1.5x ULN
Alkaline phosphatase	IU/L	F3		2.5xULN

a. CTC AE criteria
b. FDA industry toxicity grading scale for healthy volunteer adults and adolescents in preventative vaccine trials

10.9. Appendix 9: Multicenter Studies

10.9.1. Methods for Handling Centres

- In this multicentre global study, enrolment will be presented by investigator site and country.

10.10. Appendix 10: Examination of Covariates, Subgroups & Other Strata

10.10.1. Handling of Covariates, Subgroups & Other Strata

- Summaries will be presented by dose group, if the percentage of subjects within a particular dose group is small then the groups may be refined prior to final reporting.

10.10.1.1. Footnote Regarding Dose Groups

- For all data displays presented by dose group, the following footnote should be added:

  Weight bands were: TQ 50mg = ≥5-≤10kg; TQ 100mg = >10-≤20kg (Cohort 2 and 3); TQ 150mg = >10-≤20kg (Cohort 1); TQ 200mg = >20kg-≤35kg; TQ 300mg = >35kg

10.11. Appendix 11: Multiple Comparisons & Multiplicity

10.11.1. Handling of Multiple Comparisons & Multiplicity

No hypothesis testing will be performed in this study, all analyses are exploratory and so no adjustments for multiplicity are required.

10.12. Appendix 12: Model Checking and Diagnostics for Statistical Analyses

10.12.1. Statistical Analysis Assumptions

No statistical modelling is being performed. Kaplan-Meier curves are being fitted which assume that censored subjects have the same prospect of relapse as those being followed, however, it is not possible to test this assumption. All other data is being summarised only.

10.13. Appendix 13: Population Pharmacokinetic Analyses

10.13.1. Introduction

The purpose of the data analyses outlined in this document is to characterise the systemic exposure of Tafenoquine (TQ) administered as a single dose to pediatric subjects with *P. vivax* malaria with a model based population pharmacokinetic (POP PK) approach. The influence of subject demographics, baseline characteristics and any other relevant covariate on the PK of TQ in pediatric subjects with malaria will be investigated to identify a dose regimen that provides systemic TQ exposure across various weight bands in pediatric subjects similar to that in adult population.

Given the small subject numbers in this study, and the sparse nature of PK sampling, a model-based population PK analysis using non-linear mixed effects is a robust approach for assessing the PK of TQ in the pediatric population.

10.13.2. General Considerations For Data Analyses and Handling

10.13.2.1. Software

Programming will be performed in a HARP™ environment using SAS Version 9 or a later release and S-Plus Version 7 or later release. The population PK analysis will be completed using NONMEM software, Version 7 (ICON Development Solutions). Data set handling, graphical analysis and post-processing of table files will be performed with R Version 3 or later. The platform(s), operating system(s), Fortran compiler and any other software used will be described in the study report.

10.13.2.2. Data Set Preparation

POP PK analysis with NONMEM needs the data to be arranged in a specific format along with a number of indicator variables integral to the software. A summary of the dataset specifications, indicator variables and their description are given in Section 10.13.6. Variables included in the final data set will depend upon the best fit population model(s) and influential covariate(s) in this population. Therefore all indicator variables may not be included in the final model. If data sets are modified or reformatted over the course of the analysis, the file name of each version of the data set will be unique. For each generated data file, the source file and the SAS or R/S-Plus script file used for data manipulation will be archived.

The POP PK dataset will be generated on multiple occasions as the study progresses to support the planned interim analyses - up to two main interim analyses are currently planned. Any dataset generated will include all available evaluable TQ PK data up to that time. The dataset aggregation and initial modelling setup work may begin earlier than the planned interim analyses to aid any pre-programming, preliminary structural model establishment and generation of simulation and graphing scripts.

Any deviations from the analysis plan will be described in detail in the study report.

10.13.2.3. TQ Population PK dataset

For the TQ population PK analysis, patient demographic data (e.g. gender, age, weight, body mass index (BMI)), treatment, dosing and sampling dates and time will be extracted from the study database and merged with TQ plasma concentration data extracted from SMS2000 for the TQ PK population. The POP PK analysis compliant data file will be produced by or under the direct auspices of the programming support within the Clinical Statistics or Clinical Pharmacology, Modelling and Simulation groups, GlaxoSmithKline.

Due to the small study size and sparse nature of the PK sampling schedule, data from the previous adult studies with more extensive sampling (e.g. the Phase 2B dose ranging study TAF112582) may be included to stabilise the structural model as deemed appropriate. SAS or R may be used to merge the pediatric TQ PK data with adult TQ PK data. All such POP PK dataset processing scripts will be archived.

10.13.2.4. Archival Of Data Sets

Data sets, R-script used for data manipulation and/or graphics, NONMEM control stream files, NONMEM output files, NONMEM output processing programs and files obtained from processing of NONMEM output will be archived.

10.13.3. Handling of Missing Data

10.13.3.1. PK Data

If dosing and/or sampling times are missing, the relevant concentrations will be deleted from the analysis dataset and summarized in a deletion record listing by the programmer. Samples listed as having no sample (NS), no result (NR) or insufficient sample (IS) will be excluded from the PK data set and also included in the deletion record listing.

