STATISTICAL ANALYSIS PLAN

DRI12805

A RANDOMIZED, DOUBLE-BLIND, PHASE IIB STUDY TO INVESTIGATE THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF A SINGLE DOSE REGIMEN OF FERROQUINE (FQ) WITH ARTEFENOMEL (OZ439) IN ADULTS AND CHILDREN WITH UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA

AUTHOR: [redacted]
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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0 (Dated 19DEC2019) for Protocol DRI12805.

	Name	Signature	Date
Author:	[redacted]		
Position:	Statistical Scientist		
Company	IQVIA		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	[redacted]		
Position:	Chief Medical Officer		
Company	Medicines for Malaria Venture		
Approved By:	[redacted]		
Position:	Clinical Sciences Lead		
Company	Medicines for Malaria Venture		
Approved By:	[redacted]		
Position:	Statistician Group Leader		
Company	Sanofi		

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1.0	19SEP2019	[redacted]	Not Applicable
2.0	19DEC2019		Updated to reduce the number of statistical outputs and focus on key outputs for the primary population of interest (Cohort 3 and 4).

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ABBREVIATIONS

ACPR	Adequate Clinical and Parasitological Response
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BDR	Blinded Data Review
BUN	Blood Urea Nitrogen
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ETF	Early treatment failure
FCT	Time to fever clearance
FQ	Ferroquine
HLGT	High Level Group Term
HLT	High Level Term
IA	Interim Analysis
IMP	Investigational Medicinal Product
IVRS	Integrated Voice Recognition System
LCF	Late clinical failure
LDH	Lactate Dehydrogenase
LLQ	Lower Limit of Quantification
LPF	Late parasitological failure
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-To-Treat
NAI	Naturally Acquired Immunity
PCE	Parasite Clearance Estimator
PCR	Polymerase Chain Reaction
PCSA	Potentially Clinically Significant Abnormality

PCT	Time to parasite clearance
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PRR	Parasite Reduction Ratio
PT	Preferred Term
RBC	Red Blood Cell
RDT	Rapid Diagnostic Test
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SoC	Standard of Care
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
ULQ	Upper Limit of Quantification
WBC	White Blood Cell
WHO	World Health Organization

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety, pharmacokinetics (PK), pharmacokinetic/pharmacodynamics (PK/PD) and genotyping data for Protocol DRI12805 (Compounds: SSR97193/ferroquine [FQ] in association with artefenomel [OZ439]). It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.
This statistical analysis plan (SAP) is based on Amended Protocol No. 03 (i.e. integrating Protocol Amendment 03), dated 10 April 2019.
A Blinded Data Review (BDR) plan, defining populations for the interim and final analyses will be created to compliment this SAP. A separate Data Monitoring Committee (DMC) SAP is contained within the DMC Charter Version 5.0, dated 1 July 2019. Separate analysis plans will also be produced for the PK-ACPR analyses.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to determine whether a single dose combination of OZ439/FQ is an efficacious treatment for uncomplicated *P. falciparum* malaria in adults and children.

2.2. SECONDARY OBJECTIVES

The secondary objectives are:

To evaluate the efficacy of OZ439/FQ:

- To determine the incidence of recrudescence and re-infection.
- To determine the time of fever and parasite clearances.

To evaluate the safety and tolerability of OZ439/FQ in adults and children.

To evaluate the pharmacokinetics of OZ439/FQ:

- To characterize the pharmacokinetics of OZ439 in plasma, FQ and its active metabolite SSR97213 in blood.
- To determine the blood/plasma ratio for FQ and SSR97213 in some patients at limited time points in selected sites.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are to further explore efficacy of OZ439/FQ:

- To evaluate the proportion of patients with gametocytes at each parasitological assessment.
- To characterize gametocyte carriage.
- To evaluate the relationship between Adequate Clinical and Parasitological Response (ACPR) and exposure to OZ439/FQ.
- To explore the relationship between Kelch-13 genotype and parasite clearance kinetics.
- To explore in vitro drug resistance of *P. falciparum* infecting patients >14 years old in Vietnamese sites.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a multicenter, multinational, randomized, double-blind, single-dose, 3 to 4 dose-regimen study in patients with uncomplicated *P. falciparum* malaria. Adults and children were to be included sequentially in four cohorts through a progressive age step-down procedure and FQ dose step-up procedure. Dose groups could be dropped during the study following DMC decision or futility analyses.

The cohorts are defined as follows:

- Cohort 1: 14 years<age <70 years and body weight ≥35 kg
- Cohort 2: 5 years<age≤14 years
- Cohort 3: 2 years<age≤5 years
- Cohort 4: 6 months<age≤2 years

After a screening phase of up to 1 day, patients were to be centrally randomized to one of 4 possible treatment groups (OZ439/FQ: 800/400 mg, 800/600 mg, 800/900 mg and 800/1200 mg) via Integrated Voice Recognition System (IVRS) using permuted block randomization schedules. Inclusion of cohorts of decreasing age was based on review of safety data from the preceding higher age group by the DMC, as shown in Figure 1. Recruitment to the 800/1200 mg dose was dependent on a positive safety assessment by the DMC following review of the PK-QTc relationship of treatments 1, 2 and 3 in Cohort 1a and treatments 3 and 4 in Cohort 1b.
This randomization was to be stratified by region, (however due to the decision to stop recruitment in Asia [see Section 3.1.1], no patients from Asia were recruited into cohorts 3 and 4 and therefore this was not required after cohort 2) and within Africa, age class (14-70 years/Africa; 5-14 years/Africa; 2-5 years/Africa; 6 months - 2 years/Africa).

For patients ≥35 kg:

Scenario A: design with 3 treatment arms (OZ439/FQ 800/400 mg, 800/600 mg and 800/900 mg) if, following DMC review of Cohort 1a, the 4th treatment arm (OZ439/FQ 800/1200 mg) is not started or, is stopped following DMC review at the end of Cohort 1b.

Scenario B: design with 4 treatment arms (OZ439/FQ 800/400 mg, 800/600 mg, 800/900 mg and 800/1200 mg) if, following DMC review of Cohort 1a & 1b respectively, the 4th treatment arm (OZ439/FQ 800/1200 mg) is started and is continued after DMC reviews.

- Treatment arm 1 = OZ439 800 mg - FQ 400 mg
- Treatment arm 2 = OZ439 800 mg - FQ 600 mg
- Treatment arm 3 = OZ439 800 mg - FQ 900 mg
- Treatment arm 4 = OZ439 800 mg - FQ 1200 mg (if the DMC agrees to proceed with this dose).

For patients <35 kg:
Weight-adjusted doses for OZ439 predicted to achieve exposure (based on Area under the curve [AUC]) not exceeding 1.5-fold that of a 60 kg adult and not exceeding that of the lightest adult (35 kg) for the lightest patient in each weight band.

Weight adjusted doses for FQ predicted to achieve FQ and SSR97213 exposure (based on mean Cmax and AUC) not exceeding 1.3-fold that of a lightest adult (35 kg) for the lightest patient in each weight band.

