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

Title	:	Reporting and Analysis Plan for Study 200894: A double-blind, double-dummy, randomized, parallel group, placebo-controlled superiority study to evaluate the efficacy and safety of tafenoquine (SB-252263, WR238605) co-administered with dihydroartemisinin-piperaquine (DHA-PQP) for the radical cure of *Plasmodium vivax* malaria
Compound Number	:	SB-252263
Effective Date	:	06-Sep-2019

Description:

The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 200894.

This RAP is intended to describe the planned safety, efficacy and tolerability analyses required for the study.

This RAP will be provided to the study team members to convey the content of the blinded data review, Statistical Analysis Complete (SAC) and PK deliverables.

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PPD Statistics Director (Biostatistics)	06-Sep-2019	E-signature
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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 200894:

Revision Chronology:		
2015N232546_00	27-JAN-2016	Original
2015N232546_01	20-APR-2017	A secondary study objective was added to compare the efficacy of dihydroartemisinin-piperaquine (DHA-PQP) plus primaquine relative to DHA-PQP alone. A vital signs assessment was added at Day 2 to permit evaluation of time to fever clearance (secondary objective).

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Gastrointestinal (GI) tolerability was listed as an endpoint in the protocol. Data from phase 3 studies of tafenoquine, reported since the protocol was finalised, have abated previous concerns with regards GI tolerability, and hence this endpoint will not be specifically analysed. GI AEs will however still be reported in summaries of adverse events (AEs).

Additional study populations have been defined:

The Safety Open Label, Primaquine phase, Non-Relapsers (Safety OL) Population, has been defined for the summaries of adverse events for the participants who did not relapse during the double-blind phase and went onto the open-label primaquine phase at the end of the study.

The PK population has been defined as all participants for whom at least one systemic tafenoquine concentration, and associated sample date/time is available.

The ITT population has been renamed to the microbiologic-intent-to-treat population (mITT) and the definition updated to include the need for participants to have microscopically-confirmed *P. vivax* parasitemia at baseline.

The primary analysis uses a Cox's proportional hazards model as opposed to the log rank test as described in the protocol.

At the time of finalising the full RAP, it had been established that a blinded data review was not required due to 150 participants having been randomised. Details of the blinded data review are therefore not included in the RAP. It was also known that recruitment was from 2 battalions.

For the analysis of dichotomous endpoints, logistic regression analysis will be performed as opposed to exact methods as defined in the protocol. This enables battalion to be adjusted for in analyses.

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

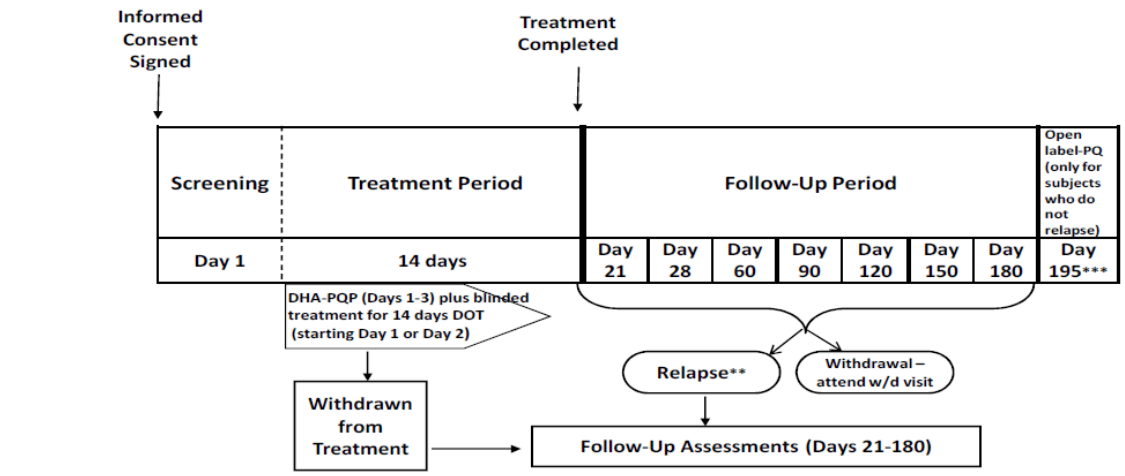
Objectives	Endpoints
Primary Objective	**Primary Endpoint**
To determine the efficacy of tafenoquine co-administered with DHA-PQP for the radical cure of *P.vivax* malaria, relative to DHA-PQP alone at 6 months.	Participants with relapse-free efficacy six months post-dosing (i.e. clearance of initial infection without subsequent microscopically confirmed recurrence during the 6 month follow up).
Secondary Objectives	**Secondary Endpoints**
To characterize the efficacy of tafenoquine relative to primaquine when co-administered with DHA-PQP.	Participants with relapse-free efficacy six months post-dosing.
To determine the efficacy of primaquine	Participants with relapse-free efficacy six

Objectives	Endpoints
co-administered with DHA-PQP relative to DHA-PQP alone	months post-dosing.
To determine the efficacy of tafenoquine co-administered with DHA-PQP relative to DHA-PQP alone at four months.	Participants with relapse-free efficacy four months post-dosing.
To determine the blood stage efficacy of tafenoquine in participants with *P.vivax* malaria when co-administered with DHA-PQP.	Time to relapse. Time to fever clearance (in participants with fever at baseline). Time to parasite clearance. Percentage of participants with recrudescence (blood stage treatment failure) on or before Day 14 (i.e. a recurrence of *P. vivax* parasites which is genetically homologous to the baseline *P. vivax* infection).
To assess the safety of tafenoquine in participants with *P.vivax* malaria when co-administered with DHA-PQP.	Incidence and severity of adverse events and Serious Adverse Events (SAEs). Incidence of clinically significant abnormal clinical laboratory tests, Electrocardiogram (ECGs) and vital signs. Change from baseline in methaemoglobin. Change from baseline in Frederica's QT Interval Corrected for Heart Rate (QTcF). Incidence of protocol defined SAEs (i.e. a decrease in haemoglobin of ≥30% or >3 g/dL from baseline or, a drop in haemoglobin below 7.0 g/dL, in the first 15 days).
To evaluate the pharmacokinetics of tafenoquine when co-administered with DHA-PQP in adult participants with *P.vivax* malaria.	Population PK parameters for tafenoquine including oral clearance (CL/F) and volume of distribution (V/F).
Exploratory Objectives	**Exploratory Endpoints**
To explore the genetics of recurrence of *P.vivax* malaria	Incidence of genetically homologous and heterologous *P.vivax* infections (determined by PCR). Whole genome sequencing of multiple parasite genes will be undertaken, if parasite count allows (to be reported separately, and not detailed in this RAP).
To explore the relationship between CYP2D6 genotype and risk of *P.vivax* relapse.	Percentage of participants relapsing analyzed according to CYP2D6 genotype.
To explore the relationship between the pharmacokinetics of tafenoquine co-administered with DHA-PQP and pharmacodynamic endpoints (if appropriate).	Population PK (e.g. tafenoquine plasma concentrations) and selected pharmacodynamic (PD) endpoints (e.g. relapse-free efficacy, change in methaemoglobin).

With regards to the efficacy endpoints, it should be noted that it is not possible to determine if a participant's recurrence of malaria is a relapse, re-infection or recrudescence. For the purposes of this RAP, the term "relapse" will be used to describe any recurrence of *P. vivax* malaria after clearance of the initial infection. "Recrudescence" applies to the term relating to recurrence for Days 1-14 of the study, where a genetically homologous parasite is suggestive of a recrudescence. Therefore, within this RAP, recrudescence will represent a subset of all of the relapses captured.

2.3. Study Design

Overview of Study Design and Key Features



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

Design Features	A double-blind, double-dummy, randomized, parallel group, placebo-controlled superiority study. Approximately 150 participants will be enrolled from the Indonesian army returning from deployment in a heavily malarious region of Indonesia. Duration of study: Up to 195 days, including screening (Day 1), and randomization to treatment (Day 1 or Day 2), 14 daily visits while receiving blinded study treatment and seven follow-up visits (Days 21, 28, 60, 90, 120, 150 and 180). Participants who do not relapse by Day 180 will attend a follow up visit on Day 195, following 14 days of open label primaquine.
Dosing	All participants will receive open label DHA-PQP on Study Days 1-3, together with TQ or PQ and matching placebo beginning on Study Day 1 or 2. TQ, or matching placebo, will be given as a single 300mg dose. Participants will receive PQ, 15mg once daily, or matching placebo, for 14 days.
Time & Events	See Appendix 2: Schedule of Activities
Treatment Assignment	Participants will be randomised 1:1:1 to receive TQ, the active comparator PQ or Placebo. GSK RANDALL NG will be used to generate randomisation schedules. Treatment allocation will occur by centralised randomisation using GSK RAMOS, accessed via an Interactive Web Recognition System (IWRS).

2.4. Statistical Hypotheses

The null hypothesis for the primary endpoint is that the 6-month relapse-free efficacy is not different between the DHA-PQP plus TQ and DHA-PQP alone treatment groups. The alternative hypothesis is that the relapse-free efficacy of the treatments is different. The hypothesis will be two-sided and tested at the 5% significance level.

3. PLANNED ANALYSES

The PK data will not be available at the time of reporting the study. PK data will therefore be reported separately at a later date.

3.1. Final Analyses (Excluding PK Data)

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

All participants have completed (or withdrawn from) the study as defined in the protocol.

All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management (with the exception of PK data).

All criteria for unblinding the randomisation codes have been met.

Randomisation codes have been distributed according to RandAll NG procedures.

3.2. Analysis of PK Data

The analysis of PK data will be performed after all required database cleaning activities for PK data have been completed and final database release and database freeze have been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility.	Study Population
Enrolled	All randomised participants.	Study Population
Safety	All randomised participants who received at least one dose of blinded study treatment. If participants receive a treatment different to their randomized treatment, they will be	Study Population Safety

Population	Definition / Criteria	Analyses Evaluated
	analysed according to the treatment actually received.	
Safety Open Label, PQ phase, Non-Relapsers (Safety OL)	All participants in the safety population who did not relapse during the double-blind phase and went onto the open-label primaquine phase at the end of the study.	Study Population Safety
Microbiologic-Intent-To-Treat (mITT)	All randomized participants who received at least one dose of blinded study treatment and have microscopically-confirmed *P. vivax* parasitaemia at baseline. Participants will be analysed according to their randomized treatment.	Efficacy
Per-Protocol (PP)	All participants in the mITT population for whom there were no major protocol deviations that impact the primary endpoint. Protocol deviations that would exclude participants from the PP population are defined in Section 4.1 (Protocol Deviations) and Appendix 1 (Protocol Deviation Management and Definition for Per-Protocol Population).	Sensitivity/ supporting analyses of efficacy data
PK population	All participants for whom at least one systemic tafenoquine concentration, and associated sample date/time is available.	PK

NOTES:

Please refer to Appendix 11: 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.

Important deviations which result in exclusion from the per protocol analysis population (major deviation) will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

Data will be reviewed prior to unblinding (where possible) and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset. Where it is not possible to review the data prior to unblinding, e.g. if a participant received an incorrect container number, the data will be reviewed before freezing the database.

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 for screening failures 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

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
2	Tafenoquine + DHA-PQP	TQ+DHA-PQP	2
3	Primaquine + DHA-PQP	PQ+DHA-PQP	3
1	Placebo + DHA-PQP	DHA-PQP only	1

Treatment comparisons will be displayed as follows using the descriptors as specified:

TQ+DHA-PQP vs DHA-PQP only
PQ+DHA-PQP vs DHA-PQP only
TQ+DHA-PQP vs PQ+DHA-PQP

For the open-label phases participants will be summarised according to their randomised treatment group, with totals also provided.

5.2. Baseline Definitions

For all endpoints, the baseline value will be the latest pre-treatment assessment with a non-missing value, including those from unscheduled visits.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

Asexual parasite and gametocyte counts

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

5.2.1. Change from Baseline

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

NOTES:

The baseline definition will be footnoted on all change from baseline displays.

5.3 Examination of Covariates, Other Strata and Subgroups

5.3.1 Covariates and Other Strata

Battalion, weight and baseline P.*vivax* asexual parasite count will be included as covariates in the time-to-event analysis of relapse-free efficacy at 6 months.

Battalion will be derived based on participant numbers as follows:

Battalion	Participant Numbers
Battalion 1	001-074
Battalion 2	075- 164

5.3.2 Examination of subgroups

If the treatment by battalion interaction is found to be statistically significant in the Cox's Proportional Hazards analysis of time to relapse, then the analysis will be conducted separately for each battalion. Similarly, the analysis of relapse-free efficacy at 4 months, and the Kaplan-Meier curves for time to relapse will be produced separately for each battalion.

5.4 Multiple Comparisons and Multiplicity

The primary comparison of interest is the comparison between TQ+DHA-PQP and DHA-PQP only for the primary endpoint, relapse-free efficacy over 6 months, in the mITT population; this is the only primary efficacy comparison so no multiplicity adjustment is needed.

5.5 Subject vs Participant Terminology

In this RAP the term participant is used when describing the planned reporting and analysis. In the data displays, trial participants should be referred to as "subjects".

5.6 Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
11.3	Appendix 3: Assessment Windows
11.4	Appendix 4: Study Phases and Treatment States for Adverse Event Data
11.5	Appendix 5: Data Display Standards & Handling Conventions
11.6	Appendix 6: Derived and Transformed Data
11.7	Appendix 7: Reporting Standards for Missing Data
11.8	Appendix 8: Values of Potential Clinical Importance

Section	Component
11.9	Appendix 9: Population Pharmacokinetic (PopPK) Analyses
11.11	Appendix 11: List of Data Displays
11.11	Appendix 12: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Safety population or Safety OL population except the overview of analysis populations and the diagnostic comparisons which will be based on the screened population.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 11: List of Data Displays.

Categorical variables will be summarized by the number and percentage of participants, and the continuous parameters will be summarized by n, mean, median, sample standard deviation, minimum and maximum unless otherwise specified.

The study population tables presented using the Safety Population will be presented from administration of first study medication (including DHA-PQP) until Day 180 visit. The tables presented using the Safety OL population will be presented from Day 180 visit + 1 day until Day 180 visit + 21 days.

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

The primary endpoint is relapse-free efficacy during the six months post-dosing.

7.1.2. Summary Measure

Hazard ratio for risk of relapse over the six months post-dosing.

7.1.3. Population of Interest

The primary efficacy analyses will be based on the microbiologic-Intent-To-Treat population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated will be the hypothetical effect if all participants had stayed on their randomised medication.

The time to the first *P. vivax* relapse will be used in the analysis.

Participants who discontinue treatment will be included in the analysis and handled the same as participants who remain on treatment as described in Section 11.6.3.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays, and will be based on GSK data standards and statistical principles.

7.1.5.1. Statistical Methodology Specification

The primary endpoint is the comparison between TQ+DHA-PQP and DHA-PQP only. A description of the analyses for the comparisons between TQ+DHA-PQP and PQ+DHA-PQP and also PQ+DHA-PQP and DHA-PQP only are also described in this section but are regarded as secondary endpoints.

Further details regarding the planned analysis and relapse free definition can be found in Section 11.6.3.

Primary Statistical Analyses
Endpoint / Variables
Relapse-free efficacy six months post-dosing
Model Specification
Cox's Proportional Hazards (CPH) model, including terms for battalion and treatment for calculation of Hazard Ratios

Primary Statistical Analyses

Kaplan-Meier estimates of relapse-free efficacy rate and time to relapse for each treatment group
mITT population

Model Checking & Diagnostics

The proportional hazards assumption should be assessed via a check of the Kaplan-Meier curves. The shape of the curves should be similar for the 3 treatment groups with the separation between the curves remaining proportional across time. A complementary log-log plot may also be used to check the proportional hazards assumption. If the proportional hazards assumption is violated a logistic regression model will be performed instead using a binary response variable of relapse free vs relapse and including battalion and treatment as covariates.

The treatment by battalion interaction will be assessed at the 10% level of significance. The CPH model will be refitted, including the main effects of treatment and battalion, and the treatment by battalion interaction. If the interaction is found to be statistically significant, then the nature of the interaction will be examined to determine if the results from the two battalions are homogeneous (treatment differences are in the same direction) or heterogeneous (treatment differences in different directions). If the latter, then the results will be presented separately for each battalion.

The impact of baseline *P.vivax* asexual parasite count and of weight on the treatment effect will be assessed by refitting the CPH model, separately for each continuous covariate, including the main effects of treatment, battalion, baseline parasite count/ weight and the treatment by baseline parasite count/ weight interaction. The interactions will be assessed at the 10% level of significance. If an interaction is found to be statistically significant, then the nature of the interaction will be examined by plotting the estimated hazards ratio and 95% CI vs baseline parasite count/ weight.

Model Results Presentation

Summary of the proportion of participants with relapse-free efficacy at six months by treatment group as n (%), including the sub-reasons for why participants are not considered relapse-free defined in Section 11.6.3 (Table 2.5). Note, only the sub-reasons that apply to the population being displayed will be included.

Analysis table (Table 2.8) will show:

Number of participants with an observed relapse and numbers of participants censored (censored prior to 6 months, and censored relapse-free at 6 months)

Estimates for time to relapse: 1st quartile, median, 3rd quartile and associated 95% confidence intervals

Kaplan-Meier estimate and 95% confidence interval of the relapse-free efficacy rate at 6 months for each treatment

Hazard ratio of TQ+DHA-PQP vs DHA-PQP only over the first 6 months and associated 95% CI and p-value from Cox's proportional hazards analysis.