10.13.3.2. Subject Demographics

Imputations of any continuous covariate value will only be performed if the variable is missing for less than 10% of the subjects and the variable is deemed necessary for the modelling effort. For continuous covariates, missing values for an individual subject will be imputed as the gender-specific median value for the study. Any changes to the imputation methods will be justified and documented. If the percentage of missing data is greater than 10%, the variable will only be evaluated in exploratory graphical displays. There may not be imputation for any missing categorical covariate value.

10.13.3.3. Handling of Data Below the Lower Limit of Quantification

TQ concentrations below the respective lower limit of quantification (LLQ) for the bio-analytical assay will be reported as NQ (Below Quantification Limit, BQL). All NQ values will be set to “.”in the population PK dataset. Individuals with all plasma concentrations reported as NQ will be included in the data set. However, a likelihood estimation method (M3) for these BQL data will not be implemented (Ahn et al) and the BQL observation rows will be ignored during model building.

10.13.3.4. Handling of Outliers

Concentration results inconsistent with the expected PK behaviour of TQ may be excluded from the modelling after investigation about possible sampling/labelling errors. Outlier detection will be based initially on visual examination of individual and pooled PK profiles. However, the final model may be retested with and without inclusion of these data points. The exclusions will be listed in the report.

10.13.4. Population PK Modelling

The POP PK analysis will be based on non-linear mixed-effects models. The analysis will be performed as recommended by the *FDA, Population Pharmacokinetics Guidance for Industry* document [FDA, 1999]. Mixed-effects models describe the influence of both fixed effects and random effects on a dependent variable, e.g. concentration or clinical endpoint. Fixed effects, THETA (θ) in NONMEM notation, are factors that are either measured or controlled. Random effects include residual error (ERR), epsilon (ε) in NONMEM notation, and between subject random effects, ETA (η) in NONMEM notation.

Population mixed effects models include the basic components:

- The structural model, which predicts the plasma concentration as a function of time and dose.
- The covariate model component, which describes the influence of fixed effects (e.g. demography, disease, treatment, concomitant medication) on the PK model population parameters.
- The between-subject variance component, which describes the inter-individual variation in PK parameters (after "correction" for fixed effects). Inter-individual or between-subject variability will be initially modelled using an exponential error model.
- The residual error model components describe the underlying distribution of the error in the measured PK variable. Various error models are available to choose from based on emerging data. The goodness-of-fit plots and any potential biases therein will aid selection of an appropriate residual variability model e.g., additive, proportional, additive plus proportional or exponential.

A visual predictive check (VPC) method will be utilized to evaluate the adequacy of the final model, including the effects of statistically significant covariates. Statistics of interest including mean derived PK parameter values will be calculated from this model based analysis.

10.13.4.1. TQ Population PK Analysis

10.13.4.1.1. Base Model

A structural model for the available TQ PK data from pediatric population will be built first, including error models. Initial selection of the simplest structural POP PK model, to be used as a valid base model, will be based on but not limited to the minimum objective function value, plausibility of parameter estimates, goodness-of-fit plots and VPC plots. The most appropriate between-subjects

variability and residual error model, will be identified and the resulting model called a BASE model. If needed different estimation methods available in recent NONMEM versions may be tested to characterize the sparse PK data.

Due to the sparse PK sampling and few subjects, only key parameters of interest may be estimated (e.g. clearance – TQ CL) as data permit. Other PK parameters (e.g. absorption rate – TQ KA) may be fixed to the population estimates obtained from the TQ POP PK analysis of data from the dose ranging Phase 2B study in adult population (TAF112582). The random effect on these parameters may be estimated as data permit. If needed, the TQ PK data from those studies may also be included in the analyses dataset to provide stability to the POP PK structural model.

Any deviations from such planned analysis will be described in detail in the study report.

10.13.4.1.2. Covariate Inclusion

Once a BASE model has been identified, covariates will be added as necessary, using predefined strategy. Currently, the doses selected for the TEACH study are based on allometric scaling of clearance based on weight. Thus while not mandatory, patient weight is likely to be included as a significant component of the structural model and will be primarily guided by emerging pediatric PK data. While unlikely that other covariates will be included in the model due to small study size, the effects of subject demographic characteristics (e.g. age, body mass index (BMI)) may be examined as data permit. The final model shall have no redundant factor but the strategy shall ensure that no significant factor is missing.

Covariate model building may be undertaken once data from all pediatric patients is available at the end of the study. The covariate modelling approach will consider the step-wise process consisting of a forward and a backward selection procedure as appropriate based on emerging data.

10.13.4.1.3. Final Model

The model that has evaluated the impact of any key clinically relevant covariates (weight and other covariates) and adequately describes the observed data will be called the FINAL model and used for simulations.

The FINAL TQ POP PK model will be used to predict the systemic TQ exposure across various weight bands in pediatric population. The POP PK model based individual post-hoc TQ CL estimates will be utilized to calculate the individual TQ exposure [AUC(0-∞) = Dose/CL]. At every interim analysis, the 95% prediction interval of AUCs based on the simulation with the population pharmacokinetic model will also be generated for the mid-point of each weight band (at a population level). See details in Section 3.1.

10.13.4.2. Interim TQ POP PK Analysis

Based on the data from the dose finding Phase 2B study in adult subjects with *P. vivax* malaria (TAF112582), initial POP PK modelling and simulation (M&S) exercise suggested that approximately 16 pediatric subjects would provide sufficient information to adequately characterize the TQ PK in this population. Hence the POP PK M&S activity will be undertaken after a total of at least 16 subjects have evaluable PK data or 12 months post study start whichever comes first. In

case these data are insufficient to adequately characterize the POP PK in the pediatric population, the sparse serial PK sampling will continue and the next M&S exercise will be performed after a total of at least 32 subjects have evaluable PK data or 24 months post study initiation, whichever comes first.