This study is an adaptive design with pre-defined interim analyses to drop doses with a high probability of futility early. Assuming the dose is not dropped early, recruitment will continue until a maximum of 150 evaluable patients per treatment arm is reached. Figure 1 shows the age step-down & FQ dose step-up procedures.

Patients likely to have higher naturally acquired immunity (NAI) i.e. African patients >5 years old to <70 years old were only to be considered for safety review, and patients likely to have lower NAI (African children ≤5 years and all Asian patients) were to be considered for safety review, and also for interim futility analyses.

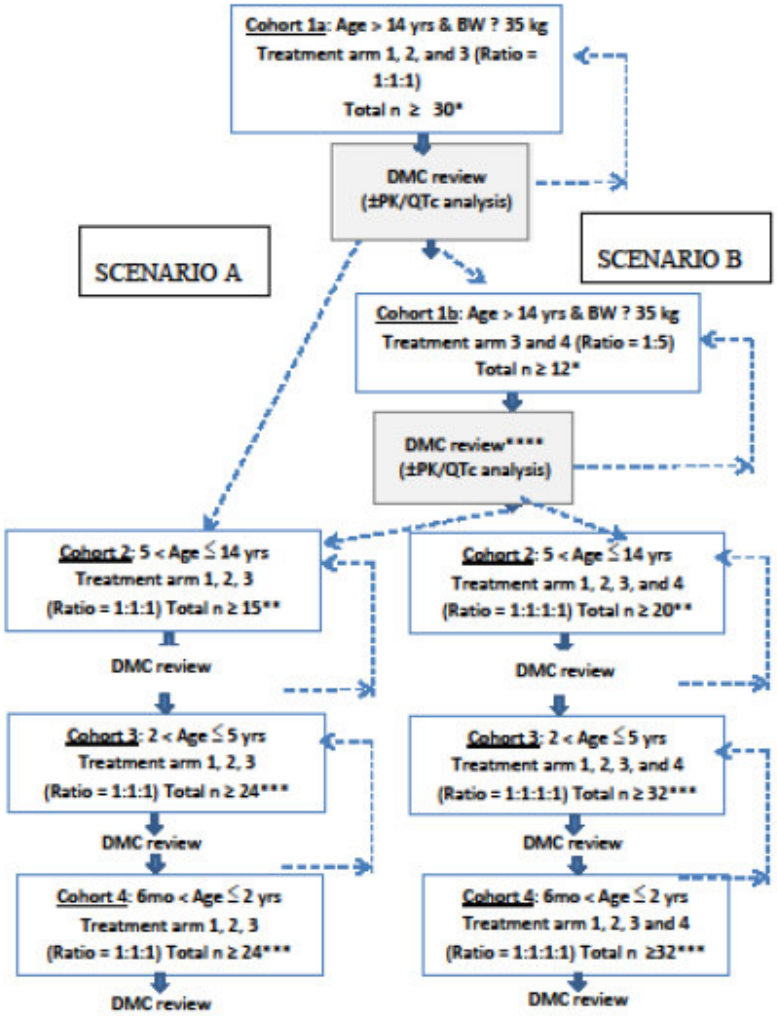
3.1.1. PROTOCOL AMENDMENT 3

Recruitment was stopped in Asia (Vietnam) on the guidance of the DMC, due to a low efficacy rate in this population. As a result of the study stop in Asia, Protocol Amendment 3 redefined the efficacy populations for the interim and final efficacy analyses to include only African children ≤5 years of age (i.e. Cohorts 3 and 4). Asian patients were excluded from the efficacy populations. A total of 21 Asian patients were recruited prior to the recruitment stop. The terms low NAI and high NAI used in the Protocol will not now be used within the Clinical Study Report (CSR) as further detailed in Section 3.4 of this SAP.

Thus, in the scenario where no dose regimen is dropped, a maximum of approximately 662 African patients (62 patients in Cohorts 1 and 2 and about 150 patients per dose group in Cohorts 3 and 4) will be recruited and

randomized from approximately 18 sites, to achieve approximately 600 African patients ≤5 years of age evaluable for the primary endpoint of Polymerase Chain Reaction (PCR)-adjusted ACPR at Day 28 (see Section 12.1 for definition of PCR-adjusted ACPR, and Section 5.4 for definition of patients evaluable for PCR-adjusted ACPR), plus the additional 21 Asian patients.

Figure 1: DMC safety review for age step-down & FQ dose step-up procedures



*:A minimum number of 10 patients (Cohort 1) per treatment arm for DMC safety & PK/QTc evaluation.

**: A minimum number of 5 patients (Cohort 2) per treatment arm for DMC review

***: A minimum number of 8 patients (Cohorts 3 & 4) per treatment arm for DMC review

After all these age step-down stages, the recruitment will be fully open. Approximately 62 patients will be recruited in Cohorts 1 and 2 for Scenario B. The remaining patients will comprise Cohorts 3 and 4. At least 10% of the lower NAI population will come from African patients of Cohort 4 (patients 6 months ≤2 years, Protocol Amendment 3).

****: DMC review before starting Cohort 2 recruitment will be made on pooled data (Cohorts 1a & 1b) with a total number of patients N ≥42.

3.1.2. DETERMINATION OF SAMPLE SIZE

Given the adaptive nature of the study design, the total number of patients to be recruited can only be estimated. Simulations for different PCR-adjusted ACPR response rates at Day 28 showed that a sample size of 150 evaluable patients per treatment arm will provide ≥80% probability to reject the null hypothesis (H0: probability of PCR-adjusted ACPR at Day 28 ≤0.90) at the final analysis, for the true rate of 96.4%. See table in Appendix 4 for details on power for different sample size and success rate hypotheses.

Recruitment will continue until each treatment arm is deemed to be futile or until 150 evaluable patients per treatment arm is reached.

In addition, a minimum of 15 African patients >5 years per treatment arm (likely to have higher NAI and therefore not included in the efficacy analysis populations i.e. the modified Intent-To-Treat [mITT] and Per Protocol [PP] populations) will be included for the DMC safety review.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 1.1 of the Protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

The following items will differ in this SAP from what is specified in Protocol Amendment 3:

- The final analysis will include patient data from doses that were stopped early for futility. Final efficacy results may be different from the Interim Analysis (IA) because recruitment may continue during the IA.
- The Protocol defines a “lower” NAI population and a “higher” NAI population. Since Asian patients are now excluded from the main analysis population, these population names are no longer useful and are therefore not used in the SAP. Instead, we define the efficacy populations (mITT and PP) which are based on the protocol defined “lower” NAI population in Africa. A separate population with African >5 years is defined based on the protocol defined “higher” NAI population.
- The Safety population defined in the SAP differs from the Protocol definition in that it also includes Asian patients. Safety sub-populations are, however, defined in the SAP, and the sum of the Cohort 3 and 4 Safety (C3&4SAF) and African >5 years Safety (A5SAF) sub-populations equate with the safety population described in the Protocol.