Hazard ratio of TQ+DHA-PQP vs PQ+DHA-PQP (secondary endpoint) over the first 6 months and associated 95% CI.

Hazard ratio of PQ+DHA-PQP vs DHA-PQP only (secondary endpoint) over the first 6 months and associated 95% CI.

Kaplan-Meier survival curves will also be produced (Figure 2.1).

Subgroup Analyses

If the treatment by battalion interaction is found to be statistically significant in the Cox's

Primary Statistical Analyses
Proportional Hazards analysis, the analysis will be conducted separately for each battalion. Similarly, the Kaplan-Meier curves for time to relapse will be produced separately for each battalion.
Sensitivity and Supportive Statistical Analyses
Per Protocol population
Repeat primary analysis with Per Protocol population. Summary of the proportion of participants with relapse-free efficacy by treatment group as n (%), including the sub-reasons for why participants are not considered relapse-free defined in Section 11.6.3 (Table 2.7). Note, only the sub-reasons that apply to the population being displayed will be included. Analysis table (Table 2.10) will show: Number of participants with an observed relapse and numbers of participants censored (censored prior to 6 months, and censored relapse-free at 6 months) Estimates for time to relapse: 1st quartile, median, 3rd quartile and associated 95% confidence intervals Kaplan-Meier estimate and 95% confidence interval of the relapse-free efficacy rate at 6 months for each treatment. Hazard ratio of TQ+DHA-PQP vs DHA-PQP only, TQ+DHA-PQP vs PQ+DHA-PQP and PQ+DHA-PQP vs DHA-PQP only over the first 6 months and associated 95% CI and p-value (TQ+DHA-PQP vs DHA-PQP) from Cox's proportional hazards analysis. Kaplan-Meier survival curves will also be produced (Figure 2.2).
Logistic Regression (Censored Participants Excluded)
Logistic regression analysis, including terms for battalion and treatment. Response variable = relapse free (confirmed at 6 months) vs relapse (confirmed relapse at or prior to 6 months). Participants who are censored prior to 6 months will be excluded from the analysis. mITT population. Presentation of results (Table 2.11): Number and percentage of participants considered relapse free and relapsers. Odds ratio of odds of relapse for TQ+DHA-PQP vs DHA-PQP only, TQ+DHA-PQP vs PQ+DHA-PQP and PQ+DHA-PQP vs DHA-PQP only and 95% CI for the odds ratios. Model checking: Goodness of fit tests and residual plots (pearson and deviance residuals to detect outliers and/or influential points) will be produced.
Logistic Regression (Missing = Failure analysis)
See Section 11.6.3 for derivation of missing=failure dataset Logistic regression analysis, including terms for battalion and treatment.mITT population. Presentation of results (Table 2.12): Number and percentage of participants considered relapse free and relapsers. Odds ratio of odds of relapse for TQ+DHA-PQP vs DHA-PQP only, TQ+DHA-PQP vs PQ+DHA-PQP and PQ+DHA-PQP vs DHA-PQP only and 95% CIs Model checking: Goodness of fit tests and residual plots (pearson and deviance residuals to detect outliers and/or influential points) will be produced.
By genetic classification of First *P. vivax* Recurrence
Repeat primary analysis censoring participants with homologous infections (Table 2.13) and censoring participants with heterologous infections (Table 2.14), present: Number of participants with an observed relapse and numbers of participants censored

Primary Statistical Analyses
Kaplan-Meier estimate and 95% confidence interval of the relapse-free efficacy rate at 6 months for each treatment. Kaplan-Meier quartile estimates and 95% confidence intervals of time to relapse Kaplan-Meier survival curves will also be produced (Figure 2.3 and Figure 2.4).

7.2. Secondary Efficacy Analyses

7.2.1. Endpoints / Variables

Relapse-free efficacy four months post-dosing
Time to relapse
Time to fever clearance
Time to asexual parasite clearance
Time to gametocyte clearance
Percentage of Participants with Recrudescence

7.2.2. Summary Measures

The summary measure for all time to event endpoints will be hazard ratios. For the percentage of participants with recrudescence the treatment difference will be calculated.

7.2.3. Population of Interest

The secondary efficacy analyses will be based on the microbiologic-Intent-To-Treat population.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated will be the hypothetical effect if all participants had stayed on their randomised medication.

The time to the first event of interest (i.e. *P. vivax* relapse, fever clearance, asexual parasite clearance or gametocyte clearance) will be used in the analysis.

Participants who discontinue treatment will be included in the analysis and handled the same as participants who remain on treatment as described in Section 11.6.3.

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays. The format of data displays will be based on GSK data standards and statistical principles.

7.2.5.1. Statistical Methodology Specification

Secondary Statistical Analyses
Endpoints / Variables
Relapse-free efficacy at 4 months

Secondary Statistical Analyses
Time to relapse Time to fever clearance Time to asexual parasite clearance Time to gametocyte clearance
Model Specification
mITT population Estimates for time to endpoint will be determined for each treatment group using Kaplan-Meier methods. Cox's proportional hazards analysis, including terms for battalion and treatment for calculation of Hazard Ratios for time to fever clearance, time to asexual parasite clearance, time to gametocyte clearance, and relapse-free efficacy at 4 months.
Model Checking & Diagnostics
The proportional hazards assumption should be assessed including a check of the Kaplan-Meier curves. The shape of the curves should be similar for the treatment groups with the separation between the curves remaining proportional across time. A complementary log-log plot may also be used to check the proportional hazards assumption. If the proportional hazards assumption is violated a logistic regression model will be performed instead using a binary response variable of event vs no event (e.g. fever clearance vs no fever clearance) and including battalion and treatment as covariates.
Model Results Presentation
Time to relapse is covered in Table 2.8. Tables 2.16 to Table 2.19: Number of participants with the endpoint and number censored Estimates for time to the endpoint: 1st quartile, median, 3rd quartile and associated 95% confidence intervals For the relapse-fee efficacy at 4 months endpoint only, the Kaplan-Meier estimate and 95% confidence interval of the relapse-free efficacy rate for each treatment at 4 months. For time to parasite clearance, time to fever clearance and relapse-free efficacy at 4 months: Hazard ratio (TQ+DHA-PQP vs DHA-PQP only, TQ+DHA-PQP vs PQ+DHA-PQP and PQ+DHA-PQP vs DHA-PQP only) and 95% confidence interval. Kaplan-Meier survival curves will be produced for time to fever clearance (Figure 2.5), time to asexual parasite clearance (Figure 2.6), and time to gametocyte clearance (Figure 2.7).
Subgroup Analyses
No subgroup analyses are planned for time to fever clearance, time to asexual parasite clearance, or time to gametocyte clearance. For relapse-free efficacy at 4 months, if the treatment by battalion interaction is found to be statistically significant in the analysis of the primary endpoint (relapse-free efficacy at 6 months), the analysis will be conducted separately for each battalion.
Sensitivity and Supportive Analyses
No sensitivity analyses are planned for these endpoints.

Secondary Statistical Analyses
Endpoint / Variable
Percentage of Participants with Recrudescence - see Section 11.6.3 for derivations including censoring

Secondary Statistical Analyses
Model Specification
Descriptive statistics only 95% Wilsons confidence intervals for percentage of participants with recrudescence in each treatment group, and the treatment difference in the percentages with 95% Newcombe confidence intervals (TQ+DHA-PQP vs DHA-PQP only, TQ+DHA-PQP vs PQ+DHA-PQP and PQ+DHA-PQP vs DHA-PQP only). mITT population
Model Checking & Diagnostics
Only summary statistics are planned for this endpoint therefore no model checking is required.
Model Results Presentation
Summary table showing the number of participants with recrudescence or censored, percentage of participants with recrudescence and 95% CI for each treatment group, plus treatment difference and 95% CI (Table 2.20).
Subgroup Analyses
No subgroup analyses are planned for this endpoint.
Sensitivity and Supportive Analyses
No sensitivity analyses are planned for this endpoint.

7.3. Exploratory Efficacy Analyses

7.3.1. Endpoints / Variables

Incidence of genetically homologous and genetically heterologous *P. vivax* infections (determined by PCR)

Percentage of participants relapsing by CYP2D6 genotype

By metabolizer class

By activity score

7.3.2. Summary Measure

Number and percentage of participants in each category at the end of the study.

7.3.3. Population of Interest

The exploratory efficacy analyses will be based on the microbiologic-Intent-To-Treat population.

7.3.4. Strategy for Intercurrent (Post-Randomization) Events

The summary statistics will be based on available data only.

7.3.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays. These will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.3.1 will be summarised using descriptive statistics and listed.

Exploratory Statistical Analyses
Endpoint / Variable
Incidence of genetically homologous and genetically heterologous *P. vivax* infections (determined by PCR) See Section 11.6.3 for derivation of a relapse.
Model Specification
Descriptive statistics only. mITT population
Model Checking & Diagnostics
Only summary statistics are planned for this endpoint therefore no model checking is required.
Model Results Presentation
Summary table (n and %) (Table 2.21) showing the proportion of participants in each treatment group with *P. vivax* relapse infections classified as genetically heterologous or homologous n will be the number of participants with a relapse Bar chart of the percentage of participants on each treatment arm with genetically heterologous or homologous infections, with 95% Wilson confidence intervals (Figure 2.8)

Exploratory Statistical Analyses
Subgroup Analyses
No subgroup analyses are planned for this endpoint.
Sensitivity and Supportive Analyses
No sensitivity analyses are planned for this endpoint.

Exploratory Statistical Analyses
Endpoint / Variable
Percentage of participants relapsing by CYP2D6 genotype – Metabolizer Class.
Model Specification
mITT population Logistic regression model adjusting for derived CYP2D6 metabolizer class (poor + intermediate combined, or extensive + ultra combined, due to low numbers of poor and ultra metabolisers in the study) within treatment arm (models fitted separately for each treatment arm) One-sided test at the 5% significance level (given published data indicating reduced CYP2D6 metabolism decreases PQ efficacy)
Model Checking & Diagnostics
Goodness of fit tests and residual plots (pearson and deviance residuals to detect outliers and/or influential points) will be produced.
Model Results Presentation
Number and percentage of participants relapse free in each metaboliser class grouping within each treatment arm Adjusted odds ratio, 90% CI and p-value
Subgroup Analyses
No subgroup analyses are planned for this endpoint.
Sensitivity and Supportive Analyses
No sensitivity analyses are planned for this endpoint.

Exploratory Statistical Analyses
Endpoint / Variable
Percentage of participants relapsing by CYP2D6 genotype – Activity Score
Model Specification
mITT population Logistic regression model adjusting for qualitative CYP2D6 Activity Score (AS) within treatment arm (models fitted separately for each treatment arm)
Model Checking & Diagnostics
Goodness of fit tests and residual plots (pearson and deviance residuals to detect outliers and/or influential points) will be produced.
Model Results Presentation
Degrees of freedom, wald chi-square and p-value of the type III effect of AS in the model
Subgroup Analyses
No subgroup analyses are planned for this endpoint.

Sensitivity and Supportive Analyses
No sensitivity analyses are planned for this endpoint.

Additional Efficacy Summaries
P. vivax asexual parasite counts (Table 2.1), mITT population: Summary statistics (n, median, Q1, Q3, min and max) at each timepoint by treatment group. Other malarial asexual parasite counts (Table 2.2), *P. vivax* gametocyte counts (Table 2.3), other malaria gametocyte counts (Table 2.4), mITT population: Summary statistics (n, median, Q1, Q3, min and max) at each timepoint by treatment group. Summary of participants with *P. vivax* gametocyte emergence post baseline (n, %), mITT population, by treatment group. Summary of participants with *P. falciparum* asexual parasite emergence post baseline (n, %), mITT population, by treatment group. Summary of the number of relapses per subject (n, %), mITT population, by treatment group.

8. SAFETY ANALYSES

The safety analyses will be based on the Safety and Safety OL populations, unless otherwise specified.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs) and Serious (SAEs) will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 11: List of Data Displays.

In addition to the standard displays the following study specific tables will be produced:

Summary of protocol-defined SAEs (Hb drop). Hb drops will be identified from the SAE page of the eCRF and confirmed by laboratory data. The laboratory data will be checked during programming to ensure there were no protocol-defined SAEs that were not reported as such.

Summary of grade 3 and grade 4 AEs.

AEs related to drug will be identified as either related to DHA-PQP or related to blinded study medication, per the 'Relationship to Investigational Product' flag in the eCRF.

8.1.2 Overview of Planned Adverse Event Analyses

Counting of AEs will be based on the number of participants – not the number of AEs. For example, if a participant reports the same AE on three occasions within the relevant time interval, that AE will only be counted once. If a participant experiences the same AE (i.e. same preferred term) more than once, they are counted only once under the count for the preferred term. If a participant experiences more than one AE in a 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 participants with each preferred term event within a SOC may exceed the total number of participants with at least one event. For the summary of AEs by maximum intensity, participants who experience the same event several times with different intensity will only be counted once with the maximum intensity.

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 treatment group and as specified in Appendix 11 and presented in order of descending frequency. The tables presented using the Safety Population will be presented from administration of first study medication (including DHA-PQP) until Day 180.. The tables presented using the Safety OL population will be presented from Day 180 visit + 1 day until Day 180 visit + 21 days.

8.2. Adverse Events of Special Interest Analyses

Categories for AEs of Special Interest are defined in Section 11.6.4.

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data may highlight additional adverse events of special interest (AESIs), therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting. AESIs will be identified prior to the unblinding of the study. The details of the planned displays are provided in Appendix 11: List of Data Displays.

8.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 11: List of Data Displays.

In addition to the standard displays the following study specific displays will be produced:

Tables:

Summary of clinical chemistry / haematology abnormalities defined as values outside of the clinical concern range as defined in Section 11.8.1.

Summary of haemoglobin categories of change from baseline (categories defined as <=20 g/L, >20 g/L to <=30 g/L, > 30 g/L).

Summary of haemoglobin declines over the first 28 days (categories defined as <=20 g/L, >20 g/L to <=30 g/L, > 30 g/L or >=30%).

Figures:

Maximum absolute methaemoglobin value over 28 days

Change from baseline in methaemoglobin over time

Data recorded at unscheduled assessments will not be included in tables and figures but will be listed, unless it fits into a visit window per Section 11.3.1.

8.3.1. Haemoglobin Declines and Related Laboratory Parameters

If a participant has a >30g/L decline from baseline haemoglobin or is found to be G6PD deficient, a haematological profile plot will be produced for the participant (Figure 3.3). This will display their haemoglobin, reticulocytes (if available), methaemoglobin and bilirubin results (total and indirect bilirubin on same plot) at each visit. The participant

ID, treatment group, sex, age and G6PD status (quantitative assay) should be included as a header for each participant's plot.

8.4. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 11: List of Data Displays.

In addition to the standard displays the following study specific tables will be produced:

Summary of QTcF values by category and visit. Categories for each post baseline timepoint are defined as:

Absolute QTcF:
≤450 msec
>450 to ≤480 msec
>480 to ≤500 msec
>500 msec

Increase from baseline QTcF:
0 to <30 msec
≥30 to <60 msec
≥60 and absolute QTcF≤480 msec
≥60 and absolute QTcF>480 msec

Summary of absolute and change from baseline in methaemoglobin

Details of blood transfusions will be listed.

Where triplicate assessments are performed (i.e. at baseline), the mean of the 3 assessments will first be derived and the summary statistics will be presented using the mean of the assessments. For categorical data, e.g. ECG findings, the worst case should be presented where data is taken in triplicate.

9. PHARMACOKINETIC ANALYSES

PK analyses will be the responsibility of Clinical Pharmacology Modelling and Simulation within GSK.

A sparse sampling scheme has been employed in the study. Predictive checks will be performed based on the existing TQ POPPK model developed with data from the Phase 3 studies. With adequate predictive performance, the model will be utilized to generate the post hoc PK parameters for individual participants from the current study. These PK parameters will then be utilized to characterize their systemic exposure.

In case of lack of fits between model predictions and observed data, the existing model developed with Phase 3 data may be adjusted to characterize TQ PK. In this scenario, the tafenoquine systemic concentration- time data will be utilized in a population PK analysis to estimate the fixed-effects parameters (including oral clearance (CL/F), volume of

distribution (V/F)) as well as the corresponding random effects (between- and within-subject variability) parameters as data permit.

In the event that the sparseness of the data does not support estimation of some PK parameters (e.g. rate of absorption), the model population parameters may be fixed to previously obtained parameter estimates from the population PK meta-analysis performed at the end of Phase 3 studies.

Additionally, if data permit, exploratory PK/PD analyses for TQ data may be undertaken to examine any relationship between PK parameters (e.g. systemic exposure) and/or clinical outcome (relapse-free efficacy) or safety parameters (e.g. change in QTcF or MetHb). Any exposure-response analyses based on emerging data will be described in detail in the study report.