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). If this interval lies within the AUC range of 55-162 µg.hr/mL for the mid-point of each weight band, serial (but sparse) sampling can be reduced 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.

The first set of 16 subjects to be enrolled in the study will be 2 or more years old. Based on the interim analyses of data from these 16 subjects, if TQ is well tolerated without any significant safety concern the enrolment will be opened to infants 6 months and older. If the 95% prediction interval of AUCs based on the simulation with the population pharmacokinetic model lies within the AUC range of 55-162 µg.hr/mL for the mid-point of each weight band, the dose strengths to be administered for the lower weight band subjects i.e. for infants 6 months to 2 years will be as listed in the protocol. Further original serial (but sparse) sampling may be limited to the subjects 6 months to 2 years.

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 with serial PK sampling and so on until the TQ PK for that weight band are adequately characterized and the 95% interval 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.

The second interim analysis will take place only if serial but sparse PK sampling is continued after the first interim analysis. At the end of any interim analysis, if the data and the M&S outcome reliably confirm the previously predicted TQ doses across various pediatric weight bands, or allow reliable estimation of TQ PK in the pediatric population, the PK sampling scheme in the subjects to be enrolled next may be modified or reduced as deemed appropriate.

At the end of any interim analysis, in the unlikely event of the data and the M&S outcome suggesting that the previously predicted TQ doses across various pediatric weight bands are grossly incorrect e.g. >2-3 fold off targeted exposure, existing pediatric PK data may be utilized to estimate a new dosing regimen. Exposure will be confirmed by continuing the sparse but serial PK sampling in the next set of 16 subjects with the new dosing scheme as deemed appropriate and necessary. One way to achieve this will be to modify the weight bands and TQ doses across the weight bands based on dose strengths. If the M&S outcome suggests that the previously predicted TQ doses across various pediatric weight bands are slightly off targeted exposure (e.g. <1.5 fold), the dosing may be continued as is, unless there are any safety concerns based on emerging data.

After study completion, the Final POP PK analysis will be performed to determine an appropriate dosing regimen across various weight bands in this population.

Any deviations from the analysis plan will be described in detail in the study report.

10.13.4.3. Final TQ POP PK Analysis

Upon completion of the study, final POP PK analysis will be undertaken. All PK evaluable data will be utilized for this analysis to confirm the dose regimen in the pediatric population across various weight bands. If the interim analysis demonstrate that the TQ PK was slightly different than previously predicted, M&S with the full dataset will be conducted to define the new dosage regimen across weight bands to ensure that the systemic TQ exposure across various weight bands in pediatric population is comparable to that in adult population. The simplest approach will be to modify the previously defined weight bands and the doses across these weight bands. The dosing scheme will be recommended in the study report.

Analysis of the TQ PK data from the pediatric study may also guide formulation of different dose strengths i.e. having fewer, more or different dose strengths than those used in the current pediatric study to support the TQ pediatric indication post approval. M&S will be undertaken to recommend the dose regimen with any new dose strengths across various pediatric population weight bands that provides exposure similar to that in adult population with the 300 mg TQ dose.

Any deviations from the analysis plan will be described in detail in the study report.

10.13.5. References

FDA, Population Pharmacokinetics, Guidance for Industry, 1999

Ahn JE, Karlsson MO, Dunne A, Ludden TM, J Pharmacokinet Pharmacodyn. 2008 Aug;35(4):401-21

10.13.6. POP PK File Specification

10.13.6.1. Pop PK Dataset File Structure

The PME compliant file structure for pop PK is a space-delimited file with each row containing the following columns of information. This file will be provided within 5 days of DBF.

Records with CONC value of NS, IS or NR will be excluded from the dataset

Item Name	Description	Code	Derivation/Comments	Dataset
ID	NONMEM sequential number starting at 1 identifying each subject	00001 – 99999	Sequential identifier for each subject starting at 1.	
CENT	Centre Identification	1= Thailand - PPD 2= Madagascar - PPD 3= Peru – PPD 4= Thailand – PPD , PPD 5= Vietnam - PPD 6= Brazil - PPD 7= Colombia - PPD 8= Thailand - PPD 9= Thailand - PPD 10= Vietnam – PPD 11=USA – PPD 12= India- PPD PPD 13= Philippines- PPD 14= Brazil- PPD 15=Ethiopia- PPD 16= Ethiopia- PPD 17=Cambodia PPD 18=Brazil- PPD 19=Peru PPD 20=SMIU Thailand- PPD 21=Thailand- PPD 22=Vietnam- PPD 23=Colombia- PPD 24=Colombia PPD	Additional centre numbers to be added based on where patients are recruited	
PT	Patient Identification Number		As per randomization; Retain all subjects with at least one measurable PK sample for the TQ analyte(s)	
STUDY		6= TAF113577		
TRTGRP	Treatment group for each study	24: TAF113577 arm		