- 2 separate PK/PD populations will be used for analysis of PK-ACPR and PK-QTc. This was ambiguous in the Protocol. The PK-QTc population is defined in this document and the PK-ACPR population is defined in a separate analysis plan.
- Given sub-populations have been defined, no by cohort summaries are planned.
- Protocol Section 11.2 defined screened patients as "as any patient who signed the informed consent and met the inclusion criteria" while in the SAP, Section 8 defines screened patients as all patients who signed informed consent irrespective of adherence to eligibility criteria.
- The Protocol specifies that the table of treatment-emergent AEs (TEAEs) will be sorted by the internationally agreed System Organ Class (SOC) order then by Preferred Terms (PTs) sorted in alphabetical order within SOC, however this ordering is not logical, therefore these tables will be sorted by the internationally agreed SOC order then by decreasing frequency of PTs in the total column.
- QTcB parameter is added as ECG parameter.

3.4. CHANGES TO ANALYSIS FROM SAP VERSION 1.0

The statistical analyses were reduced to focus the analysis on the key outputs of relevance for the stage of development, and for the primary population of interest (Cohort 3 and 4).

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analyses for DMC meetings (refer to DMC SAP contained within DMC Charter)
- Interim Analyses (test for futility; Section 4.2)
- Final Analysis (efficacy outcomes: Section 12, safety outcomes: Section 13)

4.1. DATA MONITORING COMMITTEE (DMC)

A DMC SAP describing the methodology and presentation of results for the DMC meetings is contained within the DMC Charter Version 5.0, dated 1st July 2019.

4.2. INTERIM ANALYSES

Timing

As planned in the Protocol, up to 4 interim futility analyses will be performed during the conduct of the study to stop recruitment in treatment arm(s) deemed to be futile.

Futility will be assessed in the PP population and is based on the primary endpoint of the study (PCR-adjusted

ACPR at Day 28). The PP population evaluable for the PCR-adjusted ACPR excludes patients with re-infection as described in section 13.1.

The first IA will be performed on approximately 50 evaluable patients per treatment arm, who must have completed the 28-day efficacy assessment (within the allowed time-window of Day 28, see Table A in Section 6.4.1).

Based on an estimated proportion of patients expected to be non-evaluable for the primary endpoint, approximately 220 randomized patients would be needed in order to have approximately 200 evaluable patients for the primary efficacy endpoint.

Thereafter, subsequent interim futility analyses will be performed when each additional 25 evaluable patients per treatment arm are available (i.e. 75 patients/treatment arm for the 2nd IA, 100 patients/treatment arm for the 3rd IA, 125 patients/treatment arm for the 4th IA). Since the number of randomized patients to achieve the target number of patients evaluable for the primary endpoint may change during the study dependent on geography and season etc., this will be tracked during the study to estimate the timing of each IA.

Recruitment will continue until each treatment arm is deemed to be futile or until a maximum of approximately 150 evaluable patients per remaining treatment arm reach the Day 28 evaluation point.

At each IA, a treatment arm is stopped for futility if the posterior probability of H0 (that is, response rate is below 90%) given the data accumulated at the look for the treatment arm in question is too large, that is, Pr(H0|data) ≥0.30. The treatment arm advances to the next stage if the above condition is not met (even if the observed response rate is 95% or greater).

A data cut off will be applied before each interim and DMC analysis, the date of this cut will be discussed and decided upon before each delivery.

The results of each interim futility analysis will be reviewed by the DMC.

Method

The futility for a given dose i ($1 \leq i \leq 4$) will be tested as follows:
The observed proportion of PCR-adjusted ACPR at Day 28 in treatment arm i at the time of the IA will be treated as an observation from a binomial distribution, with unknown probability of success p^i having a beta prior.
To take into account initial trust (prior information) on the unknown probability of success p^i, p^i will be following an informative *Beta(9.5, 0.5)* prior distribution.

The prior distribution of p^i will then be updated in light of the observed number of PCR-adjusted ACPR at Day 28 in the treatment arm i at the time of the IA using Bayes' formulae, to obtain the posterior distribution of p^i: $Bêta(9.5+ n^i_1, 0.5+N^i- n^i_1)$, where n^i_1 is the number of PCR-adjusted ACPR observed at Day 28 out of N^i in the

treatment arm *i*.

The following decision rule then will apply:

- If $P(X \leq 0.9) \geq 0.3$, where X is a random variable following the posterior distribution $Bêta(9.5+ n^{i}_{1}, 0.5+N^{i}- n^{i}_{1})$, then the treatment arm *i* is deemed to be futile and stopped.
- If $P(X \leq 0.9) < 0.3$, where X is a random variable following the posterior distribution $Bêta(9.5+ n^{i}_{1}, 0.5+N^{i}- n^{i}_{1})$, then the treatment arm *i* is kept until next step.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed following finalization of this SAP, relevant set of the Tables, Listings and Figures shells, the final analysis population assignments, database lock and routine study unblinding.

The final analysis is to be performed on a clean database. The database will be considered clean when:

- All outstanding data issues and queries resolved.
- All unresolvable data issues documented in the data handling report (DHR) from Data Management.
- All coding of medications and adverse events (AEs) completed.
- Serious adverse events (SAEs) reconciliation completed.
- All reconciliation of vendor data with the electronic Case Report Form (eCRF) data completed successfully.

At the final analysis, the null hypothesis will be tested and binary endpoint for the primary outcome; PCR-adjusted ACPR at Day 28, will be analyzed in a frequency table i.e. frequency, percentage and exact binomial 95% confidence intervals (two-sided by using Clopper-Pearson method for calculating binomial confidence intervals) on the PP population by treatment arm. Efficacy of the treatment arm is demonstrated if the lower limit of the exact 95% confidence interval of PCR-adjusted ACPR rate is >90% (see Section 13: Efficacy Outcomes for further details).

5. ANALYSIS POPULATIONS

Analysis populations are described below. Further details on the allocation of patients to analysis populations will be described in the BDR plan for this study. Agreement and authorization of patients included/ excluded from each analysis population will be conducted prior to the unblinding of the study and will be documented in a BDR report.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed

separately.

5.1. RANDOMIZED POPULATION [RND]

The randomized population (RND) includes all patients who have given their informed consent and who have been allocated to a randomized treatment regardless of whether the treatment kit was used or not. For analyses and displays based on RND population, patients will be classified according to the treatment to which they were randomized.

5.2. SAFETY POPULATIONS [SAF]

The safety population (SAF) will contain all patients in the RND population who receive at least one dose or part of a dose of the study medication. Patients will be classified according to the treatment actually received.

In addition, randomized patients for whom it is unclear whether they took the study medication will be included in the SAF population as randomized.

In case of an OZ439 re-dosing mistake (e.g., erroneous kit dispensing at protocol planned re-dosing, protocol planned re-dose not performed, or re-dose performed wrongly), patients will be presented in the treatment group corresponding to the initial dosing. Such cases will be tracked through quantitative deviations.