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

10. REFERENCES

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GlaxoSmithKline Document Number 2015N232546_01 200894, A double blind, double-dummy, randomised, parallel group, placebo-controlled superiority study to evaluate the efficacy and safety of tafenoquine (SB-252263, WR238605) co-administered with dihydroartemisinin-piperaquine (DHA_PQP) for the radical cure of Plasmodium vivax malaria. (Amendment 1 – 20-APR-2017)

GUI_137354, Information for Authors: Reporting and Analysis Plan (RAP), Global

SOP_54838, Development, Review & Approval of Reporting & Analysis Plan (RAP), Global

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

11. APPENDICES

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

Major protocol violations could impact the ability to assess efficacy and the primary endpoint for the study. A participant meeting any of the following criteria will be excluded from the Per Protocol population:

Number	Exclusion Description
01	Participant does not have a scheduled parasitology assessment within window for any of the Day 1-14[1], Day 21, Day 28, Day 60, Day 90, Day 120, Day 150 or Day 180 visits prior to first relapse or end of study (early withdrawal or end of follow-up)[2].
02	When in the clinic on Days 1 to 14, participant vomited a dose of study medication and either vomited the redose, or a redose was not given. Or participant did not take required number of DHA-PQP tablets on Days 1-3.
03	Violation of any of the following entry criteria: Participant had a severe malaria infection (exclusion #1) Participant had severe vomiting or diarrhoea (exclusion #2) Participants liver function test was > 2 x ULN (exclusion #4)
04	The participant has taken/received: Anti-malarials (e.g., artemisinin-based combination therapies (ACTs), mefloquine, primaquine, quinacrine) or drugs with anti-malarial activity within the past 30 days. Treatment with any investigational drug within 30 days of study entry, or within 5 half-lives, whichever is longer. A concomitant medication with an anti-malarial activity prior to first relapse or end of study (early withdrawal or end of follow-up). A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified accordingly
05	Participant did not take blinded study medication with food on Days 1-3.
06	Participant who met study treatment withdrawal criteria, as defined in protocol Section 5.4, but was not withdrawn from study treatment.
07	Participant received incorrect treatment.
08	Participants taking dose outside of the clinic that was not observed by a site staff member.

[1] For the twice daily blood smears on days 1-3, when determining exclusion from the PP population, participants were excluded if they didn't have at least one assessment on each day, without having first demonstrated clearance. The time of the assessments will not be used since visit windows around the 6-12 hour duration have not been defined.

[2] On study days 1-3, participants were scheduled to have twice daily blood smears until they had two consecutive negative smears, 6-12 hours apart. Due to errors in the parasite counts, 3 participants (participant numbers [redacted] and [redacted]) were incorrectly concluded to have negative smears which were in-fact positive, and hence missed a subsequent parasitology assessment during days 1-3. These participants will not be excluded from the PP population as a result of this missed assessment.

During the study, the data is reviewed on an ongoing basis, with protocol deviations (PDs) identified by programmatic checks and manual review. These deviations are

assessed by data management and clinical (with input from others as required), and are entered into the deviations log, with the 'Important' flag set accordingly.

The per protocol population exclusion flag is a derived variable in the analysis and reporting dataset (ADaM.ADDV). This variable is not captured in the SI or SDTM datasets. As for the 'important PD' flag, data is reviewed throughout the study to identify participants who should be excluded from the PP population. At DBR, additional programmatic checks are performed by the clinical programming team to further check for PDs. A spreadsheet of any PDs identified is provided to data management and clinical, who will add them to the deviations log with appropriate flags if not already included.

A listing will be produced for the safety population showing the individual participant numbers for each important protocol deviation. A table will be produced showing the number and percentage of participants with major protocol deviations, overall and by type of deviation.

11.2. Appendix 2: Schedule of Activities

11.2.1. Protocol Defined Schedule of Events

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

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

Time and Event Table Notes:

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

11.3. Appendix 3: Assessment Windows

11.3.1. Definitions of Assessment Windows for Analyses

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
mITT, PP, Safety	All	Day 1	Day 1	Day 1	Day 1
mITT, PP, Safety	All	Day 2	Day 2	Day 2	Day 2
mITT, PP, Safety	All	Day 3	Day 3	Day 3	Day 3
Safety	ECG	4 hours after last DHA-PQP dose	3 hours after last DHA-PQP dose	6 hours after last DHA-PQP dose	4 hours after last DHA-PQP dose
mITT, PP, Safety	All	Day 4	Day 4	Day 4	Day 4
mITT, PP, Safety	All	Day 5	Day 5	Day 5	Day 5
mITT, PP, Safety	All	Day 6	Day 6	Day 6	Day 6
mITT, PP, Safety	All	Day 7	Day 7	Day 7	Day 7
mITT, PP, Safety	All	Day 8	Day 8	Day 8	Day 8
mITT, PP, Safety	All	Day 9	Day 9	Day 9	Day 9
mITT, PP, Safety	All	Day 10	Day 10	Day 10	Day 10
mITT, PP, Safety	MetHB	Day 11	Day 11	Day 11	Day 11
mITT, PP, Safety	MetHB	Day 12	Day 12	Day 12	Day 12
mITT, PP, Safety	MetHB	Day 13	Day 13	Day 13	Day 13
mITT, PP, Safety	MetHB	Day 14	Day 14	Day 17	Day 14
mITT, PP, Safety	All except MetHB	Day 14	Day 11	Day 17	Day 14
mITT, PP, Safety	All	Day 21	Day 18	Day 24	Day 21
mITT, PP, Safety	All	Day 28	Day 25	Day 43	Day 28
mITT, PP, Safety	All	Day 60	Day 44	Day 75	Day 60
mITT, PP, Safety	All	Day 90	Day 76	Day 105	Day 90
mITT, PP, Safety	All	Day 120	Day 106	Day 135	Day 120
mITT, PP, Safety	All	Day 150	Day 136	Day 169	Day 150
mITT, PP, Safety	All	Day 180	Day 170	Day 190	Day 180
Safety OL	All	Day 180 visit + 15-21 days	Day 180 visit + 15 days	Day 180 visit + 21 days	Day 195
Note: Data collected after the nominal day 180 study visit, i.e. after the start of open label PQ for non-relapsers, will not be slotted to any visit up to and including the day 180 visit, regardless of the study day. Only the Day 195 visit window will be considered for slotting.					

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 same window. If there are multiple assessments within the same window which are not unscheduled visits, the earliest result will be used in the summaries and figures. If only unscheduled visits are included in the same window, the earliest of these results will be used in summaries and figures.

11.4. Appendix 4: Study Phases and Treatment States for Adverse Event Data

11.4.1. Study Phases

Study Phase	Definition
DHA-PQP only	Time of first administration of DHA-PQP to time of first dose of blinded study medication – 1 minute
Double blind	Time of first administration of blinded study medication to Day 180 visit
Open-label PQ phase, Non-Relapsers	Day 180 visit + 1 day to Day 180 visit+21 days for participants who do not relapse prior to Day 180 visit

Data collected outside of the above study phases, e.g. an AE with a start date after the Day 180 visit, for a participant not entering the open-label PQ phase, will be listed only.

11.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is within 30 days prior to the date of first dose of study medication (including DHA-PQP).
Concomitant	Medications with a start date on or after the first dose of study medication (including DHA-PQP), or where the medication is ongoing on the date of the first dose of study medication.

NOTES:

Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

11.4.1.2. Treatment States for Adverse Event Data

Treatment State	Definition
Onset Time Since 1st Dose (Days)	If Blinded Treatment Start Date > AE Onset Date = AE Onset Date – Blinded Treatment Start Date If Blinded Treatment Start Date ≤ AE Onset Date = AE Onset Date – Blinded 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. Can be marked as either related to DHA-PQP and/or blinded study medication.
Onset in Month 1	Blinded Treatment Start Date/Time ≤ AE Start Date/Time ≤ Blinded Treatment Start Date + 29 Days

Note that onset time is relative to the first dose of double-blind treatment medication. An SAE occurring after the first dose of DHA-PQP, but prior to the participant receiving randomised treatment would therefore have a negative onset time since first dose.

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Reporting Process

Software	
The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Area	: /arenv/arprod/sb252263/mid200894/final_01 (final analyses, excluding PK) : /arenv/arprod/sb252263/mid200894/final_02 (PK analyses)
Analysis Datasets	
Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.0).	
Generation of RTF Files	
RTF files will be generated for all tables at SAC.	

11.5.2. Reporting Standards

General
The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx): 4.03 to 4.23: General Principles 5.01 to 5.08: Principles Related to Data Listings 6.01 to 6.11: Principles Related to Summary Tables 7.01 to 7.13: Principles Related to Graphics
Formats
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, unless otherwise stated. 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, including: Proportions and their Confidence Intervals will be presented to 3 decimal places. Rates and their 95% Confidence Intervals will be presented to 1 decimal place
Planned and Actual Time
Reporting for tables, figures and formal statistical analyses: Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. Reporting for Data Listings: Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).

Unscheduled or unplanned readings will be presented within the participant's listings.
Unscheduled Visits
Unscheduled visits will not be included in summary tables unless they slot into a missing planned visit (see Section 11.3.1) in which case they will be reported as the planned visit. Unscheduled visits will not be included in figures unless they slot into a missing visit (see Section 11.3.1) in which case they will be reported as the planned visit. Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses. All unscheduled visits will be included in listings. Some scheduled laboratory results (eg Alkaline phosphatase and creatinine phosphokinase for specific participants) had to be recorded in the database as unscheduled visits to accommodate multiple laboratory codes per visit. These will however be considered scheduled visits according to the visit slotting described above and reported accordingly.
Descriptive Summary Statistics
Continuous Data: Refer to IDSL Statistical Principle 6.06.1
Categorical Data: N, n, frequency, %
Graphical Displays
Refer to IDSL Statistical Principles 7.01 to 7.13.

11.5.3. Reporting Standards for Pharmacokinetics

Pharmacokinetic Concentration Data	
NONMEM/Pop PK File	Pop-PK file (CSV format) for the POP-PK analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in Section 11.9.1 Population Pharmacokinetic (PopPK) Dataset Specification.

11.6. Appendix 6: Derived and Transformed Data

11.6.1. General

Multiple Measurements at One Analysis Time Point
If there are multiple assessments within the same window which are not unscheduled visits, the earliest result will be used in the summaries. All values will be listed. For ECGs, if there are multiple assessments at the same visit, the mean will be derived and used in any derivation of summary statistics but if listed, all data will be presented. Participants 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 first dose of DHA-PQP was taken. Study day >1 is calculated as the number of days from the date of the Study Day 1: Ref Date = Missing → Study Day = Missing Ref Date < Date of Study Day 1 → Study Day = Ref Date – Date of Study Day 1 Ref Data ≥ Date of Study Day 1 → Study Day = Ref Date – (Date of Study Day 1) + 1 Study Day 180 refers to a time point exactly 179 days after Study Day 1, whereas the 'Day 180 visit' refers to the nominal Day 180 assessments which did not necessarily occur on Study Day 180.

11.6.2. Study Population

Demographics
Body Mass Index (BMI)
Calculated as Weight (kg) / [Height $(m)^2$]

Baseline Fever
A participant is considered to have had a fever at baseline if the have a temperature recorded in their vital signs data >37.4ºC at any point prior to the first dose of study medication (including DHA-PQP).

Prior and Concomitant Medications
Medications will be coded using the latest version of GSK Drug. Prior medications = medications taken within the 30 days prior to the date of the first dose of DHA-PQP. Any medications with stop dates earlier than 30 days before the date of the first dose of DHA-PQP will not be reported in tables and listings. Concomitant medications = medications with start date on or after the start date of the first dose of DHA-PQP, or ongoing on the start date of the first dose of DHA-PQP. Medications taken prior to the study and continuing during the study will be summarised as both prior medications and concomitant medications. See Section 11.7.2.1 for the handling of missing and partial dates.

Treatment Compliance
All study medication should be administered in the presence of the Investigator or study nurse, and ingestion confirmed. On any day of in clinic dosing, a participant 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 participant is considered to be compliant with blinded medication if they successfully administer 12 doses of blinded PQ study medication and a single dose of blinded TQ medication (note, the blinded medication does not need to have been observed for a subject to be considered compliant). Participants who were randomized but did not report a treatment start date will be categorised as having zero doses.

Treatment Compliance
PQ / PQ placebo blinded treatment compliance will be calculated based on the formula: PQ / PQ placebo Blinded Treatment Compliance = Number of Actual doses / 14 Compliance could be greater than 100% if there are events of overdose. The number of participants taking <12 or ≥12 doses of PQ/PQ placebo will also be summarised. TQ / TQ placebo compliance will be summarised as if they successfully administered the dose (yes/no). DHA-PQP compliance will be summarised by number of compliant doses. If a subject vomits within 30 minutes of taking DHA-PQP on Days 1 to 3, the whole dose should be re-administered; if the subject vomits within 30-60 minutes, half the dose should be re-administered. If a subject vomits their dose and does not receive a re-dose as described, they will be considered non-compliant for that dose. If they vomit the re-dose, they will also be considered non-compliant for that dose.

G6PD Deficiency
A participant will be considered to be G6PD deficient if their fluorescent spot test has a result of 'G6PD Deficient'.

11.6.3. Efficacy

Efficacy endpoints
Relapse free efficacy at six months
Relapse is defined as any recurrence of *P.vivax* malaria after clearance of the initial infection.
Participants will be considered to have demonstrated relapse-free efficacy at six months if all of the following are true (also described in Figure 1): Participant had a non-zero *P.vivax* asexual parasite count at baseline. Participants who do not meet this criterion will be censored, with time to relapse censored at 0 days. Participant demonstrated initial clearance pf *P.vivax* parasitemia. This is defined as two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval. Participants who do not meet this criterion will be censored with time to relapse censored at 0 days. Participant has no positive asexual *P.vivax* parasite count at any assessment prior to or on Day 180 visit following initial parasite clearance. Participants who do have a positive count will be considered to have relapsed with time to relapse = (date of first positive count) – (date of Study Day 1) days. Participants did not take a concomitant medication with anti-malarial activity (excluding study treatment) at any point between Study Day 1 and their last parasite assessment. Participants who did take a drug with anti-malarial activity but never had a positive asexual *P.vivax* parasite count after initial clearance will be censored with time to relapse censored at (date of last negative parasite assessment prior to concomitant medication start) – (date of Study Day 1) days. If a participant has not had a negative assessment prior to the concomitant medication start date, they will be censored at 0 days.

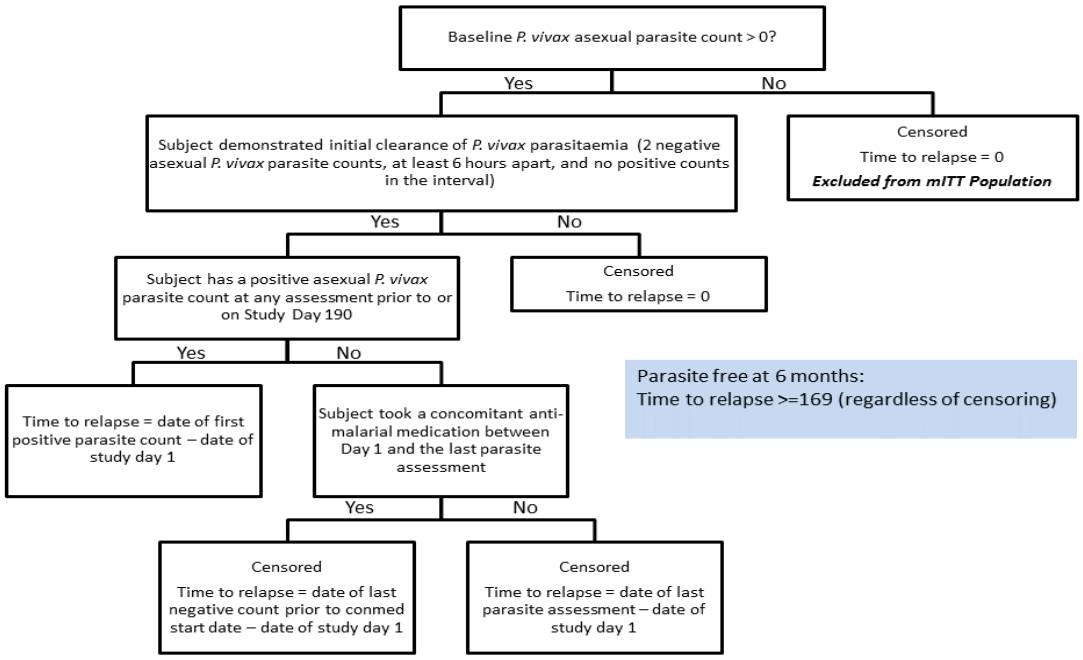
Efficacy endpoints

Participant is parasite-free at 6 months. This is defined as a negative asexual *P. vivax* parasite count at the first parasite assessment performed on or after Study Day 170.

Participants who do not have a Day 180 visit and have not already failed or been censored will be censored at (date of final parasite assessment) – (date of Study Day 1) days).

If a participant 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 participant 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 6 months



Relapse free efficacy at four months

Relapse is defined as any recurrence of *P.vivax* malaria after clearance of the initial infection.

Participants will be considered to have demonstrated relapse-free efficacy at four months if all of the following are true (also described in Figure 2):

Participant had a non-zero *P.vivax* asexual parasite count at baseline. Participants who do not meet this criterion will be censored, with time to relapse censored at 0 days.

Participant demonstrated initial clearance of *P.vivax* parasitemia. This is defined as two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval. Participants who do not meet this criterion will be censored with time to relapse censored at 0 days.

Participant has no positive asexual *P.vivax* parasite count at any assessment prior to or on

Efficacy endpoints

Study Day 135 following initial parasite clearance. Participants who do have a positive count will be considered to have relapsed with time to relapse = (date of first positive count) – (date of Study Day 1) days.