Item Name	Description	Code	Derivation/Comments	Dataset
HEALTHY	Healthy volunteer or patient	1: Healthy volunteer 2: Patient	Studies 200951, 201780 and TAF114582 are all in Healthy volunteers (i.e., HEALTHY=1)	
DOSE	Dose amount (mg) for tafenoquine (TQ, SB252263)		Fill in the intended dose amount (mg) in all cells for each patient.	TQ
AMT	Dose amount (mcg) for tafenoquine	If EVID=1, AMT= Dose amt in mcg for tafenoquine If EVID=0, AMT= 0		TQ
DAY	Study day relative to the start of study		Day = day of study relative to the TQ dose	
DATE	Date of dose or sample collected.	MM/DD/YYYY		
TIME	Time of dose sample collected.	HH:MM (24 hr)		
RTLD	Relative time of sample from most recent TQ dose (hr)	Numeric	If negative assign 0	
RTFD	Relative time of sample from first TQ dose (hr)	Numeric	If negative assign 0	
TQ	Plasma TQ concentrations (ng/mL)	Numeric If EVID = 1, DV = "." If CODE > 0 then DV = "." Else DV= conc. Value Where ADPC .AVAL ne ""or ADPC.ANL01FL="Y" Then TQ=ADPC.AVAL	3 decimal places.	TQ
LNTQ	Ln transformed Plasma TQ concentrations	Numeric	6 decimal places.	TQ
CODE	Drug concentration result code	0 = Measurable conc. 0 when EVID=1 1 = NQ/BQL 2 = NA/NR/NS/IS		
MDV	Missing Data Value (drug concentration)	1 = Yes, 0 = No If EVID = 1, MDV = 1 If EVID = 0 and CODE>0, MDV = 1 , otherwise MDV =0		
EVID	Event indicator (flag for NONMEM)	1 = Dose 0 = PK Sample		
VOMIT	Vomit within 60 min of dose	1 = Yes, vomited 0 = No 0 = PK observations -99=missing	-99 if missing in datasets	

Item Name	Description	Code	Derivation/Comments	Dataset
CNTY	Country	1=Brazil 2=Peru 3=Thailand 4=Colombia 5=Vietnam 6= India 7=USA 8=Ethiopia 9=Cambodia 10=Philippines	Other countries to be added where subjects recruited For the 114582, all are in the USA (as per the IB).	
AGE	Baseline Age of subject (yr)			
GEN	Gender of the Subject (1=M,2=F)	1=Male, 2 =Female		
RACE	Race of the Subject	1=White, 2=Black or african american, 3=Oriental or asian, 4= Hispanic, 5=Other 6= American indian or Alaska native 7= Multiple -99 =Missing		
WT	Baseline Weight of Subject (kg)			
BMI	Baseline Body mass Index (kg/m^2)		1 decimal	
PARA	Baseline parasitemia	1=Yes 0=No	-99 for all of these studies	
CONMEDS	Concomitant medications	Add if available as 1=Yes 0=No -99= Missing	1 – for subjects who have medications identified as being concomitant (could include subjects taking medications that are identified as starting prior and becoming concomitant) 0 – for subjects who do not take any concomitant medications (they may have had prior medications recorded only or no medications recorded at all) -99 is used when	

Item Name	Description	Code	Derivation/Comments	Dataset
			concomitant medication data is not collected in a study	
FORMU	Formulation	1= Tablet150 3 = Tablet50	1 = Tablet150 (150mg tablet strength) – only 300mg dose was administered with the 150mg tablet 3 = Tablet50 (50mg tablet strength) – all doses 200mg or less were administered 50mg tablets	
DUPLI	Duplicate records	DUPLI =1 for all concentrations DUPLI =2 for the duplicate concentration records for a specific date and time DUPLI=3 for samples with missing DATE/TIME records (but concentration is available) DUPLI=4 for a duplicate (second) dosing record where no vomiting of any doses occur	This variable is only provided for Study 582 Part 2 and Study 564 files. If no concentrations and time record, then we can exclude the records	

10.13.7. Output

Note, results will be displayed by age group (6m-<2years and ≥2-16 years).

10.13.7.1. Tables

The following tables may be presented (not necessarily in this order) in the report:

- Summary of Demographics in PK population
- Parameter Estimates and Standard Errors for Base Structural PK Model
- Parameter Estimates and Standard Errors from Final PK Model, Including Covariate Effects
- Summary of TQ AUC across weight bands

10.13.7.2. Figures

The following graphs may be presented (not necessarily in this order) in the report:

- Goodness of fit plots of basic and final PK model (observed TQ PK versus population predictions, observed TQ PK versus individual predictions, weighted residuals vs time, weighted residuals vs population predictions)
- Plots of base model PK parameter estimates versus influential covariates, if applicable.

  Visual Predictive Check (VPC) Plots for base and final model as applicable

10.13.7.3. Data listings

The following data listings may be presented (not necessarily in this order) in the report:

- Key of all the variables used in the model development dataset.
- Listing of the primary model development datasets.
- NONMEM output files from the base and final models
- Listing of control files used for selection of PK model as applicable (base model, intermediate model and final control file)