For patients erroneously re-dosed with FQ, patients will be presented in the treatment group with the FQ dose which is closest to the sum of the FQ doses actually administered to the patient. Such cases can only be tracked through qualitative deviations.

Non-randomized but treated patients will not be part of the SAF population. However, their safety data will be listed separately. Patients taking only a fraction of their randomized treatment but for whom the actual amount received is unknown will be presented per treatment, as randomized.

For the purpose of statistical analysis and presentation of safety data, patients will be summarized using the sub-populations described below:

5.2.1. COHORTS 3 AND 4 SAFETY POPULATION [C3&4SAF]

Includes all African patients ≤5 years of age valid for the SAF population. Patients will be classified according to the treatment actually received.

5.2.2. ASIAN SAFETY POPULATION [ASAF]

Includes all Asian patients valid for the SAF population. Patients will be classified according to the treatment actually received.

5.2.3. AFRICAN >5 YEARS SAFETY POPULATION [A5SAF]

Includes all African patients aged >5 years valid for the SAF population. Patients will be classified according to the treatment actually received.

5.3. MODIFIED INTENT-TO-TREAT POPULATIONS

5.3.1. MODIFIED INTENT-TO-TREAT POPULATION [MITT]

The mITT population includes all randomized African patients ≤5 years with parasitologically confirmed *P. falciparum* malaria at screening/ baseline, who received at least the single administration OZ439/FQ, and excluding patients who required rescue treatment due to vomiting during investigational medicinal product (IMP) administration. (Patients required rescue treatment if they vomited during or after FQ dosing and before OZ439 administration, or if they vomited within 5 minutes of OZ439 re-dosing after already having vomited within 5 minutes of the first OZ439 dosing).
African patients >5 years and Asian patients will not belong to mITT.

For analyses and displays, patients will be classified according to the randomized treatment regardless of actual treatment received.

For the purpose of statistical analysis and presentation of efficacy data, patients will also be summarized using the sub-populations described below. Their derivation will follow the same rules as for the main population of interest i.e. the mITT.

5.3.2. ASIAN MODIFIED INTENT-TO-TREAT POPULATION [AMITT]

Includes all patients valid for the Asian safety population (ASAF) as defined in Section 5.2.2 with parasitologically confirmed *P. falciparum* malaria at screening/ baseline, who received at least the single administration OZ439/FQ, and excluding patients who required rescue treatment due to vomiting during IMP administration. (Patients required rescue treatment if they vomited during or after FQ dosing and before OZ439 administration, or if they vomited within 5 minutes of OZ439 re-dosing after already having vomited within

5 minutes of the first OZ439 dosing). Patients will be classified according to the randomized treatment regardless of actual treatment received.

5.3.3. AFRICAN >5 YEARS MODIFIED INTENT-TO-TREAT POPULATION [A5MITT]

Includes all patients valid for the African >5 years safety population (A5SAF) as defined in Section 5.2.3 with parasitologically confirmed *P. falciparum* malaria at screening/ baseline, who received at least the single administration OZ439/FQ, and excluding patients who required rescue treatment due to vomiting during IMP administration. (Patients required rescue treatment if they vomited during or after FQ dosing and before OZ439 administration, or if they vomited within 5 minutes of OZ439 re-dosing after already having vomited within 5 minutes of the first OZ439 dosing). Patients will be classified according to the randomized treatment regardless of actual treatment received.

5.4. PER-PROTOCOL POPULATIONS [PP]

The PP population is defined as all mITT patients without any major protocol deviations affecting efficacy up to, and who are evaluable for PCR-crude ACPR at a pre-defined timepoint in the study. For further information regarding protocol deviations please refer to the blinded data review (BDR) plan for this study.

The composition of the PP populations for the primary (Day 28) and each secondary timepoint (Day 42 and Day 63) may differ depending on the timing of the occurrence of the major protocol deviations.

For analyses and displays, patients will be classified according to the randomized treatment.

Note, “evaluable for PCR-adjusted ACPR” relates to recrudescent infections only and hence treats re-infections as follows: Patients with re-infections occurring before the relevant endpoint day (Day 28, 42, 63) are counted as missing. Patients with re-infections occurring on the day of evaluation, (Day 28, 42, 63) are included in the population (and are counted as cured). See Table F in Section 13.3 for details of the derivation criteria of treatment outcome for crude and PCR-adjusted ACPR for the PP and mITT populations.

5.4.1. PER-PROTOCOL POPULATION AT DAY 28 [PP28]

The primary efficacy population will be the PP population at Day 28. This population contains all patients valid for the mITT population (defined in Section 5.3.1) without major protocol violations impacting efficacy assessment, who are evaluable for PCR-crude ACPR at Day 28.

Patients with other species of malaria infection at baseline (including mixed infection with *P. falciparum*) are

excluded from the PP28 population.

5.4.2. PER-PROTOCOL POPULATION AT DAY 42 [PP42]

The PP population at Day 42 contains all patients valid for the mITT population (defined in Section 5.3.1) without major protocol violations impacting efficacy assessment, who are evaluable for PCR-crude ACPR at Day 42.

Patients with other species of malaria infection at baseline (including mixed infection with *P. falciparum*) are excluded from the PP42 population.

5.4.3. PER-PROTOCOL POPULATION AT DAY 63 [PP63]

The PP population at Day 63 contains all patients valid for the mITT population (defined in Section 5.3.1) without major protocol violations impacting efficacy assessment, who are evaluable for PCR-crude ACPR at Day 63.

Patients with other species of malaria infection at baseline (including mixed infection with *P. falciparum*) are excluded from the PP63 population.

For the purpose of statistical analysis and presentation of efficacy data, patients will also be summarized using the sub-populations described below. Their derivation will follow the same rules as for the main population of interest i.e. the PP28, PP42 and PP63.

5.4.4. ASIAN PER-PROTOCOL POPULATIONS [APP28, APP42, APP63]

Includes all patients valid for the Asian mITT population (AmITT) as defined in Section 5.3.2 without major protocol deviations affecting efficacy up to, and who are evaluable for PCR-crude ACPR at a pre-defined timepoint in the study.

5.4.5. AFRICAN >5 YEARS PER-PROTOCOL POPULATIONS [A5PP28, A5PP42, A5PP63]

Includes all patients valid for the African >5 years mITT population (A5mITT) as defined in Section 5.3.3 without major protocol deviations affecting efficacy up to, and who are evaluable for PCR-crude ACPR at a pre-defined timepoint in the study.

5.5. PHARMACOKINETIC POPULATION

The PK population will comprise all treated patients (SAF) with at least one evaluable blood sample for PK post double-blind IMP administration and with adequate documentation of date of dosing and date of sampling.