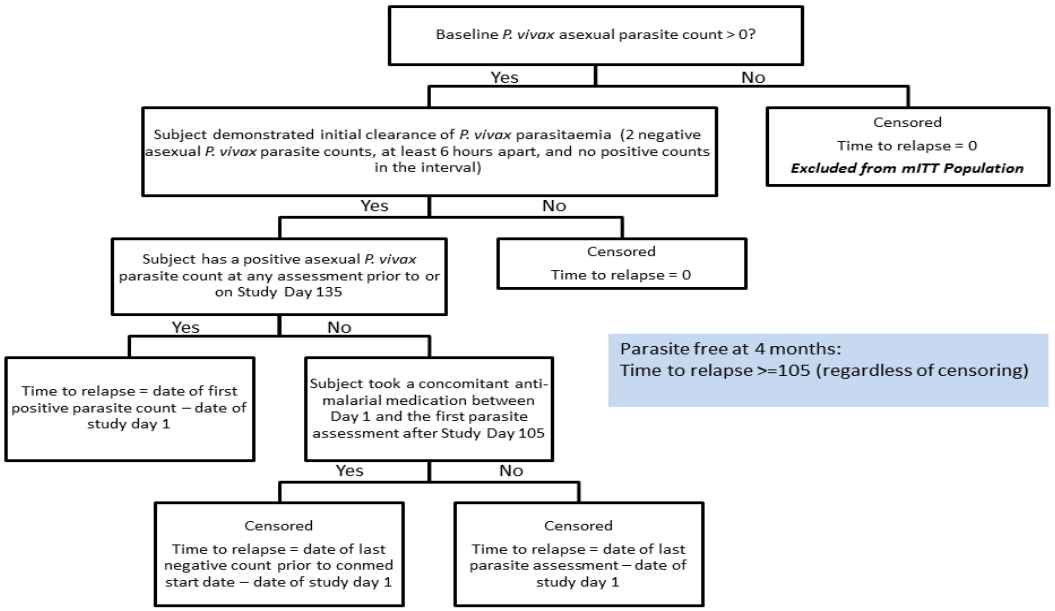
Participants did not take a concomitant medication with anti-malarial activity (excluding study treatment) at any point between Study Day 1 and their first parasite assessment after Study Day 105 (up to and including Study Day 135). Participants who did take a drug with anti-malarial activity but never had a positive asexual *P.vivax* parasite count after initial clearance will be censored with time to relapse censored at (date of last negative parasite assessment prior to concomitant medication start) – (date of Study Day 1) days. If a participant has not had a negative assessment prior to the concomitant medication start date, they will be censored at 0 days.

Participant is parasite-free at 4 months. This is defined as a negative asexual *P. vivax* parasite count at the first parasite assessment performed on or after Study Day 105 (up to and including Study Day 135).

Participants who do not have a Day 120 visit and have not already failed or been censored will be censored at (date of final parasite assessment prior to Day 120) – (date of Study Day 1) days.

If a participant 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 participant 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 2 Flowchart of algorithm for relapse-free efficacy at 4 months



Efficacy endpoints

Relapse free efficacy at 6 months missing=failure definition

In addition to those with a positive asexual *P. vivax* parasite count at any assessment prior to or on Study Day 190, the following participants will also be defined to have relapsed:

Participant did not demonstrate initial clearance of *P. vivax* parasitaemia (i.e. did not have two negative asexual *P. vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval)

Participant took a concomitant medication with anti-malarial activity at any point between Study Day 1 and their last parasite assessment. A list of all concomitant medications will be reviewed by a GSK clinician prior to unblinding the study, and classified accordingly.

Participant does not have a parasite assessment between Study Day 170 and 190.

Participants with a zero *P. vivax* asexual parasite count at baseline will be excluded from the analysis.

Genetic classification of relapse (heterologous/homologous)

Relapse-free efficacy at 6 months will be assessed separately according to whether the first *P. vivax* re-infection is homologous or heterologous to the original infection. The definition is as detailed above but heterologous infections will be censored at the time at which they occur for the endpoint looking at homologous infections only; and homologous infections will be censored at the time at which they occur for the endpoint looking at heterologous infections only.

Recrudescence

A participant will be considered to have had a recrudescence if the following are true:

Included in mITT population

Participant had a positive *P. vivax* asexual parasite count at baseline and demonstrates clearance (i.e. two negative asexual P. *vivax* parasite counts, with at least 6 hours between the counts, and no positive counts in the interval).

Participant has a positive genetically homologous asexual *P. vivax* parasite count on or before Study Day 14, after their zero count in days 1 to 5.

The following participants will have a censored time to recrudescence of 0 days:

Participant had no asexual *P. vivax* parasites at baseline.

Participant had a positive P.*vivax* asexual parasite count at baseline but had no subsequent zero asexual parasite count within study Days 1-5.

If a participant does not meet the definition of recrudescence, but took a concomitant medication with anti-malarial activity between Study Day 1 and Study Day 14, they will be censored, with time to recrudescence censored at (date of last negative parasite assessment prior to concomitant medication start) – (date of Study Day 1). If a participant has not had a negative assessment prior to the concomitant medication start date, they will be censored at 0 days.

All other participants will be censored with time to recrudescence censored at their last parasite assessment on or before Study Day 14, with time to recrudescence = (date of final parasite assessment) – (date of Study Day 1).

Number of Relapses

A participant is considered to have had at least one relapse if they:

demonstrated initial clearance of *P.vivax* parasitemia (defined as two negative asexual *P.*

Number of Relapses
vivax parasite counts, with at least 6 hours between the counts, and no positive counts in the interval) subsequently had a positive asexual *P.vivax* parasite count at any assessment up to and including their Day 180 visit. A participant is considered to have had a subsequent relapse if they: demonstrated clearance of *P.vivax* parasitemia following their previous relapse (defined as a negative asexual *P. vivax* parasite count) subsequently had a positive asexual *P.vivax* parasite count at any assessment up to and including their Day 180 visit.

Clearance time
Parasite (PCT)
Defined as: time needed to clear asexual parasite from the blood i.e. parasite numbers falling below the limit of detection in the thick blood smear and remaining undetectable ≥6 hours later. If a participant has a non-zero asexual *P. vivax* parasite count at baseline, and prior to Study Day 8 has two negative counts with at least 6 hours between the counts and no positive parasite counts within this time period, parasite clearance time will be defined as the time elapsed between the first dose of study medication (including DHA-PQP) and the first of these negative counts (measured in hours). Participants with a negative parasite count at baseline will be censored with a parasite clearance time of 0 hours. All other participants will be censored at the time of the last non-missing assessment prior to Study Day 8.
Gametocyte (GCT)
Defined as: time from first dose until the first slide that was gametocyte negative and remained so at the next slide reading. Any participant with negative *P. vivax* gametocytes at baseline will be censored with a time to gametocyte clearance of 0 days. For all other participants, gametocyte clearance will be considered to have been achieved once a negative gametocyte value has been seen, unless the next gametocyte count is positive. Time to clearance will then be defined as (time to first negative value) – (time of first dose of study medication including DHA-PQP). Subjects who fail to reach this endpoint will be censored at the visit of their final gametocyte assessment.
Fever (FCT)
Defined as: time from first dose of treatment to the time when body temperature falls to normal and remains normal for at least 48 hours up to the Day 7 visit. Any participant who does not have a temperature in excess of 37.4^0C at any point prior to the first dose of study medication (including DHA-PQP) on Study Day 1 will be censored with a fever clearance time of 0 hours. Participants will also be censored at time 0 if the method of temperature measurement is not consistent throughout Study Days 1 to 7 (i.e., method is not consistently oral, tympanic, or axillary). Fever clearance is considered to have been achieved once an initial temperature of >37.4^0C is reduced to a value ≤37.4^0C, in the absence of value >37.4^0C in the following 48 hours

Clearance time
up to the Day 7 visit. Participants who do not demonstrate this endpoint prior to final assessment of Study Day 3 will be censored at that time point. Participants with missing data in Study Days 1-3 will be censored at the last available temperature assessment, if they do not meet the definition of fever clearance before the Day 7 visit.

CPD2D6 Activity and Metabolizer Phenotype
Eijkman Institute will provide CYP2D6 *alleles which will be used to derive metabolizer class (Poor metabolizer (PM), Intermediate metabolizer (IM), Extensive metabolizer (EM), Ultra metabolizer (UM)). Each of the two CYP2D6 *alleles, comprising the genotype, will be assigned a value relative to its activity compared to the *1 reference allele: Value of 0 for null activity alleles: *3, *4, *5, *6, *7, *8, *11, *15 Value of 0.5 for reduced activity alleles: *9, *10, *14, *17, *29, *41 Value of 1 for fully functional alleles: *1, *2, *35 For all *alleles that are not captured above, the activity score will be determined prior to unblinding the data. Alleles denoting gene duplications, represented by 'xN', will receive double the non-duplicated value. For example, *1xN will receive a value of 2 whereas *1 receives a value of 1. The CYP2D6 Activity Score (AS) [Gaedigk, 2008] is then calculated as the sum of activity values from the two alleles comprising the genotype. For example, a participant with 2 null alleles will have an AS of 0; one null and one reduced activity allele will have a score of 0.5; or one null allele and one fully functional allele will have an AS of 1. The CYP2D6 phenotype will be classified based on the AS and follows the Dutch Pharmacogenomics Working Group [DPWG] classification scheme, where: Poor metabolizer if AS = 0 Intermediate metabolizer if AS = 0.5 or 1 Extensive metabolizer if AS = 1.5 or 2 Ultra metabolizer if AS ≥ 2.5

11.6.4. Safety

Adverse Events

Adverse Events

All AEs reported up to and including the Day 180 visit (Day 195 visit for participants who do not relapse during the study) following enrolment of a participant into the study will be documented for participants in the Safety Population (or Safety OL Population).

These will be recorded and coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). All terms applied will be reviewed by a GSK physician prior to unblinding. If any malaria related coded terms are considered to have lost useful information in the coding step (e.g., if a verbatim term of '*Plasmodium vivax* malaria' is mapped to 'malaria'), he/she will recommend a study-specific code, which will be documented. The process will be completed prior to study unblinding.

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 participant is alive, or Grade 5 if an SAE and the participant dies (i.e. the highest intensity possible) for the summary of AEs by maximum intensity.

See Section 11.7.2 for more information on missing and partial dates.

Common AEs are those occurring in ≥5% of participants 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.

AE's of Special Interest

AEs of special interest are:

Haematological events

AEs with a system organ class (SOC) of "Nervous System Disorders"

AEs with a SOC of "Psychiatric Disorders"

AEs with a SOC of "Renal and Urinary Disorders"

AEs with a SOC of "Hepatobiliary Disorders"

Haematological events will be identified by GSK physicians, prior to unblinding, from a list of all unique preferred terms observed within the study.

Laboratory Parameters

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

Example 1: 2 decimal places = '< x' becomes x – 0.01

Example 2: 1 decimal place = '> x' becomes x + 0.1

Example 3: 0 decimal places = '< x' becomes x – 1

Where laboratory assessments were conducted at more than one laboratory, e.g. a single participant may have had their data analysed at different laboratories at different visits, the results will be pooled in the summaries, i.e. all data will be included regardless of the laboratory at which the sample was analysed. A review by the GSK clinical team has shown the normal ranges to be sufficiently similar across the different laboratories, thus pooling of the data is appropriate.

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: $$mean\ arterial\ blood\ pressure = \frac{(systolic\ blood\ pressure + 2(diastolic\ blood\ pressure)}{3}$$

11.7. Appendix 7: Reporting Standards for Missing Data

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	A participant is considered to have completed the double-blind study if they are randomized to blinded study treatment and complete the Day 180 visit. A participant is considered to have completed the open-label PQ phase of the study if they are included in the safety OL population and complete the Day 195 visit. Withdrawn participants will not be replaced in the study. All available data from participants 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.

11.7.2. 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: These data will be indicated by the use of a "blank" in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	Any participants with outlying results may be excluded in additional *ad hoc* summaries and/or statistical analyses. These will be documented along with the reason for exclusion in the clinical study report, but the primary conclusions will remain based on the full population sets.

11.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in participant listing displays.
Adverse Events	It is not possible to record partial dates in the eCRF for AEs. Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. AEs with entirely missing start dates will be assumed to have started during the double-blind treatment phase for reporting. AEs where the start date is equal to that of blinded study medication, but where the start time is unknown will be assumed to have started during the double-blind treatment phase. AEs with an onset date on or after that of DHA-PQP administration, and where blinded medication was taken on a later date, will be considered to have started during the DHA-PQP phase. AEs with missing end dates and/or times are not anticipated to affect reporting

Element	Reporting Detail
	(with the exception that duration will be missing in the listings of AEs).
Concomitant medications / Medical History	**Missing Dates** Where the start or stop date of a concomitant medication record is entirely unknown and is totally missing at the time of reporting, the eCRF flags 'Taken prior to study?' and 'Ongoing medication?' will be used in order to derive whether it is prior or concurrent. If these flags are also missing, then it will be assumed that it is concurrent. 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. **Partial Dates** 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.

11.7.2.2. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Relapse-free efficacy and time to event endpoints	For all analyses of the mITT population, participants will not be excluded from any statistical analyses. From the Day 28 assessment onwards, participants who have not relapsed but fail to have an evaluable parasite smear within the visit window for any scheduled visit will be excluded from the PP population. See Section 11.6.3 for further details on how missing assessments will be censored.
Derived variables	For derived variables, details of how any missing eCRF data will be handled are provided in Section 11.6

11.8. Appendix 8: Values of Potential Clinical Importance

11.8.1. Laboratory Values

Element	Reporting Detail
F2 flag	Denotes a value that has increased or decreased from baseline by more than a specified amount.
F3 flag	Denotes a value that falls outside an extended normal range. This range is independent of any change from baseline or other values.

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Haemoglobin	G/L	F2	Decline from baseline ≥30% or decline from baseline >30 g/L	
	g/dL	F3	7	
Platelets	$x10^9$/L	F3	50	
Lymphocytes	$x10^9$/L	F3	0.5	4
Eosinophils	$x10^9$/L	F3		1.5
Reticulocytes	$x10^{12}$/L	F3		1xULN

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
BUN (Urea) [b]	mmol/L	F3		11.067
Creatinine[a]	μmol/L	F2		3x baseline
		F3		3x ULN
Aspartate aminotransferase	IU/L	F3		3x ULN
Alanine aminotransferase	IU/L	F3		3x ULN
Alkaline phosphatase	IU/L	F3		2.5xULN
Total bilirubin	μmol/L	F3		1.5x ULN
Indirect bilirubin	μmol/L	F3		1.5x ULN
Creatine kinase [a]	IU/L	F3		5x ULN

CTC AE criteria

FDA industry toxicity grading scale for healthy volunteer adults and adolescents in preventative vaccine trials

11.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTcF Interval	*msec*		> 480
Change from Baseline			
Increase from Baseline QTcF	msec		≥ 60

NOTE: Both criteria (absolute and change from baseline) must be met to be of clinical concern.

11.8.3. Vital Signs (Normal Ranges)

The following normal ranges will be applied to vital signs (note that a value falling outside of the associated range does not mean that the value is necessarily of potential clinical concern).

Vital Sign Parameter	Units	Lower[1]	Upper[1]
Systolic Blood Pressure	mmHg	90	120
Diastolic Blood Pressure	mmHg	60	80
Respiratory Rate	Breaths/minute	12	18
Heart Rate	Beats/minute	60	100
Temperature	°C	36.5	37.3

[1] These values represent the normal range for vital sign parameters. Values < lower limit or > upper limit should be flagged.

11.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

11.9.1. Pharmacokinetic NONMEM Dataset Specification

Item Name	Description	Code	Derivation/Comments	Dataset
ID	NONMEM sequential number starting at 1 identifying each participant	00001 – 99999	Sequential identifier for each participant starting at 1.	
CENT	Centre Identification	27 = Indonesia	Additional centre numbers to be added based on where patients are recruited	
PT	Patient Identification Number		As per randomization; Retain all participants with at least one measurable PK sample for the TQ analyte(s)	
STUDY		9=200894		
TRTGRP	Treatment group for each study	24: 200894 - 300 mg arm		
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	

Item Name	Description	Code	Derivation/Comments	Dataset
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 180 min of dose	1 = Yes, vomited 0 = No 0 = PK observations -99=missing	-99 if missing in datasets	
CNTY	Country	11 = Indonesia	Other countries to be added where participants recruited For the 114582, all are in the USA (as per the IB).	

Item Name	Description	Code	Derivation/Comments	Dataset
AGE	Baseline Age of participant (yr)			
GEN	Gender of the Participant (1=M,2=F)	1=Male, 2 =Female		
RACE	Race of the Participant	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 Participant (kg)			
BMI	Baseline Body mass Index (kg/m2)		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 participants who have medications identified as being concomitant (could include participants taking medications that are identified as starting prior and becoming concomitant) 0 – for participants 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 concomitant medication data is not collected in a study	
FORMU	Formulation	1= Tablet 2= Capsule		
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	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	

Item Name	Description	Code	Derivation/Comments	Dataset
		(but concentration is available) DUPLI=4 for a duplicate (second) dosing record where no vomiting of any doses occurs.		

11.9.2. Population Pharmacokinetic (PopPK) Methodology

11.9.2.1. Pharmacokinetic Model Development

The population PK analysis will be performed in the following sequence of steps:

Predictive check with existing POPPK model.

Model development

Covariate analysis.

Model refinement.

Model evaluation.