10.13.7.4. Interim Analysis Outputs

- Population PK Model predicted AUCs [Mean (95% PI)] across weight bands

10.14. Appendix 14: Abbreviations & Trade Marks

10.14.1. Abbreviations

Abbreviation	Description
A&R	Analysis and Reporting
ADaM	Analysis Data Model
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUC(0-∞)	Area Under the Concentration-time Curve Extrapolated to Infinity
BUN	Blood Urea Nitrogen
bpm	beats per minute
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CL	Apparent Systemic Clearance
CPK	Creatine kinase
CPMS	Clinical Pharmacology Modelling and Simulation
CQ	Chloroquine
CSR	Clinical Study Report
CS	Clinical Statistics
CTR	Clinical Trial Register
DP	Decimal Places
DRE	Disease Related Events
eCRF	Electronic Case Record Form
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
G6PD	Glucose-6-phosphate Dehydrogenase
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
GUI	Guidance
HARP	Harmonisation of Analysis and Reporting Project
Hb	Hemoglobin
Hcg	Human Chorionic Gonadotropin
Hct	Hematocrit
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
INR	International Normalised Ratio
IP	Investigational Product
IVRS	Interactive Voice Response System
MCV	Mean Cell Volume
mITT	Microbiologic-Intent-To-Treat
PD	Pharmacodynamic

Abbreviation	Description
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PT	Preferred Term
QC	Quality Control
RBC	Red Blood Count
RAP	Reporting & Analysis Plan
RTF	Revisable Form Text
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	Standard Operation Procedure
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures & Listings
TQ	Tafenoquine
WCC	White Blood Cell Count

10.14.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
NONMEM
R
SAS
S-PLUS

10.15. Appendix 15: List of Data Displays

10.15.1. Data Display Numbering

The following numbering will be applied for RAP generated displays for the interim analyses:

Section	Tables	Figures
Study Population	1.1 to 1.7	None
Efficacy	2.1 to 2.2^	2.1
Safety	3.1 to 3.15	3.1 to 3.5
Pharmacokinetic*	None	4.1 to 4.2
Pharmacogenetic	None	None
Section	**Listings**	
ICH Listings	1	
Other Listings	2 to 3	

^Table 2.2 produced for interim analysis 2 only.
*PK outputs produced by CPMS are detailed separately in Section 10.13.7.

The following numbering will be applied for RAP generated displays for the final analysis:

Section	Tables	Figures
Study Population	1.1 to 1.22	None
Efficacy	2.1 to 2.4	2.1
Safety	3.1 to 3.37	3.1 to 3.15
Pharmacokinetic*	None	4.1 to 4.2
Pharmacogenetic	5.1	None
Section	**Listings**	
ICH Listings	1 to 18	
Other Listings	19 to 31	

*PK outputs are detailed separately in Section 10.13.7.

10.15.2. Deliverable

Delivery	Description
IA1	Interim Analysis 1
IA2	Interim Analysis 2
SAC	Final Statistical Analysis Complete

10.15.3. Study Population Tables

Study Population Tables						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Populations Analysed						
1.1.	1.1	Screened	SA1	Summary of Analysis Populations	IDSL .	IA1, IA2, SAC
Subject Disposition						
1.2.	1.2	Safety	IE1	Summary of Inclusion/Exclusion Criteria Deviations		IA1, IA2, SAC
1.3.	1.3	Safety	ES1	Summary of Subject Disposition	ICH E3, GSK CTR, FDAAA, EudraCT Include footnote stating the weight band for each dose (see SA1).	IA1, IA2, SAC
1.4.		Safety	NS1	Summary of Number of Subjects Enrolled by Country and Site ID	EudraCT .	SAC
1.5.		Screened	ES6	Summary of Reasons for Screen Failure	.	SAC
Protocol Deviations						
1.6.	1.4	Safety	DV1	Summary of Important Protocol Deviations	ICH E3	IA1, IA2, SAC
Demographic and Baseline Characteristics						
1.7.	1.5	Safety	DM1	Summary of Demographic Characteristics	Include age, sex, ethnicity, race detail, weight, height and BMI, Present age as continuous variable only, do not categorise.	IA1, IA2, SAC

Study Population Tables						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.8.	1.6	PK	DM1	Summary of Demographic Characteristics	Include age, sex, ethnicity, race detail, weight, height and BMI, Present age as continuous variable only, do not categorise.	IA1, IA2, SAC
1.9.		Safety	DM5	Summary of Race and Racial Combinations	ICH E3, GSK CTR, FDA, FDAAA, EudraCT	SAC
1.10.		Safety	DM6	Summary of Race and Racial Combination Details	ICH E3, FDA	SAC
1.11.		Safety	DM1	Summary of Baseline Characteristics	Include G6PD enzyme activity (IU/gHb) and G6PD as a % of site median.	SAC
1.12.		Safety	SA4	Summary of Malarial Signs and Symptoms		SAC
1.13.		Safety	SA5	Summary of Splenomegaly at Baseline		SAC
1.14.		Safety	SA6	Summary of Previous Episodes of Malaria		SAC
Prior and Concomitant Medications and Conditions						
1.15.		Safety	CM1	Summary of Prior Medications (Excluding Chloroquine)	Add footnote 'Only medications taken prior to the start date and time of first dose of study medication, and within 30 days of Study Day 1 are included.' ICH E3	SAC
1.16.		Safety	SA15	Summary of the Number (%) of Subjects Taking Prior Chloroquine		SAC

Study Population Tables						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.17.		Safety	CM1	Summary of Concomitant Medications	ICH E3 Add footnote 'Subjects were expected to take chloroquine prior to starting study treatment, but the course could be ongoing at the time that the subject took their first dose of study medication. This ongoing chloroquine usage is excluded from this summary. Any subsequent doses of chloroquine (e.g. to treat a P.vivax a malaria relapse) are included in this summary.	SAC
1.18.		Safety	MH1	Summary of Current Medical Conditions by Body System	ICH E3	SAC
1.19.		Safety	MH1	Summary of Past Medical Conditions by Body System	ICH E3	SAC
1.20.		Safety	MH4	Summary of Current Specific Medical Conditions		SAC
1.21.		Safety	MH4	Summary of Past Specific Medical Conditions		SAC
Treatment Compliance						
1.22.	1.7	Safety	SA7	Summary of Treatment Compliance	ICH E3	IA1, IA2, SAC