5.6. PHARMACOKINETIC/PHARMACODYNAMIC POPULATION

There are two PK/PD populations. An efficacy PK/PD population for exploration of the relationship between concentration and ACPR, and a PK/PD ECG population for exploration of the relationship between concentration and ECG. The efficacy PK/PD population will be defined in a separate analysis plan and will be reported in a separate PK/PD report. The PK/PD ECG population will contain all patients included in the PK population and having a baseline QTc assessment and at least one post-baseline assessment in QTc evaluation regarding the three PK/QTc analyses (one for Cohort 1a, a second polling Cohorts 1a & 1b, and final analysis including all cohorts).

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Reference start date is defined as the day of the first dose of study medication (Day 0 is the day of the first dose of study medication). For patients randomized but not treated, reference start date is defined as the day of randomization. Study Day will be calculated from the reference start date and will be used to show start/ stop day of assessments and events. Study Day will appear in every listing where an assessment date or event date appears: *Study Day = (date of event – reference date)*.

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix 2 Partial Date Conventions.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the value collected on Day -1 (or Day 0 if screening and IMP administration are performed on the same day). If any of the scheduled baseline tests are repeated, the last rechecked values will be considered as baselines, provided they were done before the start of IMP administration.

For patients randomized but not treated, baseline is defined as the last non-missing measurement taken on or before the reference start date.

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

Unscheduled visit measurements of safety data, i.e. laboratory data, vital signs, and electrocardiogram (ECG), will be included in the by-time point summaries, and will be used for computation of baseline, worst values, and potentially clinically significant abnormalities (PCSAs).

In the case of a retest (same visit number assigned), the measurement nearest the visit date will be used for by-visit summaries.

Early termination data will be mapped to the next available visit number for by-visit summaries and also reported together as a separate End of Treatment visit.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. WINDOWING CONVENTIONS

Time windows are used to assigned protocol planned time points based on the actual timing of the considered assessment rather than based on the theoretical timing of the visit it comes from.

The actual hour of an assessment (scheduled or unscheduled) for which the date and time are available is calculated in number of hours from the date and time of IMP start as: *(date & time of assessment - date & time of IMP start)*.

While the actual day of an assessment is calculated in number of days from the date of IMP start as: *(date of assessment - date of IP start)*.

In case, the actual timing is outside below time windows, then the assigned time point comes down to the actual timing.

Handlings of assessments performed outside defined time windows will depend on the analyses and are detailed in dedicated sections, as well as handling of several assessments performed within the same time window.

6.4.1. TIME WINDOWS FOR EFFICACY EVALUATION

Before Day 4, time points assigned to scheduled or unscheduled parasitemia and to concomitant - i.e. from the same visit - body temperature, will be based on the actual hour of the blood thick film and allowed time windows, as specified in Table A. In case, the blood thick film is missing at a visit, but body temperature assessment is

available, then the theoretical time point of the visit will be assigned because only the date (no time) of assessment is collected for body temperature.

Table A: Time windows definition for assessments performed on or before Day 3

Protocol planned time point	Allowed deviation from targeted hour	Corresponding window of time for blood film actual hour
Hour 6	-1/+2 hours	5 hours to 8 hours
Hour 12*	-1/+2 hours	11 hours to 14 hours
Hour 18	-1/+2 hours	17 hours to 20 hours
Hour 24 (Day 1)	-1/+2 hours	23 hours to 26 hours
Hour 36 (Day 1)	-2/+3 hours	34 hours to 39 hours
Hour 48 (Day 2)	± 3 hours	45 hours to 51 hours
Hour 72 (Day 3)	± 4 hours	68 hours to 76 hours

* Scheduled for cohort 1 only.

From Day 4, time points assigned to scheduled or unscheduled parasitemia or body temperature will be based on the actual day of assessment and allowed time windows, as specified in Table B.

Table B: Time windows definition from Day 4

Protocol planned time point	Allowed deviation from targeted day	Allowed window of time for day of assessment
Day 5	± 1 day	4 days to 6 days
Day 7	+ 1 day	7 days to 8 days
Day 10	± 1 day	9 days to 11 days
Day 14	- 2 days	12 days to 14 days
Day 15-18	Not applicable	15 days to 18 days
Day 21	± 2 days	19 days to 23 days
Day 24-25	Not applicable	24 days to 25 days
Day 28	- 2 days / + 10 days	26 days to 38 days
Day 42	- 3 days / + 17 days	39 days to 59 days
Day 63	- 3 days / + 17 days	60 days to 80 days

6.4.2. TIME WINDOWS FOR SAFETY EVALUATION

In the case where more than one assessment of a safety parameter falls within the same time window, only the assessment closest to the targeted time point will be used. In cases where two assessments are equally close to the targeted time point, the first assessment will be used.

6.4.2.1. TIME WINDOWS FOR LABORATORY EVALUATION

Table C: Time windows for laboratory evaluation

Protocol planned time point	Time window for actual day of laboratory assessment
Baseline	Before IMP start
Day 3	After IMP start to Day 4
Day 7	Day 5 to Day 10
Day 14	Day 11 to Day 17
Day 21*	Day 18 to Day 24
Day 28	Day 25 to Day 31

* only for patients >5 years old.

6.4.2.2. TIME WINDOWS FOR VITAL SIGNS EVALUATION

Only the date (no time) of assessment is collected for vital signs, therefore, time windows are only defined for actual timing greater or equal to 4 days. For lower timings, the eCRF visit will be used. In particular, baseline will be Visit 1 assessment.

Table D: Time windows for vital signs evaluation

Protocol planned time point	Time window for actual day of vital sign assessment
Day 7	Day 4 to Day 8
Day 10	Day 9 to Day 11
Day 14	Day 12 to Day 17
Day 21	Day 18 to Day 24
Day 28	Day 25 to Day 34
Day 42	Day 35 to Day 44
Day 63	Day 45 to Day 69

6.4.2.3. TIME WINDOWS FOR ECG EVALUATION

Table E: Time windows for ECG evaluation

Protocol planned time point	Time window for ECG assessment timing
Baseline	Before IMP start
Hour 2	After IMP end to <3 hours

Protocol planned time point	Time window for ECG assessment timing
Hour 4	3 hours to <5 hours
Hour 6	5 hours to <7 hours
Hour 8	7 hours to <10 hours
Hour 12	10 hours to <18 hours
Hour 24	18 hours to <36 hours
Day 3	36 hours to <Day 5
Day 7	Day 5 to <Day 9

Using the date and time of the first record from the triplicate ECG before Day 4, and using only the date thereafter.

6.5. STATISTICAL TESTS

The default significant level will be 5%; confidence intervals will be 95%, all tests will be two-sided, and no adjustment for multiplicity will be applied, unless otherwise specified in the description of the analyses.

6.6. COMMON CALCULATIONS

Demographic formulas:

- Age at randomization in years: (date of randomization - date of birth)/365.25
- Age at randomization in months: (date of randomization - date of birth)/30.4375
- Time from first diagnosis of current malaria infection in days: (date of randomization - date of diagnosis of current malaria infection)

Change from baseline: *(test value at visit x – baseline value)*
Percent change from baseline: *(change from baseline / baseline value)*100*

6.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4

7. STATISTICAL CONSIDERATIONS

7.1. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally. Randomization to

treatment arms within Cohort 2 is stratified by region.