11.9.2.2. Predictive Check

The starting point for the analysis will be the existing population PK model developed based on data from Phase 3 studies (TAF112582 Part 2 and TAF116564). Predictive check of observed INSPECTOR data with the existing POPPK model will be performed through visual predictive checks. If the existing model adequately predicts the data, then the model will be used to generate the post hoc PK parameters for participants enrolled in the INSPECTOR study (e.g. NONMEM option MAXEVAL=0). These PK parameters may then be used to characterize the systemic TQ exposure. If there is lack of fit between the model predictions and observed INSPECTOR data, then the model may be adjusted as described in the following steps.

11.9.2.3. Model Development

Based on analysis of the DETECTIVE Part1 and 2 data, a 2 compartment model will be used as a starting point for the structural model for further analysis. Briefly, a two compartment model with first order elimination and absorption (Ka) with a lagtime, CL/F, Vc/F, V3/F, Q/F and an additive error model adequately fitted the log-transformed plasma concentration data for tafenoquine. Based on results of preliminary analysis, log concentrations may be utilized for model building.

Since the sparse PK sampling may not allow reliable estimation of all PK parameters, information about some PK parameters may be borrowed from historic population PK

model (e.g. absorption rate constant Ka). Alternatively, the data from this study may be combined with PK data from historic studies for population PK modeling as appropriate.

11.9.2.4. Covariate analysis

Covariate analysis will be performed for tafenoquine to explore measurable sources of PK variability. Covariate effects will be considered for the model parameters clearance (CL/F) and volume of distribution (V_c/F), and may be explored for a limited number of other parameters deemed appropriate, depending upon the physiological plausibility.

11.9.2.5. Model refinement

Model refinement steps will be performed, including, where appropriate, exploration of model improvement through reparameterization, interpretation of magnitude of the variability, interpretation of standard errors of the fixed and random effects parameters, and simplification of covariate models. A covariate may be retained or removed from the final model based on clinical and physiological relevance. Those covariates with minimal clinically relevant impact may be excluded from the final model for parsimony.

11.9.2.6. Model evaluation

Non-parametric bootstrapping may be performed to test model robustness. The precision of parameters may also be estimated from bootstrap runs. The model performance may be evaluated by performing predictive check. A visual predictive check method will be utilized to evaluate model performance. At least 200 replicates of the original dataset will be simulated, based on the final model, and a 95% prediction interval (PI) computed for the concentration-time profile based on the simulated datasets. The observed concentration versus time data will be overlaid on this prediction interval to visually assess the concordance between the simulated and observed data.

11.10. Appendix 10: Abbreviations & Trade Marks

Abbreviations

Abbreviation	Description
ACT	Artemisinin-Based Combination Therapy
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Events of Special Interest
AS	Activity Score
AUC0-t	Area Under the Concentration-time Curve from Time of Dosing to Last Quantified Concentration
AUC0-inf	Area Under the Concentration-time Curve Extrapolated to Infinity
A&R	Analysis and Reporting
BSV	Between subject variability
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CL/F	Oral Clearance
CPH	Cox Proportional Hazards
CS	Clinical Statistics
CSR	Clinical Study Report
DHA-PQP	Dihydroartemisinin Piperaquine
DP	Decimal Places
DRE	Drug Related Event
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
EM	Extensive Metaboliser
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
G6PD	Glucose-6-phosphate Dehydrogenase
GI	Gastrointestinal
GSK	GlaxoSmithKline
GUI	Guidance
HARP	Harmonisation of Analysis and Reporting Project
Hb	Haemoglobin
Hct	Human Chorionic Gonadotropin
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IM	Intermadiate Metaboliser
IMMS	International Modules Management System
ITT	Intent To Treat
IWRS	Interactive Web Recognition System
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Microbiologic-Intent to Treat

Abbreviation	Description
OL	Open label
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PM	Poor Metaboliser
PP	Per Protocol
PQ	Primaquine
PT	Preferred Term
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RTF	Rich Text Format
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SOP	Standard Operation Procedure
TLF	Tables, Listings & Figures
TQ	Tafenoquine
T1/2	Terminal Phase Elimination Half-Life
UM	Ultra Metaboliser
V/F	Volume of Distribution

Trademarks

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11.11. Appendix 11: List of Data Displays

Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.34	
Efficacy	2.1 to 2.29	2.1 to 2.11
Safety	3.1 to 3.43	3.1 to 3.12
Pharmacokinetic	4.1	4.1
Section	**Listings**	
ICH Listings	1 to 31	
Non-ICH Listings	32 to 49	

Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn or TTEn	EFF_Tn or TTEn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln

Non-Standard displays are indicated in the 'IDSL/Example Shell'.

Deliverable

Delivery	Description
Headline	Headline Results
SAC	Final Statistical Analysis Complete (excluding PK data)
PK	Final analysis of PK data

11.11.1. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Participant Disposition					
1.1	Safety	ES1	Summary of Subject Disposition for the Participant Conclusion Record	ICH E3, FDAAA, EudraCT Include a total column.	SAC
1.2	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3 Include a total column.	SAC
1.3	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment, by Battalion	Page by Battalion. Include a total column.	SAC
1.4	Safety	ES4	Summary of Subject Disposition at Each Study Phase	ICH E3 Separate phase for: Blinded treatment and Open-label PQ treatment Include a total column.	SAC
1.5	Screened	IE1	Summary of Inclusion/Exclusion Criteria Deviations for Screening Failures	Only include data for screening failures (inclusion or exclusion deviations for randomised subjects will be captured within the important protocol deviations).	SAC
1.6	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
1.7	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure, by Battalion	Journal Requirements	SAC
1.8	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID	EudraCT/Clinical Operations	SAC
1.9	Enrolled	NS1	Summary of Number of Subjects by Battalion		SAC
Protocol Deviations					
1.10	Safety	DV1	Summary of Important Protocol Deviations	ICH E3	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Populations Analysed					
1.11	Screened	SP1	Summary of Study Populations	IDSL	Headline, PK
1.12	Safety	SP2	Summary of Exclusions from the Per Protocol Population	IDSL	SAC
Demographic and Baseline Characteristics					
1.13	Safety	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT Include age, sex, ethnicity, geographic ancestry, weight, height, BMI,. Height, Weight and BMI are collected in VITALS_SCR_CR. VITALS where VISITNUM=10 and PTMNUM=20. All other parameters are collected on DEMO.	Headline
1.14	Safety	DM1	Summary of Demographic Characteristics by Battalion	Table as overall Demographics table but paged by battalion.	SAC
1.15	Safety	DM1	Summary of Baseline Characteristics	Include G6PD Enzyme activity (IU/gHb) only. G6PD enzyme activity is collected in G6PD_PHENO_3.	SAC
1.16	Safety	DM1	Summary of Baseline Characteristics by Battalion	Table as overall Baseline Characteristics table but paged by battalion.	SAC
1.17	Enrolled	DM11	Summary of Age Ranges	EudraCT	SAC
1.18	Safety	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC
1.19	Safety	DM6	Summary of Race and Racial Combinations Details		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Prior and Concomitant Medications and Conditions					
1.20	Safety	CM1	Summary of Prior Medications	Add footnote 'Only medications taken prior to the start date and time of first dose of study medication (open-label DHA-PQP), and within 30 days of Study Day 1 are included.' ICH E3	SAC
1.21	Safety	CM1	Summary of Concomitant Medications (DHA-PQP only and Double Blind Phase)	ICH E3	Headline
1.22	Safety OL	CM1	Summary of Concomitant Medications (Open-Label, PQ Phase, Non-Relapsers)	ICH E3	SAC
1.23	Safety	CM1	Summary of Paracetamol Usage (DHA-PQP only and Double Blind Phase)		SAC
1.24	Safety	POP_T1	Summary of Malarial Signs and Symptoms		SAC
1.25	Safety	POP_T6	Number (%) of Subjects with Fever at Baseline	Fever is defined as a temperature >37.4ºC	SAC
1.26	Safety	MH1	Summary of Current Medical Conditions by Body System	ICH E3 Taken from Medical Conditions eCRF page.	SAC
1.27	Safety	MH1	Summary of Past Medical Conditions by Body System	ICH E3 Taken from Medical Conditions eCRF page.	SAC
1.28	Safety	MH4	Summary of Current Specific Medical Conditions	Taken from Disease History eCRF page.	SAC
1.29	Safety	MH4	Summary of Past Specific Medical Conditions	Taken from Disease History eCRF page.	SAC
1.30	Safety	POP_T2	Summary of Splenomegaly at Baseline		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.31	Safety	POP_T2	Summary of Previous Episodes of Malaria	Include category for unknown, if necessary.	SAC
Exposure and Treatment Compliance					
1.32	Safety	POP_T3	Summary of Study Medication Compliance and Exposure	ICH E3	Headline
1.33	Safety	POP_T5	Summary of Subjects for Whom Treatment Medication was Observed		SAC
Diagnostic					
1.34	Screened	POP_T4	Comparison of G6PD Fluorescent Spot Test (FST) and Enzyme Activity Test		SAC

11.11.2. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Parasite counts					
2.1	mITT	EFF_T1	Summary of P.vivax Asexual Parasites at all Timepoints		SAC
2.2	mITT	EFF_T1	Summary of Other Malarial Asexual Parasites at all Timepoints	Page by parasite	SAC
2.3	mITT	EFF_T1	Summary of P.vivax Gametocytes at all Timepoints		SAC
2.4	mITT	EFF_T1	Summary of Other Malarial Gametocytes at all Timepoints	Page by gametocyte	SAC
Relapse free efficacy					
2.5	mITT	EFF_T2	Summary of Relapse-Free Efficacy at 6 Months		SAC
2.6	mITT	EFF_T2	Summary of Relapse-Free Efficacy at 6 Months by Battalion		SAC
2.7	PP	EFF_T2	Summary of Relapse-Free Efficacy at 6 Months		SAC
2.8	mITT	TTE1	Survival Analysis of Relapse-free Efficacy over 6 months	See mock shells example template.	Headline
2.9	mITT	EFF_T7	Summary of Covariate and Treatment*Covariate Interaction Significance For Cox Proportional Hazards Model of Relapse-Free Efficacy Over 6 Months		SAC
2.10	PP	TTE1	Survival Analysis of Relapse-free Efficacy over 6 months		SAC
2.11	mITT	EFF_T3	Logistic Regression Analysis of Relapse-free Efficacy at 6 months (Subjects Censored Prior to 6 Months Excluded)	Add footnote: "Subjects who do not demonstrate initial clearance, take a concomitant medication with anti-malarial activity, have a missing Day 180 assessment, or have a zero P. vivax asexual parasite count at baseline are excluded from the analysis."	SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.12	mITT	EFF_T3	Logistic Regression Analysis of Relapse-free Efficacy at 6 months (Missing = Failure Analysis)	Add footnotes: "Subjects who do not demonstrate initial clearance, take a concomitant medication with anti-malarial activity or have a missing Day 180 assessment are counted as relapses." "Subjects with a zero *P. vivax* asexual parasite count at baseline are excluded from the analysis."	SAC
2.13	mITT	TTE1	Survival Analysis of Genetically Heterologous Relapse-Free Efficacy over 6 Months – Homologous P. vivax Relapses Censored	Add footnote: Homologous relapses are censored at the point at which they occur.	SAC
2.14	mITT	TTE1	Survival Analysis of Genetically Homologous Relapse-Free Efficacy over 6 Months – Heterologous Relapses Censored	Add footnote: Heterologous relapses are censored at the point at which they occur.	SAC
2.15	mITT	EFF_T2	Summary of Relapse-Free Efficacy at 4 Months		SAC
2.16	mITT	TTE1	Survival Analysis of Relapse-free Efficacy over 4 months	See mock shells example template.	SAC
Time to Event endpoints					
2.17	mITT	TTE3	Analysis of Time to Asexual Parasite Clearance	Give time in hours.	SAC
2.18	mITT	TTE3	Analysis of Time to Gametocyte Clearance	Give time in hours.	SAC
2.19	mITT	TTE3	Analysis of Time to Fever Clearance	Give time in hours.	SAC
Other Efficacy endpoints					
2.20	mITT	TTE6	Analysis of Recrudescence (Blood Stage Failure) Rates		SAC
2.21	mITT	EFF_T4	Incidence of Genetically Homologous and Genetically Heterologous P. vivax Infections (determined by PCR)		SAC
2.22	mITT	EFF_T9	Number (%) of Subjects Within Each CYP2D6 Metaboliser Class		SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.23	mITT	EFF_T5	Analysis of Subjects with Relapse-Free Efficacy at 6 Months by CYP2D6 Metaboliser Class – Logistic Regression – Poor and Intermediate Metabolisers vs Extensive and Ultra Metabolisers		SAC
2.24	mITT	EFF_T8	Effect of CYP2D6 Activity Score (AS) on Relapse-Free Efficacy at 6 Months – Logistic Regression		SAC
2.25	mITT	EFF_T6	Summary of P. vivax Gametocyte Emergence		SAC
2.26	mITT	EFF_T6	Summary of *P. falciparum* Asexual Parasite Emergence	n row does not need to be presented. Column 1 category should read: "Number of subjects with emergent P.falciparum at any stage".	SAC
2.27	mITT	TTE1	Survival Analysis of Relapse-free Efficacy over 6 months – by Battalion	See mock shells example template. Only produce display if more than one battalion is included in study and interaction is significant.	SAC
2.28	mITT	TTE1	Survival Analysis of Relapse-free Efficacy over 4 months – by Battalion	See mock shells example template. Only produce display if more than one battalion is included in study and interaction is significant.	SAC
2.29	mITT	EFF_T10	Summary of the Number of Relapses per Subject		SAC

11.11.3. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Relapse free efficacy					
2.1	mITT	TTE10	Kaplan-Meier Survival Curves for Time to Relapse		Headline
2.2	PP	TTE10	Kaplan-Meier Survival Curves for Time to Relapse		SAC
2.3	mITT	TTE10	Kaplan-Meier Survival Curves for Time to Genetically Heterologous Relapse – Homologous P. vivax Relapses Censored		SAC
2.4	mITT	TTE10	Kaplan-Meier Survival Curves for Time to Genetically Homologous Relapse – Heterologous P. vivax Relapses Censored		SAC
2.5	mITT	TTE10	Kaplan-Meier Survival Curves for Time to Fever Clearance	Give time in hours.	SAC
2.6	mITT	TTE10	Kaplan-Meier Survival Curves for Time to Parasite Clearance	Give time in hours.	SAC
2.7	mITT	TTE10	Kaplan-Meier Survival Curves for Time to Gametocyte Clearance	Give time in hours.	SAC
2.8	mITT	EFF_F1	Incidence (95% Confidence Interval) of Genetically Homologous and Genetically Heterologous P. vivax relapses		SAC
2.9	mITT	TTE10	Kaplan-Meier Survival Curves for Time to Relapse – by Battalion	Only produce display if treatment by battalion interaction is significant.	SAC
2.10	mITT	EFF_F2	Estimated Hazard Ratio (95% CI) for Time to Relapse by Baseline Asexual Parasite Count (TQ+DHA-PQP Vs DHA-PQP Only)	Only produce display if treatment by baseline asexual parasite count interaction is significant.	SAC
2.11	mITT	EFF_F2	Estimated Hazard Ratio (95% CI) for Time to Relapse by Weight (TQ+DHA-PQP Vs DHA-PQP Only)	Only produce display if treatment by weight interaction is significant.	SAC

11.11.4. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.1	Safety	AE1	Summary of All Adverse Events by System Organ Class, Preferred Term and Treatment Phase	ICH E3 Add footnote: 'Events are ordered based on Total incidence'. Include total column. Include DHA-PQP only and Double-Blind treatment phases.	SAC
3.2	Safety OL	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term (Open-Label, PQ Phase, Non-Relapsers)	Order events in descending order by incidence in TQ+DHA-PQP arm only. Include total column.	SAC
3.3	Safety	AE3	Summary of All Adverse Events During the Double-Blind Treatment Phase, by Preferred Term and Frequency	Order events in descending order by incidence in TQ+DHA-PQP arm only. Add footnote: 'Events are ordered based on incidence in TQ+DHA-PQP arm'. Include total column.	SAC
3.4	Safety	AE3	Summary of Common (>=5% in Any Treatment Group) Adverse Events During the Double-Blind Treatment Phase by Overall Frequency	ICH E3 Order events in descending order by incidence in TQ+DHA-PQP arm only. Add footnote: 'Events are ordered based on incidence in TQ+DHA-PQP arm'. Include total column.	Headline

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.5	Safety	AE15	Summary of Common (>=5% in Any Treatment Group) Non-serious Adverse Events During the Double-Blind Treatment Phase by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT Include total column.	SAC
3.6	Safety	AE5A	Summary of All Adverse Events During the Double-Blind Treatment Phase by System Organ Class, Preferred Term and Maximum Intensity	IDSL Order events in descending order by total incidence within each treatment group. Add footnote: 'Events are ordered based on total incidence within each treatment group'	SAC
3.7	Safety	AE3	Summary of Common (>=5%) Grade 2-4 Adverse Events During the Double-Blind Treatment Phase by Overall Frequency	ICH E3 Include total column.	SAC
3.8	Safety	AE1CP	Summary of DHA-PQP-Related Adverse Events (as Reported by the Investigator) During the Double-Blind Treatment Phase by System Organ Class and Preferred Term	Order events in descending order by incidence in TQ+DHA-PQP arm only. Add footnote: 'Events are ordered based on incidence in TQ+DHA-PQP arm' Include total column.	Headline
3.9	Safety	AE1CP	Summary of Blinded Treatment-Related Adverse Events (as Reported by the Investigator) During the Double-Blind Treatment Phase, by System Organ Class and Preferred Term	IDSL Order events in descending order by incidence in TQ+DHA-PQP arm only. Add footnote: 'Events are ordered based on incidence in TQ+DHA-PQP arm'	Headline