10.15.4. Efficacy Tables

Efficacy: Tables						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Parasite counts						
2.1.		Safety	SA8	Summary of Parasite Presence at all Timepoints		SAC
Relapse-free efficacy						
2.2.	2.1	mITT	SA9	Summary of Relapse-Free Efficacy at 4 months		IA1, IA2, SAC
2.3.	2.2	mITT	TTE6	Survival Analysis of Relapse-Free Efficacy over 4 months		IA2, SAC
Other Efficacy endpoints						
2.4.		mITT	SA10	Summary of *P. falciparum* Asexual Parasite Emergence	Change display to a listing if 5 or fewer subjects in total	SAC

10.15.5. Efficacy Figures

Efficacy: Figures						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Relapse-free efficacy						
2.1.	2.1	mITT	TTE10	Kaplan-Meier Survival Curve for Relapse-Free Efficacy over 4 Months		IA1, IA2, SAC

10.15.6. Safety Tables

Safety: Tables						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)						
3.1.	3.1	Safety	AE1	Summary of All Treatment Emergent Adverse Events by System Organ Class and Preferred Term	ICH E3 Add footnote: 'Events are ordered based on Total incidence'. Please check data to determine how many subjects had events of vomiting occurring on day 1, and add a footnote to provide this information, e.g. "Of the X subjects with AEs of vomiting, Y experience vomiting on Day 1"'.	IA1, IA2, SAC
3.2.		Safety	AE3	Summary of Common Treatment Emergent Adverse Events (>=10% in Any Treatment Group) by Preferred Term	ICH E3, GSK CTR Order events in descending order.	SAC
3.3.		Safety	AE15	Summary of Common (>=10% in Any Treatment Group) Non-serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC

Safety: Tables						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.4.	3.2	Safety	AE3	Summary of All Drug-Related Treatment Emergent Adverse Events by Preferred Term	GSK CTR Order events in descending order. Please check data to determine how many drug-related events of vomiting occurred on day 1, and add a footnote to provide this information, e.g. 'All drug-related AEs of vomiting occurred on day 1', or '9 of the 10 drug-related AEs of vomiting occurred on day 1'.	IA1, IA2, SAC
3.5.	3.3	Safety	AE5B	Summary of All Drug-related Treatment Emergent Adverse Events by System Organ Class and Maximum Grade or Intensity	The following AE grades should be displayed: 1, 2, 1+2, 3, 4, All Grades. Output should be displayed for all subjects combined only (not by dose group).	IA1, IA2, SAC
3.6.		Safety	AE5A	Summary of Treatment Emergent Adverse Events by Maximum Grade or Intensity	Add footnote: 'Events are ordered based on Total incidence'	SAC
3.7.		Safety	AE3	Summary of All Treatment Emergent Adverse Events by Preferred Term	Order events in descending order.	SAC
3.8.	3.4	Safety	AE3	Summary of Treatment Emergent Adverse Events with Onset on or Prior to Study Day 7	Add footnote: 'Events are ordered based on Total incidence'	IA1, IA2, SAC
3.9.	3.5	Safety	AE3	Summary of Treatment Emergent Adverse Events with Onset Date on Study Days 8-15	Add footnote: 'Events are ordered based on Total incidence'	IA1, IA2, SAC
3.10.	3.6	Safety	AE3	Summary of Treatment Emergent Adverse Events with Onset on Study Days 16-29	Add footnote: 'Events are ordered based on Total incidence'	IA1, IA2, SAC
3.11.	3.7	Safety	AE3	Summary of Treatment Emergent Adverse Events with Onset Date in Month 2 or 3	Add footnote: 'Events are ordered based on Total incidence'	IA1, IA2, SAC

Safety: Tables						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.12.	3.8	Safety	AE3	Summary of Treatment Emergent Adverse Events with Onset After Month 3	Add footnote: 'Events are ordered based on Total incidence'	IA1, IA2, SAC
Serious and Other Significant Adverse Events						
3.13.		Safety	AE3	Summary of Fatal Serious Treatment Emergent Adverse Events	GSK CTR Order events in descending order.	SAC
3.14.		Safety	AE1	Summary of Serious Treatment Emergent Adverse Events by System Organ Class	GSK CTR, IDSL Add footnote: 'Events are ordered based on Total incidence'	SAC
3.15.	3.9	Safety	AE3	Summary of Serious Treatment Emergent Adverse Events by Preferred Term	GSK CTR Order events in descending order.	IA1, IA2, SAC
3.16.		Safety	AE3	Summary of Drug-Related Treatment Emergent Serious Adverse Events by Preferred Term	GSK CTR Order events in descending order.	SAC
3.17.		Safety	AE3	Summary of Drug-Related Fatal Serious Treatment Emergent Adverse Events by Preferred Term	GSK CTR Order events in descending order.	SAC
3.18.		Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAA, EudraCT	SAC
3.19.		Safety	AE3	Summary of Treatment Emergent Adverse Events Leading to Withdrawal from the Study	IDSL Order events in descending order.	SAC
3.20.		Safety	AE1	Summary of Treatment Emergent Adverse Events Considered to be Potentially Hematologically-Related	Add footnote: 'Events are ordered based on Total incidence'	SAC
3.21.		Safety	AE3	Summary of Grade 3 and Grade 4 Treatment-Emergent Adverse Events by Preferred Term	Include Grade 3 and Grade 4 events only. Order events in descending order.	SAC