7.2. MISSING DATA

Missing efficacy data will be handled as described in Section 13.3 and in each specific subsection of Section 13 of this SAP.

For categorical variables, patients with missing data will not be included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data will be presented.

7.2.1. HANDLING OF MEDICATION MISSING/PARTIAL DATES/TIMES

No imputation of medication start/end dates will be performed. If a medication date is missing or partially missing the conventions detailed in Appendix 2 will be used to assign the medication to a period (prior, concomitant or post treatment), note medications can occur in more than one period.

7.2.2. HANDLING OF AES WITH MISSING OR PARTIAL DATE/TIME OF ONSET

No imputation of adverse event start/end dates will be performed. If an AE date is missing or partially missing the conventions detailed in Appendix 2 will be used to assign the AE as treatment-emergent or not.

7.2.3. HANDLING OF AES WHEN MISSING DATE AND TIME OF FIRST IMP ADMINISTRATION

When the date and time of the first IMP administration is missing, all AEs that occurred on or after the day of randomization should be considered as TEAEs. The exposure duration should be kept as missing.

7.2.4. HANDLING OF MISSING ASSESSMENT OF RELATIONSHIP OF AES TO IMP

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the AE considered as such in the frequency tables of possibly related AEs, but no imputation should be done at the data

level.

7.2.5. HANDLING OF PCSAS

If a patient has a missing baseline, he will be grouped in the category "normal/missing at baseline".

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; e.g. for eosinophils the PCSA is >0.5 GIGA/L or > Upper Limit of Normal (ULN) if ULN ≥0.5 GIGA/L; when ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or considered in the computation of PCSA values.

7.3. MULTIPLE COMPARISONS/ MULTIPLICITY

No adjustment for multiplicity of comparisons will be applied for primary or for secondary analyses. The overall type I error rate may therefore exceed 5%.

7.4. EXAMINATION OF SUB-POPULATIONS AND SUBGROUPS

Summaries will be produced for the following sub-populations as described in Section 13.4:

- Cohorts 3 and 4 combined
- Asian
- African >5 years

It should be noted that the study was not designed to detect treatment effect with high statistical power within sub-populations other than the sub-population that forms the efficacy population (Cohorts 3 and 4 combined).

The following subgroups will be assessed and described within the efficacy analysis sections. These subgroups will be used to further explore the data collected for the mITT and PP populations only (i.e. Cohort 3 and 4).

- Country (Benin, Gabon, Kenya, Mozambique, Uganda, Burkina Faso)
- Baseline parasitemia (≤Q1, >Q1 to ≤ Q2, >Q2 to ≤Q3, >Q3)
- Age at randomization (≤2.0 years, >2.0 to ≤5.0 years)
- Weight at screening (<7 kg, ≥7 to <10 kg, ≥10 to <15 kg, ≥15 to <24 kg)

8. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study.
Patient disposition and withdrawals, and reasons for exclusion from each analysis population and protocol deviations, including inclusion and exclusion criteria will be presented for the RND population.

This section describes patient disposition for both patient study status and the analysis populations.

Screened patients are defined as any patient who signed the informed consent.

Randomized patients consist of all patients for whom there is a signed informed consent/ assent form and who have had a treatment kit number allocated and recorded in the IVRS database, regardless of whether the treatment kit was used or not.

For patient study status, the total number of patients in each of the following categories will be presented in the CSR using summary tables Cohort 3 and 4 combined, Asian, and African >5 years separately and also overall:

- Screened patients
- Screen failure patients and reasons for screen failure
- Non-randomized but treated patients, only if occurring
- Randomized patients
- Randomized but not treated patients, only if occurring
- Randomized and treated patients
- Patients who met criteria for established anti-malarial treatment
- Patients who prematurely discontinued the study (overall and by main reason for discontinuation)
- Status at last study contact (information coming from the patient status panel and computation of lost to follow-up status as defined below).

For all categories of patients (except for the screened and non-randomized categories) percentages will be calculated using the number of randomized patients in the considered population as denominator in tables giving numbers and percentages by treatment group. This summary will also be provided by treatment group within each age range and country in the Cohort 3 and 4 population.

A patient is considered lost to follow-up at the end of the study if he/she is not assessed using the procedure normally planned for the end-of-study visit and if the time from the last successful contact (from the vital patient status case report form) to the last protocol planned visit is greater than 3 days.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, and other critical or major deviations will be summarized in tables giving numbers and percentages of deviations by treatment group, in the mITT population.

Additionally, the various analysis populations (e.g. safety, efficacy, pharmacokinetics, pharmacokinetics/pharmacodynamics, exploratory) will be summarized in a table giving numbers and percentages of patients by treatment group, in the randomized population.

Safety populations:

- Cohorts 3 and 4 Safety population
- Asian Safety population
- African >5 years Safety population

Efficacy populations:

- PP populations (at Days 28, 42 and 63 and overall)
- mITT populations

Pharmacokinetics populations:

- PK population
- PK/PD population

A listing of populations with reasons of exclusion will also be provided.

8.1. RANDOMIZATION AND DRUG DISPENSING IRREGULARITIES

Randomization and drug-dispensing irregularities occur whenever:

A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, c) a patient is randomized twice, or d) a non-existent patient is randomized.

OR

A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a non-randomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the CSR. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Non-randomized, treated patients will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

- Kit dispensation without IVRS transaction
- Erroneous kit dispensation
- Kit not available
- Non-eligible patient randomized by error
- Patient randomized twice
- Stratification error
- Randomization of a non-existent patient
- Patient switched to another site

9. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the RND population.

No statistical testing will be carried out for demographic or other baseline characteristics.
Continuous and qualitative variables will be summarized using descriptive statistics. Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each treatment group and overall. Categorical and ordinal data will be summarized using the number of available data, the number and percentage of patients in each category by treatment group and overall.

9.1. DEMOGRAPHIC CHARACTERISTICS

The following demographic characteristics will be captured and be reported for this study. Parameters will be summarized by treatment group and overall for all patients, and separately for Cohorts 3 and 4 combined, African patients >5 years sub-population and Asian patient sub-population. Analyses for the C3&4SAF population will be included in the appendices if the size of the C3&4SAF population is different (>10%) from the size of that in the RND population for any treatment group.

- Gender (Male, Female)
- Race (White, Black or African American, Asian, Other)
- Region (Asia, Africa), derived from the patient's site number. Note: Region will be captured only on the all randomized patients summary table as by definition the region will be 'Africa' for summary tables on the Cohorts 3 and 4 and on the African patients >5 years sub-populations and 'Asia' for summary table on the Asian patient sub-population.
- Age at randomization in years to 1 decimal place (quantitative and qualitative variables: ≤2, >2 – ≤5, >5 – ≤14, >14 - <18, ≥18)
- Age at randomization in months to 1 decimal place for Cohort 3 and 4 summary table
- Weight at screening in kg (quantitative variable recorded to 1 decimal place, qualitative variable: (<5, ≥5 - <7, ≥7 - <10, ≥10 - <15, ≥15- <24, ≥24 - <35, ≥ 35))
- Body Mass Index (BMI) at screening in kg/m^2 (quantitative variable recorded to 1 decimal place,

qualitative variable: (<30, ≥30) for summaries of African >5 years and Asian sub-populations

9.2. OTHER BASELINE CHARACTERISTICS

No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

No specific description of the efficacy parameters will be provided at baseline. If relevant, the baseline values will be described along with each efficacy analysis.