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.10	Safety	AE5A	Summary of Blinded Treatment-Related Adverse Events (as Reported by the Investigator) During the Double-Blind Treatment Phase, by Maximum Intensity, System Organ Class and Preferred Term	IDSL Order events in descending order by total incidence within each treatment group. Add footnote: 'Events are ordered based on total incidence within each treatment group'	SAC
3.11	Safety	AE3	Summary of Common (>=5%) Blinded Treatment-Related Grade 2-4 Adverse Events During the Double-Blind Treatment Phase, by Overall Frequency	ICH E3	SAC
3.12	Safety	AE1	Summary of Adverse Events During the Double-Blind Treatment Phase, with Onset On or Prior to Study Day 29 by System Organ Class and Preferred Term	Add footnote: 'Events are ordered based on Total incidence'	Headline
Serious and Other Significant Adverse Events					
3.13	Safety	AE1	Summary of Serious Adverse Events by System Organ Class, Preferred term and Treatment Phase	Add footnote: 'Events are ordered based on Total incidence' Include total column. Include DHA-PQP only and Double-Blind treatment phases.	Headline
3.14	Safety OL	AE1CP	Summary of Serious Adverse Events with Onset During the Open-Label, PQ Only Treatment Phase by SOC and Preferred Term	Order events in descending order by incidence in TQ+DHA-PQP arm only. Add footnote: 'Events are ordered based on incidence in TQ+DHA-PQP arm'. Include total column.	Headline
3.15	Safety	AE16	Summary of Serious Adverse Events by System Organ Class, Preferred Term and Treatment Phase (Number of Subjects and Occurrences)	FDAA, EudraCT Include total column. Include DHA-PQP only and Double-Blind treatment phases.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.16	Safety	AE1CP	Summary of Adverse Events During the Double-Blind Treatment Phase Leading to Withdrawal from the Study by System Organ Class and Preferred Term	IDSL Order events in descending order by incidence in TQ+DHA-PQP arm only. Add footnote: 'Events are ordered based on incidence in TQ+DHA-PQP arm' Include total column.	Headline
3.17	Safety	AE1CP	Summary of Adverse Events During the Double-Blind Treatment Phase Leading to Discontinuation from Study Treatment by System Organ Class and Preferred Term	IDSL Order events in descending order by incidence in TQ+DHA-PQP arm only. Add footnote: 'Events are ordered based on incidence in TQ+DHA-PQP arm' Include total column.	Headline
3.18	Safety	AE1CP	Summary of Adverse Events of Special Interest During the Double-Blind Treatment Phase by System Organ Class and Preferred Term	Order events in descending order by incidence in TQ+DHA-PQP arm only. Add footnote: 'Events are ordered based on incidence in TQ+DHA-PQP arm' Include total column.	Headline
3.19	Safety	AE3	Summary of protocol defined Hb SAEs During the Double-Blind Treatment Phase		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.20	Safety	AE3	Summary of Grade 3 and Grade 4 Adverse Events During the Double-Blind Treatment Phase by Preferred Term	Include Grade 3 and Grade 4 events only. Order events in descending order by incidence in TQ+DHA-PQP arm only. Add footnote: 'Events are ordered based on incidence in TQ+DHA-PQP arm' Include total column.	SAC
Laboratory: Chemistry					
3.21	Safety	LB1	Summary of Chemistry Data	Present values for all treatment groups and valid lab parameters at each visit.	Headline
3.22	Safety	LB1	Summary of Chemistry Changes from Baseline	ICH E3 Present change from baseline values for all treatment groups and valid lab parameters at each visit.	Headline
3.23	Safety	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	SAC
3.24	Safety	SAFE_T1	Summary of Clinical Chemistry Laboratory Data Outside the Reference Range (F3)		SAC
Laboratory: Haematology					
3.25	Safety	LB1	Summary of Haematology Data	Present values for all treatment groups and valid lab parameters at each visit.	Headline
3.26	Safety	LB1	Summary of Hematology Changes from Baseline	ICH E3 Present change from baseline values for all treatment groups and valid lab parameters at each visit.	Headline

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.27	Safety	LB15	Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	SAC
3.28	Safety	SAFE_T1	Summary of Haematology Laboratory Data Outside the Reference Range (F3)		SAC
3.29	Safety	SAFE_T2	Summary of Categories of Change from Baseline Haemoglobin (G/L) Data by Time		Headline
3.30	Safety	SAFE_T3	Summary of Haemoglobin Declines Over First 28 Days		SAC
Laboratory: Urinalysis					
3.31	Safety	UR1	Summary of Urinalysis Dipstick Results	IDSL	SAC
Hepatobiliary (Liver)					
3.32	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	SAC
3.33	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	SAC
ECG					
3.34	Safety	EG1	Summary of ECG Findings	IDSL	SAC
3.35	Safety	EG2	Summary of Absolute ECG Values by Visit	Include Heart Rate, RR Interval, QRS Duration, Uncorrected QT Interval and QTcF	SAC
3.36	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL Include Heart Rate, RR Interval, QRS Duration, Uncorrected QT Interval and QTcF	SAC
3.37	Safety	SAFE_T5	Summary of QTcF Values by Category and Visit		Headline
3.38	Safety	EG11	Summary of Maximum Increase in QTcF Values Post-Baseline Relative to Baseline Category over the First 7 Days		Headline

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Vital signs					
3.39	Safety	VS1	Summary of Absolute Values in Vital Signs by Visit	ICH E3 Include Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Blood Pressure, Respiratory Rate and Temperature.	SAC
3.40	Safety	VS1	Summary of Change From Baseline in Vital Signs by Visit	ICH E3 Include Systolic Blood Pressure, Diastolic Blood Pressure, Mean Arterial Blood Pressure, Respiratory Rate and Temperature.	SAC
3.41	Safety	VS3	Summary of Worst Case Vital Sign Results Relative to Normal Range Post-Baseline Relative to Baseline	IDSL	SAC
Methaemoglobin					
3.42	Safety	LB1	Summary of Absolute Values in Methaemoglobin by Visit		SAC
3.43	Safety	LB1	Summary of Change From Baseline in Methaemoglobin by Visit		SAC

11.11.5. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events					
3.1	Safety	AE10	Common (>=5% in Any Treatment Group) Adverse Events and Relative Risk During the Double-Blind Treatment Phase	IDSL	SAC
Laboratory					
3.2	Safety	LB11	LFT Profile Plots	Only for subjects with >3 ULN in ALT or AST. Add footnote to this effect. The subject ID, treatment group, sex, age and race should be included as a header for each subject's plot. Include Alk. Phos, ALT, AST, Total Bili., and Indirect Bili.	SAC
3.3	Safety	LB11	Haematology Profile Plots	Only for subjects with a >30g/L decline from baseline haemoglobin or found to be G6PD deficient Add footnote to this effect. The subject ID, treatment group, sex, age and G6PD status should be included as a header for each subject's plot. Parameters to include are haemoglobin, reticulocytes (if available), methaemoglobin and bilirubin results (total and indirect bilirubin on same plot)	SAC

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.4	Safety	LB11	Clinical Chemistry Profile Plots	Only for subjects change from baseline in urea or creatinine > 50% Add footnote to this effect. The subject ID, treatment group, sex, age and race should be included as a header for each subject's plot. Parameters to include are creatinine and urea (present the results relative to ULN).	SAC
3.5	Safety	LB10	Distribution of Maximum LFTs by Treatment Group		SAC
3.6	Safety	LB7	LFT Shift from Baseline to Maximum Value		SAC
3.7	Safety	LB8	Matrix Display of Maximum LFT Values		SAC
3.8	Safety	SAFE_F1	Maximum Absolute Methaemoglobin Value Over 28 Days		SAC
3.9	Safety	LIVER14	Scatter Plot of Maximum vs. Baseline for ALT	IDSL	SAC
3.10	Safety	LIVER9	Scatterplot of Maximum ALT vs. Maximum Total Bilirubin	IDSL	SAC
Methaemoglobin					
3.11	Safety	SAFE_F2	Change from Baseline in Methaemoglobin over time	Display up to 28 days	SAC
Vital Signs					
3.12	Safety	LB9	Boxplot of Mean Arterial Blood Pressure by Timepoint and Treatment Group	IDSL Display LB9 includes the ULN and identifies subjects who have a value >2xULN. The ULN is not defined for arterial blood pressure, so this is not required. The figure should just include all of the data at each visit.	SAC

11.11.6. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PK General Summaries					
4.1	PK	PK05	Population PK parameters	To be done by CPMS	PK Study Report

11.11.7. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PK General Summaries					
4.1	PK	PK17	Mean Concentration-Time plot	To be done by S&P	PK

11.11.8. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Participant Disposition					
1	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
2	Safety	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
3	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC
4	Safety	BL1	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	SAC
5	Safety	TA1	Listing of Planned and Actual Treatments	IDSL	SAC
Protocol Deviations					
6	Safety	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
7	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Populations Analysed					
8	Safety	SP3	Listing of Subjects Excluded from Any Population	ICH E3	SAC, PK
Demographic and Baseline Characteristics					
9	Safety	DM2	Listing of Demographic Characteristics	ICH E3 Include year of birth, age, sex, ethnicity, height, weight and BMI.	SAC
10	Safety	DM9	Listing of Race	ICH E3	SAC
Prior and Concomitant Medications					
11	Safety	CM3	Listing of Prior and Concomitant Medications	IDSL Include concomitant medications and prior medications taken within 30 days of first dose of study medication	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Exposure and Treatment Compliance					
12	Safety	EX3	Listing of Exposure Data	ICH E3 See mock shell example for additional columns to be included.	SAC
Adverse Events					
13	Safety	AE8	Listing of All Adverse Events by Treatment Phase	ICH E3 Include DHA-PQP only and Double-Blind treatment phases. Include flag for double blind period	SAC
14	Safety	AE8	Listing of All Adverse Events with Onset During the Open-Label Treatment Phase	ICH E3 Add footnote: Listing includes AEs reported by non-relapsers who entered the open-label treatment phase, and any reported by relapsers after their Day 180 study visit.	SAC
15	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events with Onset During the Double-Blind Treatment Phase	ICH E3	SAC
16	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events with Onset During the Open-Label Treatment Phase	ICH E3 Add footnote: Listing includes AEs reported by non-relapsers who entered the open-label treatment phase, and any reported by relapsers after their Day 180 study visit.	SAC
17	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms and Verbatim Text	IDSL	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Serious and Other Significant Adverse Events					
18	Safety	AE8	Listing of Fatal Serious Adverse Events by Treatment Phase	ICH E3 Include DHA-PQP only and Double-Blind treatment phases.	SAC
19	Safety OL	AE8	Listing of Fatal Serious Adverse Events with Onset During the Open-Label Treatment Phase	ICH E3	SAC
20	Safety	AE8	Listing of Non-Fatal Serious Adverse Events by Treatment Phase	ICH E3 Include DHA-PQP only and Double-Blind treatment phases.	SAC
21	Safety OL	AE8	Listing of Non-Fatal Serious Adverse Events with Onset During the Open-Label Treatment Phase	ICH E3	SAC
22	Screened	AE8	Listing of Serious Adverse Events – Screening Failures		SAC
23	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC
24	Safety	AE8	Listing of Adverse Events Leading to Withdrawal From Study / Permanent Discontinuation of Study Treatment with Onset During the Double-Blind Treatment Phase	ICH E3	SAC
25	Safety	AE8	Listing of Disease Related Events with Onset During the Double-Blind Treatment Phase	ICH E3	SAC
Hepatobiliary (Liver)					
26	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	IDSL	SAC
27	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	IDSL	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
All Laboratory					
28	Safety	LB5	Listing of Laboratory Data with Abnormalities of Potential Clinical Importance		SAC
29	Safety	LB5	Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Importance	ICH E3	SAC
30	Safety	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC
31	Safety	UR2A	Listing of Urinalysis Data	ICH E3	SAC

11.11.9. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Demographic and Baseline Characteristics					
32	Screened	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
33	Safety	DM2	Listing of Baseline Characteristics	Include G6PD enzyme activity (IU/gHb) and baseline *P.vivax* asexual parasite count.	SAC
34	Safety	POP_L1	Listing of Malaria Signs and Symptoms at Baseline		SAC
35	Safety	MH2	Listing of Past and Current Medical Conditions		SAC
36	Safety	POP_L2	Listing of Diagnostic Test Results		SAC
Compliance					
37	Safety	POP_L3	Listing of Compliance Data		SAC
Efficacy					
38	mITT	EFF_L1	Listing of Results of Efficacy Endpoints		SAC
39	mITT	EFF_L2	Listing of Malarial Parasite Counts		SAC
40	mITT	EFF_L3	Listing of Time to Fever Clearance Data		SAC
Hepatobiliary (Liver)					
41	Safety	LIVER5	Listing of Liver Event Results and Time of Event Relative to Treatment		SAC
42	Safety	LIVER6	Listing of Liver Event Information for RUCAM Score		SAC
43	Safety	LIVER7	Listing of Liver Biopsy Details		SAC
44	Safety	LIVER8	Listing of Liver Imaging Details		SAC
ECG					
45	Safety	EG3	Listing of ECG Values		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
46	Safety	EG5	Listing of ECG Findings		SAC
Vital Signs					
47	Safety	VS4	Listing of Vital Signs	Include mean arterial BP	SAC
Blood Transfusions					
48	Safety	SAFE_L2	Listing of Blood Transfusions		SAC
Pharmacokinetic					
49	PK	PK07	Listing of PK concentrations for the Tafenoquine treatment group		PK

11.11 Appendix 12: Example Mock Shells for Data Displays

Population : Safety

POP_T1
Summary of Malarial Signs and Symptoms

Symptom	Severity	TQ+DHA-PQP (N=xx)	PQ+DHA-PQP (N=xx)	DHA-PQP only (N=xx)	Total (N=xx)
Any malarial signs and symptoms present	Yes	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	No	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Chills and rigours	Absent	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Mild	xx (xx%)	xx (xx%)	xx (xx%)	xxx (xx%)
	Moderate	xx (xx%)	xx (xx%)	xx (xx%)	xxx (xx%)
	Severe	xx (xx%)	xx (xx%)	xx (xx%)	xxx (xx%)
Headache	...	...	...	...	...
Other - fever	Absent	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Mild	xx (xx%)	xx (xx%)	xx (xx%)	xxx (xx%)
	Moderate	xx (xx%)	xx (xx%)	xx (xx%)	xxx (xx%)
	Severe	xx (xx%)	xx (xx%)	xx (xx%)	xxx (xx%)
	...	...	...	...	...

Programmers' note: Repeat for all signs and symptoms collected at baseline, including those categorised as other (i.e. summarise the free text since it has been recorded consistently across subjects).

Programmers' note: If a subject has any symptom present (regardless of severity, and including "Other"), they will be classed as "Yes" in the "Any malarial signs and symptoms present" row. If all symptoms are recorded as absent they will be "No".

Population : Safety

POP_T2
Summary of Splenomegaly at Baseline

	TQ+DHA-PQP (N=xx)	PQ+DHA-PQP (N=xx)	DHA-PQP only (N=xx)	Total (N=xx)
Does the patient currently have splenomegaly?				
Yes	xx (xx%)	xx (xx%)	xx (xx%)	xxx (xx%)
No	xx (xx%)	xx (xx%)	xx (xx%)	xxx (xx%)

Population : Safety

POP_T3
Summary of Study Medication Compliance and Exposure

		TQ+DHA-PQP (N=xx)	PQ+DHA-PQP (N=xx)	DHA-PQP only (N=xx)	Total (N=xx)
Number of compliant doses of DHA-PQP	n	Xx	Xx	Xx	xxx
	0	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	2	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	3	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Was subject compliant* with blinded treatment dosing?	n	Xx	Xx	Xx	xxx
	Yes	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	No	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Was subject compliant with TQ / TQ placebo dosing?	n	Xx	Xx	Xx	xxx
	Yes	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	No	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Blinded PQ / PQ placebo compliance (%)	n	Xx	Xx	Xx	Xx
	Mean	xx	xx	xx	xx
	SD	xx	xx	xx	xx
	Min	xx	xx	xx	xx
	Median	xx	xx	xx	xx
	Max	xx	xx	xx	xx
Total Number of Doses of PQ / PQ Placebo Taken	n	Xx	Xx	Xx	xxx
	<12	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	≥12	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	Missing	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Note: A dose which was vomited but where the patient was successfully re-dosed was considered to be compliant.
*A subject is considered compliant with dosing if they successfully administered 12 or more doses of PQ or PQ matched placebo and a single dose of TQ or TQ matched placebo.

Population: All subjects screened

POP_T4

Comparison of G6PD Fluorescent Spot Test (FST) and G6PD Enzyme Activity Test

	Result of Fluorescent Spot Test (FST)			
	G6PD Normal	G6PD Deficient	Other	Not Done
G6PD enzyme activity (IU/gHb)				
n	xx	xx	xx	xx
Mean	xx.xx	xx.xx	xx.xx	xx.xx
SD	xx.xxx	xx.xxx	xx.xxx	xx.xxx
Median	xx.xx	xx.xx	xx.xx	xx.xx
Min	xx.x	xx.x	xx.x	xx.x
Max	xx.x	xx.x	xx.x	xx.x

Note: The site median for G6PD enzyme activity is 7.29 IU/gHb. 70% of the site median is 5.1 IU/gHb.