Safety: Tables						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Laboratory: Chemistry						
3.22.	3.10	Safety	SA11	Summary of Clinical Chemistry Data by Time		IA1, IA2, SAC
3.23.	3.11	Safety	SA12	Summary of Change from Baseline in Clinical Chemistry Data by Time	ICH E3	IA1, IA2, SAC
3.24.		Safety	LB2	Summary of Worst Case Chemistry Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline		SAC
Laboratory: Hematology						
3.25.	3.12	Safety	SA11	Summary of Hematology Data by Time and Sex	Add sex column	IA1, IA2, SAC
3.26.	3.13	Safety	SA12	Summary of Change from Baseline in Hematology Data by Time and Sex	ICH E3 Add sex column	IA1, IA2, SAC
3.27.		Safety	LB17	Summary of Worst Case Hematology Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline	ICH E3	SAC
3.28.		Safety	SA13	Summary of Categories of Change from Baseline Hemoglobin (G/L) Data by Time		SAC
3.29.	3.14	Safety	SA13	Summary of Categories of Change from Baseline Hemoglobin (G/L) Data by Time and Sex	Add sex column	IA1, IA2, SAC
3.30.		Safety	SA14	Summary of Hemoglobin Declines over First 10 Days		SAC
3.31.		Safety	SA14	Summary of Hemoglobin Declines over First 10 Days by Sex	Add sex column	SAC
Hepatobiliary (Liver)						
3.32.		Safety	LIVER1	Summary of Liver Events Assessment	IDSL	SAC

Safety: Tables						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.33.		Safety	LIVER2	Summary of Time on Treatment Before Liver Event		SAC
3.34.		Safety	LIVER3	Summary of Liver Biopsy Details		SAC
3.35.		Safety	LIVER4	Summary of Liver Imaging Details		SAC
	3.15	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	Only include rows for: - ALT≥5xULN - ALT≥3xULN - ALT≥3xULN and Bilirubin ≥2xULN (>35% direct) or INR>1.5, if measured.	IA1, IA2
Vital signs						
3.36.		Safety	VS1	Summary of Absolute Values in Vital Signs by Visit	ICHE3 Include Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Blood Pressure, Heart Rate, Respiratory Rate and Temperature	SAC
3.37.		Safety	VS1	Summary of Change From Baseline in Vital Signs by Visit	ICHE3 Include Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Blood Pressure, Heart Rate, Respiratory Rate and Temperature	SAC

10.15.7. Safety Figures

Safety: Figures						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events						
3.1.		Safety	AE10	Plot for Common Adverse Events (>=10% in Any Treatment Group) by Overall Frequency	IDSL	SAC
Clinical laboratory endpoints						
3.2.	3.1	Safety	LB9	Boxplot of Hematological Parameters by Visit and Dose Group – Hemoglobin	Include all subjects in the figure. For min section, use nadir up to Day 8 visit.. Use result/LLN on the Y-axis	IA1, IA2, SAC
3.3.	3.2	Safety	LB9	Boxplot of Hematological Parameters by Visit and Dose Group – Hemoglobin change from Baseline	For max section, include maximum decline for all subjects, including where this is actually an increase. Use result on the y-axis	IA1, IA2, SAC
3.4.		Safety	LB9	Boxplot of Hematological Parameters by Visit and Dose Group – WCC	Use result on the y-axis	SAC
3.5.		Safety	LB9	Boxplot of Hematological Parameters by Visit and Dose Group – Platelets	Use result on the y-axis	SAC
3.6.		Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Dose Group – ALT	Use result/ULN on the y-axis	SAC
3.7.		Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Dose Group – AST	Use result/ULN on the y-axis	SAC
3.8.		Safety	LB9	Boxplot of Clinical Chemistry Parameters by Visit and Dose Group – Creatinine	Use result/ULN on the y-axis	SAC
3.9.	3.3	Safety	SF1	Maximum Fall in Hemoglobin over First 10 Days by Enzyme Activity	Subjects with decline of >30g/L or ≥30% in hemoglobin only	IA1, IA2, SAC

Safety: Figures						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.10.	3.4	Safety	LB11	LFT Profile Plots	Individual plots for all subjects at each interim analysis. Only for subjects with >3 ULN in ALT or AST at SAC. Add footnote to this effect. Parameters to include are Alkaline phosphatase, ALT, AST and Total Bilirubin. The subject ID, dose, sex, age and race should be included as a header for each subject's plot.	IA1, IA2, SAC
3.11.	3.5	Safety	LB11	Hematology Profile Plots	Individual plots for all subjects at each interim analysis. Only for subjects with a >30g/L or ≥30% decline from baseline hemoglobin or found to be G6PD deficient at SAC. Add footnote to this effect. Parameters to include are hemoglobin, absolute reticulocyte, methemoglobin and bilirubin results (total and indirect bilirubin on same plot). The subject ID, dose, sex, age, weight and G6PD status should be included as a header for each subject's plot.	IA1, IA2, SAC