9.2.1. DISEASE CHARACTERISTIC AT BASELINE

Time in days from first diagnosis of current malaria infection as quantitative and qualitative (0, 1 - 2, >2) variables.
Parameter will be summarized by treatment group and overall for all patients and separately for Cohorts 3 and 4 combined, African patients >5 years sub-population and Asian patient sub-population. For the Cohorts 3 and 4, parameter will also be summarized within each country. Analyses for the C3&4SAF population will be included in the appendices if the size of the C3&4SAF population is different (>10%) from the size of that in the RND population for any treatment group.

Any technical details related to computation are described in Section 6.6.

9.3. SURGICAL AND MEDICAL HISTORY

Medical or surgical history other than uncomplicated malaria will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at IQVIA three months prior to database lock or data cut-off for interim deliverables. The dictionary version in effect will be displayed in a footnote.

Medical or surgical history reported in the eCRF will be presented by SOC and PT for the RND population.

10. MEDICATIONS

Medications taken prior to screening and until the end of the study, including anti-malarial medications other than IMP, are to be reported in the dedicated eCRF pages.

- 'Prior' medications are medications which started and stopped prior to the first dose of study medication.
- 'Concomitant' medications are medications which:

  - started prior to, on or after the first dose of study medication and started no later than 63 days following end of study medication,
    AND
  - ended on or after the date of first dose of study medication or were ongoing at the end of the study.
- 'Post' medications are medications which started more than 63 days following the last dose of study medication.

Any technical details related to imputation for missing dates are described in Appendix 2.

Prior, concomitant medications and anti-malarial medications will be presented for the RND population by treatment group and overall for all patients.

'Post' medications will be listed only.

All medications will be presented as coded by the World Health Organization (WHO)-Drug Dictionary considering the first digit of the anatomical therapeutic chemical (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). The dictionary version in effect will be displayed in a footnote. All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, patients may be counted more than once for a single medication. The numbers and percentages of patients in each level will be presented.

10.1. PRIOR MEDICATIONS

Prior medications, including anti-malarial medications taken prior to the first dose of study medication, will be summarized by anatomic and therapeutic category. The tables will be sorted by decreasing frequency of ATCs (anatomic or therapeutic categories) based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs, alphabetical order will be used.

10.2. CONCOMITANT MEDICATIONS

Concomitant medications, excluding anti-malarial medications taken after the first dose of study medication, will be summarized by anatomic and therapeutic category. The tables will be sorted by decreasing frequency of ATCs (anatomic or therapeutic categories) based on the incidence in the highest dose experimental arm. In case of equal frequency regarding ATCs, alphabetical order will be used.

In addition, the following specific medication may be summarized if deemed necessary:

- Paracetamol

10.3. ANTI-MALARIAL MEDICATION TAKEN AFTER STUDY MEDICATION

Anti-malarial medications other than IMP taken after the first dose of study medication will be summarized by anatomic and therapeutic category and presented according to three time periods in line with efficacy time points:

- Day 0 - Day 28 period: defined as the period of time starting the first IMP intake day and ending with the Day 28 time window defined in Section 6.4.1.
- Day 0 - Day 42 period: defined as the period of time starting the first IMP intake day and ending with the Day 42 time window defined in Section 6.4.1.
- Day 0 - Day 63 period: defined as the period of time starting the first IMP intake day and ending with the Day 63 time window defined in Section 6.4.1. For this period, summary will be repeated separately for Cohorts 3 and 4 combined, African patients >5 years sub-population and Asian patient sub-population.

11. STUDY MEDICATION ADMINISTRATION AND EXPOSURE

IMPs intake and exposure will be summarized by actual treatment group for the SAF population.
Study drug administration and associated information collected at the time of administration, such as fasting status, method of administration (capsule/suspension), total/partial administration and reason for partial administration, occurrence and timing of vomiting, will be summarized for initial administration of FQ and OZ, and where applicable, for OZ re-dosing.
Duration of administration will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum).

11.1. DERIVATIONS

Durations are calculated as follows:

- Time between FQ and OZ administrations, separately for FQ given as capsules and FQ given as solution:
  (start date and time of OZ intake) - (start date and time of FQ intake.)
  Not defined in cases where FQ is given after OZ.
- Duration of OZ administration, for initial administration and, if any, for re-dose separately:
  (end date and time of OZ intake) - (start date and time of OZ intake)
- Overall administration duration for initial administration:
  (end date and time of OZ intake (initial administration)) - (start date and time of FQ intake).
  Not defined in cases where FQ is given after OZ.

12. STUDY MEDICATION COMPLIANCE

Calculation of study medication compliance is not applicable as this is a single-dose treatment administration.

Cases of overdose (defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug) will constitute an adverse event of special interest (AESI - serious or non-serious) if symptomatic and will be listed as such. Asymptomatic overdose must be reported as a standard AE.

13. EFFICACY OUTCOMES

13.1. DEFINITIONS

Treatment outcome is to be established according to the following modified standard WHO classification. Refer to Glossary of the Protocol, according to a modification of the standard WHO classification, WHO Methods for surveillance of antimalarial drug efficacy, 2009:

Early treatment failure (ETF) (Day 1 to 3) = 'Yes' if any of the following criteria are met:

- Danger signs or severe malaria on Day 1, 2 or 3 in the presence of parasitemia.
- Parasitemia on Day 2 higher than on Day 0, irrespective of axillary temperature.
- Parasitemia on Day 3 with axillary temperature ≥37.5 ºC.
- Parasitemia on Day 3 ≥25% of count on Day 0.

Late clinical failure (LCF) (Day 4 to 63) = 'Yes' if any of the following criteria are met:

- Danger signs or severe malaria in the presence of parasitemia on any day between Day 4 and Day 63 in patients who did not previously meet any of the criteria of ETF.
- Presence of parasitemia on any day between Day 4 and Day 63 with axillary temperature ≥37.5 ºC (or history of fever) in patients who did not previously meet any of the criteria of ETF.

Late parasitological failure (LPF) = 'Yes' if any of the following criteria are met:

- Presence of parasitemia on any day between Day 7 and Day 63 and axillary temperature <37.5 ºC in patients who did not previously meet any of the criteria of ETF or LCF.

Treatment failure is defined as patients who met any of the criteria for ETF, LCF or LPF.