Population : Safety

POP_T5

Summary of Subjects for Whom Treatment Medication was Observed

		TQ+DHA-PQP (N=xx)	PQ+DHA-PQP (N=xx)	DHA-PQP only (N=xx)	Total (N=xx)
Number of doses of DHA-PQP Observed	n	Xx	Xx	Xx	xxx
	0	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	1	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	2	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	3	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Was Tafenoquine/Tafenoquine Placebo Dosing Observed?	n	Xx	Xx	Xx	xxx
	Yes	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	No	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Number of doses of Primaquine/Primaquine Placebo Observed	n	Xx	Xx	Xx	xxx
	<12	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	12	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	13	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	14	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Note: If a subject vomited their dose and was re-dosed, both doses must have been observed, and it will count as a single dose within the table.

Population : Safety

POP_T6

Number (%) of Subjects with Fever at Baseline

		TQ+DHA-PQP (N=xx)	PQ+DHA-PQP (N=xx)	DHA-PQP only (N=xx)	Total (N=xx)
Fever	n	Xx	Xx	Xx	xxx
	Yes	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
	No	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Note: Fever is defined as a temperature >37.4°C.

Population: Microbiologic Intent-to-Treat

EFF_T1
Summary of P.vivax asexual parasites at all time points

Parasite: *Parasite (units)*

		TQ+DHA-PQP (N=xx)	PQ+DHA-PQP (N=xx)	DHA-PQP only (N=xx)	Total (N=xx)
Day 1 (1st assessment)	n	Xx	Xx	Xx	xxx
	Median	x.xx	x.xx	x.xx	x.xx
	Q1	x.xx	x.xx	x.xx	x.xx
	Q3	x.xx	x.xx	x.xx	x.xx
	Min.	x.xx	x.xx	x.xx	x.xx
	Max.	x.xx	x.xx	x.xx	x.xx
Day 1 (2nd assessment)	n	Xx	Xx	Xx	xxx
	Median	x.xx	x.xx	x.xx	x.xx
	Q1	x.xx	x.xx	x.xx	x.xx
	Q3	x.xx	x.xx	x.xx	x.xx
	Min.	x.xx	x.xx	x.xx	x.xx
	Max.	x.xx	x.xx	x.xx	x.xx

Programmer's note: Repeat for all visits where slide reading is performed (Day 2 1st assessment, Day 2 2nd assessment, Day 3 1st assessment, Day 3 2nd assessment, Day 7, Day 14, Day 21, Day 28, Day 60, Day 90, Day 120, Day 150, Day 180).

Population: <Microbiologic Intent-to-Treat / Per Protocol>

EFF_T2

Summary of Relapse-Free Efficacy at 6 Months

	TQ+DHA-PQP (N=xx)	PQ+DHA-PQP (N=xx)	DHA-PQP only (N=xx)	Total (N=xx)
Subjects with relapse-free efficacy at 6 months (primary analysis)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
1. Subjects failing to demonstrate initial parasite clearance	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
2. Subjects with recurrence of parasitaemia in 6 months after initial clearance	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
3. <Subjects take drug with anti-malarial action in first 6 months (and were not parasitaemic)>	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
4. Subjects who are not confirmed parasite-free at 6-month assessment	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Note: Subjects who meet any of the <three/four> criteria will not be considered to be relapse-free at 6 months in the primary analysis approach.

Programmers note: Subjects who do not have a 6-month assessment and do not meet any of the other criteria defined should be included in the "subjects who are not confirmed parasite-free at 6-month assessment" category.

Population: Microbiologic Intent-to-Treat

TTE1

Survival Analysis of Relapse-Free Efficacy over 6 Months

	TQ+DHA-PQP (N=xxx)	PQ+DHA-PQP (N=xxx)	DHA-PQP only (N=xxx)
Number of Subjects			
Subjects observed to relapse prior to or at 6 months	xx (xx%)	xx (xx%)	xx (xx%)
Censored, prior to 6 month assessment [1]	xx (xx%)	xx (xx%)	xx (xx%)
Censored, relapse-free at 6 months	xx (xx%)	xx (xx%)	xx (xx%)
Relapse-free efficacy rate at 6 months [2]			
Estimate	xx%	xx%	xx%
95% CI	(xx%, xx%)	(xx%, xx%)	(xx%, xx%)
Estimates for time to relapse (Days) [2]			
1st Quartile	xx.x	xx.x	xx.x
95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
Median	xx.x	xx.x	xx.x
95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
3rd Quartile	xx.x	xx.x	xx.x
95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
Hazard ratio vs DHA-PQP only [3]			
Estimate	x.xxx	x.xxx	
95% CI	(x.xxx, x.xxx)	(x.xxx, x.xxx)	
p-value	x.xxx	x.xxx	
Hazard ratio vs PQ+DHA-PQP [2]			
Estimate	x.xxx		

95% CI		(x.xxx, x.xxx)
Number needed to treat per treatment group before one extra success was seen compared to DHA-PQP only	Xx (xx,xx)	Xx (xx,xx)

[1] Subjects are censored if they did not have P.*vivax* at baseline, or took a drug with anti-malarial action despite not having malaria parasites, or did not have a 6 month assessment.
[2] Kaplan-Meier methodology
[3] Estimated from Cox's Proportional Hazards Analysis, adjusting for Battalion.
A hazard ratio<1 indicates a lower chance of relapse compared to DHA-PQP only.

Population: Microbiologic Intent-to-Treat

EFF_T3

Logistic Regression Analysis of Relapse-Free Efficacy at 6 Months (Subjects Censored Prior to 6 Months Excluded)

					Comparison with DHA-PQP Only		
Treatment Group	N	n	Subjects Relapse Free (%)	Subjects Relapsed (%)	Adjusted Odds Ratio of Relapse	95% CI	p-value
TQ+DHA-PQP	Xx	Xx	Xxx (xx%)	Xxx (xx%)	x.xx	(x.xx, x.xx)	0.xxx
PQ+DHA-PQP	Xx	Xx	Xxx (xx%)	Xxx (xx%)	x.xx	(x.xx, x.xx)	0.xxx
DHA-PQP Only	Xx	xx	Xxx (xx%)	Xxx (xx%)			

Note: Model includes terms for battalion and treatment.
An odds ratio <1 represents a smaller chance of relapse compared to DHA-PQP only.

Population: Microbiologic Intent-to-Treat

TTE3

Analysis of Time to <Asexual Parasite Clearance>

	TQ+DHA-PQP (N=xxx)	PQ+DHA-PQP (N=xxx)	DHA-PQP only (N=xxx)
Number of Subjects			
Relapse	xx (xx%)	xx (xx%)	xx (xx%)
Censored	xx (xx%)	xx (xx%)	xx (xx%)
Estimates for Time to Clearance (Days) [1]			
1st Quartile	xx.x	xx.x	xx.x
95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
Median	xx.x	xx.x	xx.x
95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
3rd Quartile	xx.x	xx.x	xx.x
95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
Adjusted Hazard Ratio vs DHA-PQP only [2]			
Estimate	x.xx	x.xx	
95% CI	(x.xx, x.xx)	(x.xx, x.xx)	
p-value	x.xxx	x.xxx	
Adjusted Hazard ratio vs PQ+DHA-PQP [2]			
Estimate	x.xxx		
95% CI	(x.xxx, x.xxx)		

[1] Kaplan-Meier methodology

[2] Estimated from Cox's proportional Hazards Analysis, adjusting for Battalion.
A hazard ratio <1 indicates a lower risk of [endpoint] compared to DHA-PQP only.

Population: Microbiologic Intent-to-Treat

EFF_T4

Incidence of Genetically Homologous and Genetically Heterologous P. vivax Infections (determined by PCR)

	TQ+DHA-PQP (N=xx)	PQ+DHA-PQP (N=xx)	DHA-PQP only (N=xx)
n [1]	Xx	Xx	Xx
P. vivax classified as genetically heterologous by PCR	Xx (xx%)	Xx (xx%)	Xx (xx%)
P. vivax classified as genetically homologous by PCR	Xx (xx%)	Xx (xx%)	Xx (xx%)

[1] n = number of subjects with an infection

Population: Microbiologic-Intent-to-Treat

TTE6
Summary of recrudescence (blood stage failure) rates

	TQ+DHA-PQP (N=xx)	PQ+DHA-PQP (N=xx)	DHA-PQP only (N=xx)
Number of Subjects			
Recrudescence before Study Day 14	xx (xx%)	xx (xx%)	xx (xx%)
Censored	xx (xx%)	xx (xx%)	xx (xx%)
Recrudescence rate			
Estimate	xx%	xx%	xx%
95% CI	(xx%,xx%)	(xx%,xx%)	(xx%,xx%)
Difference from DHA-PQP only			
Estimated Difference	xx%	xx%	
95% CI	(xx%, xx%)	(xx%, xx%)	
Difference from PQ+DHA-PQP			
Estimated Difference	xx%		
95% CI	(xx%, xx%)		

Population: Microbiologic-Intent-to-Treat

EFF_T5

Analysis of Subjects with Relapse-Free Efficacy at 6 Months by CYP2D6 Metaboliser Class - Logistic Regression

Treatment Group Effect Tested	n	Number of Subjects Relapse Free	Adjusted Odds Ratio vs. EM+UM	90% CI	p-value
TQ+DHA-PQP					
Poor or Intermediate Metaboliser	xx	xx (xx%)	x.x	(x.x, x.x)	x.xxx
Extensive or Ultra Metaboliser	xx	xx (xx%)			
PQ+DHA-PQP					
Poor or Intermediate Metaboliser	xx	xx (xx%)	x.x	(x.x, x.x)	x.xxx
Extensive or Ultra Metaboliser	xx	xx (xx%)			
DHA-PQP only					
Poor or Intermediate Metaboliser	xx	xx (xx%)	x.x	(x.x, x.x)	x.xxx
Extensive or Ultra Metaboliser	xx	xx (xx%)			

Note: Model includes term for CYP2D6 Metaboliser Class. Metaboliser class is determined from the CYP2D6 activity score (AS) as follows: Poor AS=0; Intermediate AS=0.5 or 1; Extensive AS=1.5 or 2; Ultra AS≥2.
A value over 1 represents benefit over the Extensive Metaboliser + Ultra Metaboliser group.

Population: Microbiologic-Intent-to-Treat

EFF_T6
Summary of P.vivax Gametocyte Emergence

	TQ+DHA-PQP (N=xx)	PQ+DHA-PQP (N=xx)	DHA-PQP only (N=xx)	Total (N=xx)
n	Xx	xx	xx	xx
Number of subjects with emergent gametocytes post-baseline	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Note: Subjects who had P.vivax gametocytes at baseline are not included.

Population: Microbiologic-Intent-to-Treat

Table EFF_T7

Summary of Covariate and Treatment*Covariate Interaction Significance For Cox Proportional Hazards Model

Terms in the model	Degrees of Freedom	Wald Chi-Square	p-value
Battalion	xx	x.xx	x.xxx
Treatment*Battalion	xx	x.xx	x.xxx
Baseline Asexual Parasite Count	xx	x.xx	x.xxx
Treatment*Baseline Asexual Parasite Count	xx	x.xx	x.xxx

Model fitted first with covariate and treatment, then with covariate, treatment and treatment by covariate interaction

Population: Microbiologic-Intent-to-Treat

Table EFF_T8

Effect of CYP2D6 Activity Score (AS) on Relapse-Free Efficacy at 6 Months – Logistic Regression

	Degrees of Freedom	Wald Chi-Square	p-value
CYP2D6 Activity Score [1]			
DHA-PQP Only	xx	x.xx	x.xxx
TQ+DHA-PQP	xx	x.xx	x.xxx
PQ+DHA-PQP	xx	x.xx	x.xxx

[1] Model fitted with CYP2D6 Activity Score + battalion separately for each Treatment.
Note: p-value from a 2-sided test presented.

Population: Microbiologic-Intent-to-Treat

Table EFF_T9

Number (%) of Subjects Within Each CYP2D6 Metaboliser Class

	TQ+DHA-PQP (N=xx)	PQ+DHA-PQP (N=xx)	DHA-PQP only (N=xx)
CYP2D6 Metaboliser Class			
Poor Metaboliser	xx (xx%)	xx (xx%)	xx (xx%)
Intermediate Metaboliser	xx (xx%)	xx (xx%)	xx (xx%)
Extensive Metaboliser	xx (xx%)	xx (xx%)	xx (xx%)
Ultra Metaboliser	xx (xx%)	xx (xx%)	xx (xx%)

Metaboliser class is determined from the CYP2D6 activity score (AS) as follows: Poor AS=0; Intermediate AS=0.5 or 1; Extensive AS=1.5 or 2; Ultra AS≥2.5.

Population: Microbiologic-Intent-to-Treat

Table EFF_T10

Summary of the Number of Relapses per Subject

	TQ+DHA-PQP (N=xx)	PQ+DHA-PQP (N=xx)	DHA-PQP only (N=xx)
Number of Relapses			
n	xx	xx	xx
0	xx (xx%)	xx (xx%)	xx (xx%)
1	xx (xx%)	xx (xx%)	xx (xx%)
2	xx (xx%)	xx (xx%)	xx (xx%)
3	xx (xx%)	xx (xx%)	xx (xx%)

Population: Safety

Table SAFE_T1
Summary of Chemistry Data Outside the Reference Range

Lab Test: <Parameter (units)>

Timepoint	Clinical Concern Category	TQ+DHA-PQP (N=xx)	PQ+DHA-PQP (N=xx)	DHA-PQP only (N=xx)
Day 1	n	xx (xx%)	xx (xx%)	xx (xx%)
	Low	xx (xx%)	xx (xx%)	xx (xx%)
	High	xx (xx%)	xx (xx%)	xx (xx%)
Day 3	n	xx (xx%)	xx (xx%)	xx (xx%)
	Low	xx (xx%)	xx (xx%)	xx (xx%)
	High	xx (xx%)	xx (xx%)	xx (xx%)
…				
Any Time On-treatment	n	xx (xx%)	xx (xx%)	xx (xx%)
	Low	xx (xx%)	xx (xx%)	xx (xx%)
	High	xx (xx%)	xx (xx%)	xx (xx%)

Population: Safety

SAFE_T2

Summary of Categories of Change from Baseline Haemoglobin (G/L) Data by Treatment and Time

Treatment	N	Visit	Haemoglobin drop	n	Mean	SD	Median	Min	Max
TQ+DHA-PQP	xx	Day 3	<=20 g/L	xx	xxx.x	xxx.xx	xxx.x	xx	xx
			>20 g/L to <=30 g/L	xx	xxx.x	xxx.xx	xxx.x	xx	xx
			>30 g/L	xx	xxx.x	xxx.xx	xxx.x	xx	xx
			<=20 g/L	xx	xxx.x	xxx.xx	xxx.x	xx	xx
			>20 g/L to <=30 g/L	xx	xxx.x	xxx.xx	xxx.x	xx	xx
			>30 g/L	xx	xxx.x	xxx.xx	xxx.x	xx	Xx

Population: Safety

SAFE_T3
Summary of Haemoglobin Declines over first 28 days

	TQ+DHA-PQP	PQ+DHA-PQP	DHA-PQP only	Total
Maximum decline from baseline				
<=20 g/L	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
>20 g/L to <=30 g/L	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
>30 g/L or >=30%	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)

Population: Safety

SAFE_T4
Summary of Time on Treatment Before Liver Event

	TQ+DHA-PQP (N=xx)	PQ+DHA-PQP (N=xx)	DHA-PQP only (N=xx)
Subjects reporting at least one liver event	xx (xx%)	xx (xx%)	xx (xx%)
Subjects with events occurring while receiving study treatment	xx (xx%)	xx (xx%)	xx (xx%)
Subjects with events occurring after stopping study treatment	xx (xx%)	xx (xx%)	xx (xx%)
Time from start of treatment to event (days)			
n	xx	xx	xx
Mean	x.x	x.x	x.x
sd	x.x	x.x	x.x
Median	x.x	x.x	x.x
Minimum	x.x	x.x	x.x
Maximum	xx.x	xx.x	xx.x
Time from most recent treatment to event (days)*			
n	xx	xx	xx
Mean	x.x	x.x	x.x
sd	x.x	x.x	x.x
Median	x.x	x.x	x.x
Minimum	x.x	x.x	x.x
Maximum	xx.x	xx.x	xx.x

* For events which occur during treatment, time from treatment to event is set to one day.

Population: Safety

SAFE_T5
Summary of QTcF Values (msec) by Category and Visit

Actual Relative Time Result	TQ+DHA-PQP (N=xx)	PQ+DHA-PQP (N=xx)	DHA-PQP only (N=xx)
Maximum post baseline change			
n	xx	xx	xx
Increase 0 - <30	xx (xx%)	xx (xx%)	xx (xx%)
Increase >=30 - <60	xx (xx%)	xx (xx%)	xx (xx%)
Increase >=60 and QTcF <=480	xx (xx%)	xx (xx%)	xx (xx%)
Increase >=60 and QTcF >480	xx (xx%)	xx (xx%)	xx (xx%)
Baseline			
n	xx	xx	xx
<=450	xx (xx%)	xx (xx%)	xx (xx%)
>450 to <=480	xx (xx%)	xx (xx%)	xx (xx%)
>480 to <=500	xx (xx%)	xx (xx%)	xx (xx%)
>500	xx (xx%)	xx (xx%)	xx (xx%)
Day 3			
n	xx	xx	xx
<=450	xx (xx%)	xx (xx%)	xx (xx%)
>450 to <=480	xx (xx%)	xx (xx%)	xx (xx%)
>480 to <=500	xx (xx%)	xx (xx%)	xx (xx%)
>500	xx (xx%)	xx (xx%)	xx (xx%)
Increase 0 - <30	xx (xx%)	xx (xx%)	xx (xx%)
Increase >=30 - <60	xx (xx%)	xx (xx%)	xx (xx%)
Increase >=60 and QTcF <=480	xx (xx%)	xx (xx%)	xx (xx%)
Increase >=60 and QTcF >480	xx (xx%)	xx (xx%)	xx (xx%)
...			