Safety: Figures						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.12.		Safety	LB11	Clinical Chemistry Profile Plots	Only for subjects with >3 ULN in ALT or AST or change from baseline in urea or creatinine > 50% Add footnote to this effect. Parameters to include are creatinine, creatine kinase and urea. The subject ID, dose, sex, age and race should be included as a header for each subject's plot.	SAC
3.13.		Safety	LB10	Distribution of Maximum LFTs		SAC
3.14.		Safety	LB7	LFT Shift from Baseline to Maximum Value		SAC
3.15.		Safety	LB8	Matrix Display of Maximum LFT Values		SAC

10.15.8. Pharmacokinetic Figures

Pharmacokinetic: Figures						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Blood Sampling Comparison						
4.1	4.1	PK	SF2	Correlation Between Venous Blood Sampling and Microsampling Concentrations		IA1, IA2, SAC
4.2	4.2	PK	SF3	Bland-Altman Plot of Agreement Between Venous Blood Sampling and Microsampling Concentrations		IA1, IA2, SAC

10.15.9. Pharmacogenetic Tables

Pharmacogenetic: Tables						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PGx General Summaries						
5.1		Enrolled	GN1	Summary of Subject Accountability for PGx		SAC

10.15.10. ICH Listings

ICH: Listings						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population - Subject Disposition						
1.		Safety	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
Study Population - Protocol Deviations						
2.		Safety	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
3.		Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Study Population - Populations Analysed						
4.		Safety	LA1	Listing of Subjects Excluded from Any Population	ICH E3	SAC
Study Population - Demographic and Baseline Characteristics						
5.		Safety	DM2	Listing of Demographic Characteristics	ICH E3	SAC
6.		Safety	DM9	Listing of Race	ICH E3	SAC
Study Population – Exposure						
7.		Safety	LA2	Listing of Exposure Data	ICH E3	SAC
Safety - Adverse Events						
8.	1	Safety	AE8	Listing of All Adverse Events	ICH E3 Include flag for treatment emergent	IA1, IA2, SAC
9.		Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
Safety - Serious and Other Significant Adverse Events						
10.		Safety	AE8	Listing of Fatal Serious Adverse Events	ICH E3 Include reasons for considering AE to be serious	SAC

ICH: Listings						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
11.		Safety	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3 Include reasons for considering AE to be serious	SAC
12.		Safety	AE8	Listing of Adverse Events Leading to Withdrawal From Study	ICH E3	SAC
13.		Safety	AE8	Listing of Disease Related Events	ICH E3	SAC
Safety - All Laboratory endpoints						
14.		Safety	LB5	Listing of Laboratory Data with Abnormalities of Potential Clinical Importance	ICH E3 Include footnotes similar to the following (as appropriate): NR flags are determined based on the original values and ranges provided by the laboratory (i.e. based on non-converted values not shown in this standard display). For WBC absolute differentials and absolute reticulocytes, the normal ranges are not available. The NR flag for these absolute parameters are based on the corresponding percentages.	SAC

ICH: Listings						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
15.		Safety	LB5	Listing of Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance	ICH E3 Include footnotes similar to the following (as appropriate): NR flags are determined based on the original values and ranges provided by the laboratory (i.e. based on non-converted values not shown in this standard display). For WBC absolute differentials and absolute reticulocytes, the normal ranges are not available. The NR flag for these absolute parameters are based on the corresponding percentages.	SAC
16.		Safety	UR2a	Listing of Urinalysis Data	ICH E3 All subjects	SAC
Safety - Hepatobiliary (Liver)						
17.		Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Criteria	IDSL	SAC
Safety - Vital Signs						
18.		Safety	VS4	Listing of Vital Signs	Include mean arterial BP	SAC

10.15.11. Non-ICH Listings

Non-ICH: Listings						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Study Population - Subject Disposition						
19.		Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
20.		Safety	TA1	Listing of Planned and Actual Treatments	IDSL	SAC
Study Population - Demographic and Baseline Characteristics						
21.		Safety	LA3	Listing of Malaria Signs and Symptoms at Baseline		SAC
22.		Safety	MH2	Listing of Past and Current Medical Conditions		SAC
Study Population - Concomitant Medication						
23.		Safety	CM10	Listing of Prior and Concomitant Medications	Include concomitant medications and prior medications taken within 30 days of first dose of study medication. Add footnote: Includes concomitant medications and prior medications taken within 30 days of first dose of study medication.	SAC
Study Population - Compliance						
24.		Safety	LA4	Listing of Compliance Data		SAC
Efficacy						
25.		Safety	LA5	Listing of Results of Efficacy Endpoints		SAC
26.		Safety	LA6	Listing of Malarial Slide Readings		SAC

Non-ICH: Listings						
No.	**IA No.**	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Pharmacokinetics						
27.		PK	PK07	Listing of PK Concentrations	Change the standard template heading from “Planned Time Point” to “Planned Sample”. Remove “Time Deviation” column.	SAC
Safety - Adverse Events						
28.		Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms and Verbatim Text	IDSL	SAC
Safety – Laboratory endpoints						
29.	2	Safety	LA7	Listing of Methemoglobin		IA1, IA2, SAC
30.	3	Safety	LA8	Listing of Creatinine		IA1, IA2, SAC
Safety – Hepatobiliary (Liver)						
31.		Safety	LIVER8	Listing of Liver Imaging Details		SAC

10.16. Appendix 16: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request.