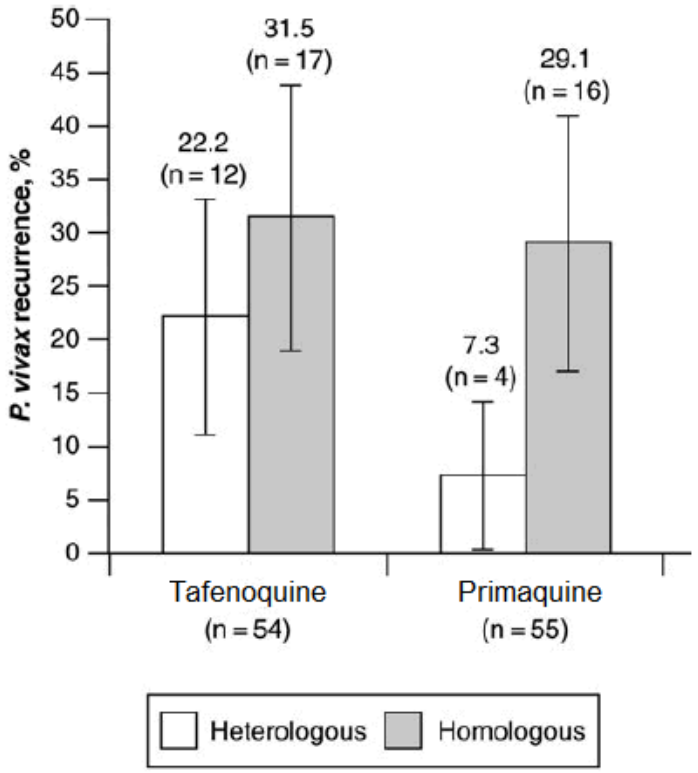
Note: If triplicate measurements are reported at a timepoint (as planned on Day 1, and occasionally

occurring at other visits), the data summarized in the table is the mean of the triplicate measurements.
Note: Day 1 pre DHA-PQP dose is considered as baseline.

Population: Microbiologic Intent to Treat

EFF_F1

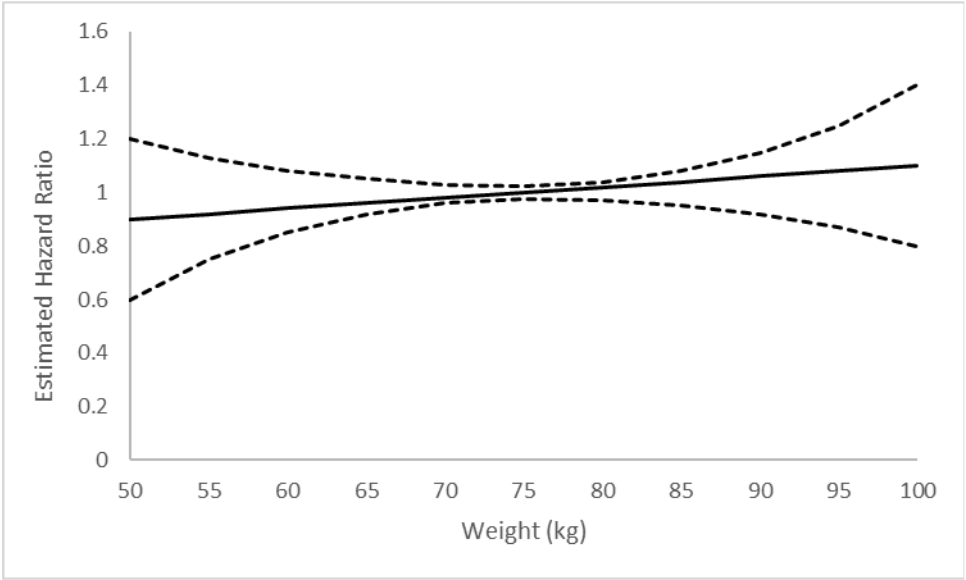
Incidence (95% Confidence Interval) of Genetically Homologous and Genetically Heterologous P. vivax Infections



n = number of P. *vivax* relapses
Bars represent 95% Wilson confidence intervals
Note to programmers: Include Bars for all 3 treatment groups.

Population: Microbiologic Intent to Treat

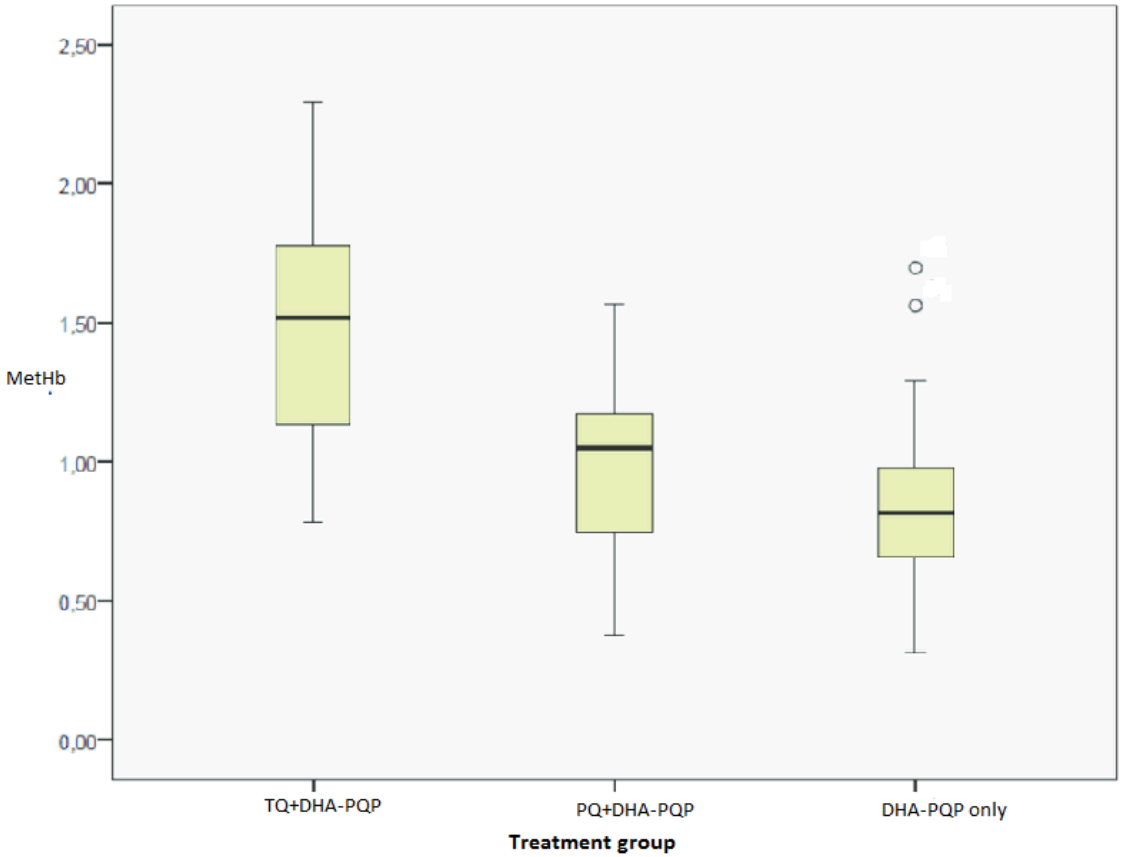
EFF_F1
Estimated Hazard Ratio (95% CI) for Time to Relapse by Weight (TQ+DHA-PQP Vs DHA-PQP Only)



Note: Estimates are derived from a model containing terms for treatment, batallion, weight and the treatment by weight interaction.

Population: Safety

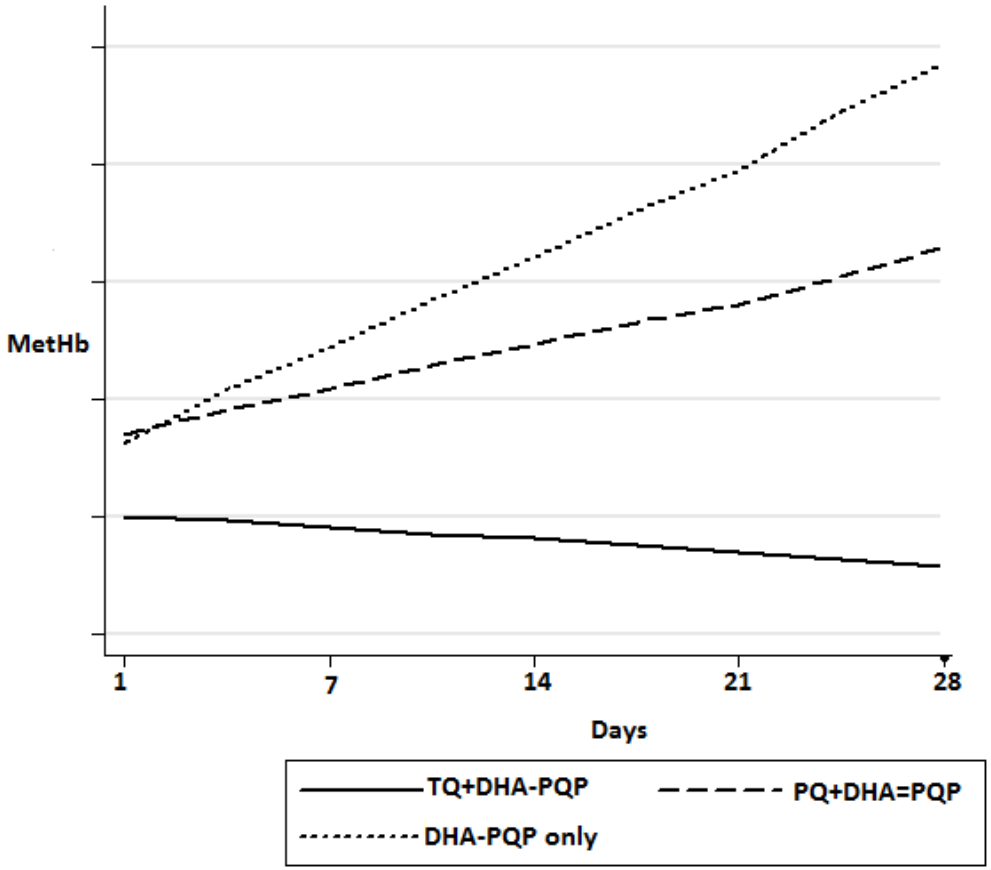
SAFE_F1
Plot of Maximum Absolute Methaemoglobin Value Over 28 Days by Treatment Group



Population: Safety

SAFE_F2

Plot of Change in Methaemoglobin over time by Treatment Group



Population: Safety

EX3
Listing of Exposure Data

Randomised Treatment	Site ID	Unique Subj.	Actual Treatment	Start Date/ Start Time of Dose	Dose Form	TQ dose taken with food?	Dose vomited within 60 minutes?	Subject observed taking medication?
<TQ+DHA-PQP>	xxxxx	xxxx	<TQ>	YYYY-MM-DD/ HH:MM	<Tablet>	<N/Y>	<N/Y>	<N/Y>
			<DHA-PQP>	YYYY-MM-DD/ HH:MM	<Tablet>	<N/Y>	<N/Y>	<N/Y>
			<PQ Placebo>	YYYY-MM-DD/ HH:MM	<Tablet>	<N/Y>	<N/Y>	<N/Y>
<PQ+DHA-PQP>	xxxxx	xxxx	<PQ>	YYYY-MM-DD/ HH:MM	<Tablet>	<N/Y>	<N/Y>	<N/Y>
			<DHA-PQP>	YYYY-MM-DD/ HH:MM	<Tablet>	<N/Y>	<N/Y>	<N/Y>
			<TQ Placebo>	YYYY-MM-DD/ HH:MM	<Tablet>	<N/Y>	<N/Y>	<N/Y>

…

Population: Safety

POP_L1
Listing of Malarial Signs and Symptoms

Treatment	Site ID/ Unique Subj.	Start date of first malaria symptoms	Study Day	Signs and symptoms	Severity of malaria symptoms
TQ+DHA-PQP	xxxxxx/ xxx	DDMMMYYYY	1	Chills and rigors	xxx
				Headache	xxx
				Dizziness	xxx
				Abdominal Pain	xxx
				Anorexia	xxx
				Nausea	xxx
				Vomiting	xxx
				Diarrhoea	xxx
				Pruritis/itching	xxx
				Coughing	xxx
				Other ACHES	xxx

Etc.

Population: Safety

POP_L2
Listing of Diagnostic Test Results

Treatment	Site ID/ Unique Subj.	Fluorescent Spot Test	G6PD Enzyme Activity
TQ+DHA-PQP	xxxxxx/ Xxx	<Normal/ Deficient/ Other>	x.xx

Etc.

Population: Safety

POP_L3
Listing of Compliance Data

Treatment	Site ID	Unique Subj.	Number of compliant doses of DHA-PQP	Compliant with TQ / TQ Placebo	Number of compliant doses of PQ / PQ Placebo	PQ/ PQ Placebo Compliance (%)	Compliant with blinded study treatment dosing*
<TQ+DHA-PQP>	xxxxx	xxxx	Xx	<N/Y>	Xx	Xx%	<N/Y>
		xxxx	xx	<N/Y>	xx	Xx%	<N/Y>
…							

*A subject is considered compliant with dosing if they successfully administered 12 or more doses of PQ or PQ matched placebo and a single dose of TQ or TQ matched placebo.

Population: Microbiologic-Intent-to-Treat

EFF_L1
Listing of Results of Efficacy Endpoints

Treatment: <TQ+DHA-PQP / PQ+DHA-PQP / DHA-PQP only>

Site ID/ Unique Subj.	Age(y)/ Sex/ Race	Endpoint	Time to Event (Days) [1]	Outcome	Reason For Outcome [1]
xxxxxx/ xxx	xx/ xxxx/ xxxx	Relapse-free efficacy at six months	xxx	Success	<Subjects with relapse-free efficacy at 6 months (primary analysis)
		Relapse-free efficacy at six months (missing at D180= failure)		Success	
		Recrudescence (blood stage treatment failure)	xxx	Success	Subjects with no recrudescence (blood stage treatment failure)

...

[1] Time to Event and Reason for Outcome are only given where appropriate

Population: Microbiologic-Intent-to-Treat

EFF_L2

Listing of Malarial Parasite Counts

Treatment: <TQ+DHA-PQP / PQ+DHA-PQP / DHA-PQP only>

Site ID/ Unique Subj.	Timepoint	Sample Date/ Time	Study Day	Parasite	-Parasite Count (/microL)- Asexual	Gametocyte
xxxxxx/ xxx	Day 1 Assessment 1	DDMMMYYYY/ HH:MM	x	*P. vivax*	xxx	xxx
				P. falciparum Other: *P.ovale*, *P.malariae*		
	Day 2 Assessment 1	DDMMMYYYY/ HH:MM	x	*P. vivax*	xxx	xxx
				P. falciparum Other: *P.ovale*, *P.malariae*		
	Day 2 Assessment 2	DDMMMYYYY/ HH:MM	x	*P. vivax*	xxx	xxx
				P. falciparum Other: *P.ovale*, *P.malariae*		
	Day 3 Assessment 1	DDMMMYYYY/ HH:MM	x	*P. vivax*	xxx	xxx
				P. falciparum Other: *P.ovale*, *P.malariae*		

...

Population: Microbiologic-Intent-to-Treat

EFF_L3

Listing of Time to Fever Clearance data

Treatment: <TQ+DHA-PQP / PQ+DHA-PQP / DHA-PQP only>

Site ID/ Unique Subj.	Age(y)/ Sex/ Race	Time to Clearance (Hours) [1]	Outcome
xxxxxx/ xxx	xx/ xxxx/ xxxx	xxh xxm	<Censored/success>
xxxxxx/ xxx	xx/ xxxx/ xxxx	xxh xxm	<Censored/success>
xxxxxx/ xxx	xx/ xxxx/ xxxx	xxh xxm	<Censored/success>
xxxxxx/ xxx	xx/ xxxx/ xxxx	xxh xxm	<Censored/success>
xxxxxx/ xxx	xx/ xxxx/ xxxx	xxh xxm	<Censored/success>
....			

[1] Time to Clearance of zero and outcome of Censored denotes a subject who did not have fever at baseline

Population: Safety

SAFE_L2
Listing of Blood Transfusions

Treatment	Site ID	Unique Subj.	Age	Sex	Race	Visit	Visit Date
TQ + DHA-PQP	XXXX	XXXX	XX	M/F	XXXXXX	XXXX	XXXXX

Note: Visit is the visit at which the check box was ticked to state the subject had a blood transfusion since their previous visit. Details of the transfusion itself should have been reported as a concomitant medication.