Re-emergence/Recurrence (recrudescence and re-infection): The appearance of asexual parasites after clearance of initial infection irrespective of genotype.
Recrudescence: The appearance of asexual parasites after clearance of initial infection with a genotype identical to that of parasites present at baseline. Recrudescence is confirmed by microscopy (positive blood smear) and by genotyping PCR analysis.
Re-infection: The appearance of asexual parasites after clearance of initial infection with a genotype that differs from that of parasites present at baseline. Re-infection is confirmed by microscopy (positive blood smear) and by

genotyping PCR analysis. Confirmed new infection will not be regarded as treatment failure or recrudescence.

Adequate Clinical and Parasitological Response (ACPR) is defined as absence of parasitemia on Day (D), irrespective of axillary temperature, in patients who did not previously meet any of the criteria of treatment failure; ETF, LCF or LPF.

PCR crude ACPR does not distinguish between re-infection (by a new clone of parasite) and recrudescence (re-emergence of the original clone of parasite that was present at baseline); i.e. presence of either a new clone or genotypically identical parasite will be considered a treatment failure.

PCR-adjusted ACPR applies only to recrudescence; (i.e. patients with re-infection are considered non-evaluable for the analysis of PCR-adjusted ACPR). Presence of a genotypically identical parasite will be considered a treatment failure (See Table F for derivations).

The following aspects are to be used in the above definitions:

- *P. falciparum* asexual parasite count and other species results as obtained from the Thick and Thin Malaria Blood Film data.
- Parasitemia refers to *P. falciparum* asexual parasites present (count >0 parasites/µL).
- Day 0 (or Day -1 if screening slide collected within 4 hours of dosing) refers to Baseline *P. falciparum* asexual parasites (/µL).
- Body temperature - Presence of signs and symptoms of complicated/severe malaria as obtained from the eCRF.
- Analysis windows defined in Section 6.4.1 are taken into account.
- PCR-analysis results:
    - Recrudescence or Re-infection as determined by PCR analysis as specified above.
    - Indeterminate. If no genotyping result is available following re-emergence due to a missing or unusable sample, or uninterpretable result, the reasons for the missing data must be indicated; i.e., sample not taken, missing follow-up sample, no PCR result or uninterpretable result.
    - Negative. 'No PCR result', hence 'No' *P. falciparum* DNA detected.

13.2. OBJECTIVES

The primary objective is to determine whether a single dose combination of OZ439/FQ is an efficacious treatment for uncomplicated *P. falciparum* malaria in adults and children. This will be evaluated in terms of:

- PCR-adjusted ACPR at Day 28.

The secondary objectives are:

- To determine the incidence of recrudescence and re-infection. This will be evaluated in terms of:

  - PCR-adjusted ACPR at Day 42 and 63.
  - Crude ACPR at Day 28, 42 and 63.
  - Incidence rate up to Day 63 of:
    - Re-emergence.
    - Recrudescence.
    - Re-infection.

- To determine the time to relief of fever and parasite clearance. This will be evaluated in terms of:
  - Parasite clearance time (PCT).
  - Fever clearance time (FCT):
  - Parasite reduction ratio (PRR).

- To evaluate the safety and tolerability of OZ439/FQ in adults and children.

- To evaluate the pharmacokinetics of OZ439/FQ:
  - To characterize the pharmacokinetics of OZ439 in plasma, FQ and its active metabolite SSR97213 in blood.
  - To determine the blood/plasma ratio for FQ and SSR97213 in some patients at limited time points in selected sites.

The exploratory objectives are to further explore the efficacy of OZ439/FQ. This will be evaluated in order:

- To evaluate the proportion of patients with gametocytes at each parasitological assessment.
- To characterize gametocyte carriage.
- To evaluate the relationship between ACPR and exposure to OZ439/FQ.
- To explore the relationship between Kelch-13 genotype and parasite clearance kinetics.
- To explore in vitro drug resistance of *P. falciparum* infecting patients >14 years old in Vietnamese sites.

In order to evaluate the data collected and complete each objective, all efficacy analyses will be presented by treatment arm and overall for the populations (see Section 5)) as detailed in Section 13.4, and by subgroups (see Section 7.4).

In addition to the efficacy analyses planned for the PP and mITT populations and associated sub-groups, a subset of efficacy analyses will be conducted on the African >5 years A5mITT and A5PP populations and on the Asian AmITT and APP populations to allow full reporting of the data.

13.3. CRUDE AND PCR-ADJUSTED ACPR OUTCOME DERIVATION

The below table summarizes the treatment outcome assignment for both crude and PCR-adjusted ACPR at

Day (D) for the mITT and PP populations, and for the A5mITT, AmITT, A5PP and APP populations. Possible treatment outcome for crude and PCR-adjusted ACPR at Day (D) are:

1 = Cure.
2 = Failure.
3 = Missing.

Table F: Derivation Criteria of Treatment Outcome Crude ACPR and PCR-adjusted ACPR at Day (D)

Criteria	PP Population		mITT Population	
	Treatment Outcome Crude ACPR	**Treatment Outcome PCR-adjusted ACPR**	**Treatment Outcome Crude ACPR**	**Treatment Outcome PCR-adjusted ACPR**
Completed up to Day (D) without re-emergence (re-infection/ recrudescence) of parasites after initial clearance, thus ACPR at Day (D).	Cure	Cure	Cure	Cure
Missing assessment on Day (D), but parasite free (No *P. falciparum* asexual parasites) after Day (D).	Cure	Cure	Cure	Cure
Missing assessment on Day (D), no more assessments thereafter.	Missing	Missing	Failure	Failure
Missing assessment on Day (D), recrudescence (confirmed by PCR-adjusted result) at first assessment after Day (D).	Failure	Failure	Failure	Failure
Missing assessment on Day (D), re-infection (confirmed by PCR-adjusted result) at first assessment after Day (D).	Failure	Cure	Failure	Cure
Re-infection before Day (D) (thus on or after Day 7 to before Day (D))	Failure	Missing	Failure	Failure

Criteria	PP Population		mITT Population	
	Treatment Outcome Crude ACPR	**Treatment Outcome PCR-adjusted ACPR**	**Treatment Outcome Crude ACPR**	**Treatment Outcome PCR-adjusted ACPR**
Re-infection on Day (D).	Failure	Cure	Failure	Cure
Recrudescence before or on Day (D) (thus on or after Day 7 to Day (D))	Failure	Failure	Failure	Failure
Re-emergence before or on Day (D) but PCR-adjusted result is indeterminate, negative or missing.	Failure	Missing	Failure	Failure
Late clinical failure from Day 4 to Day 6.	Failure	Failure	Failure	Failure
Early treatment failure from Day 1 to Day 3.	Failure	Failure	Failure	Failure
Other *Plasmodium* species before Day (D) (in the absence of *P. falciparum*).	Missing	Missing	Failure	Failure
Other *Plasmodium* species on Day (D) (in the absence of *P. falciparum*).	Cure	Cure	Cure	Cure
Other *Plasmodium* species before or on Day (D) (in the presence of *P. falciparum*), PCR-analysis result missing, negative or indeterminate.	Failure	Missing	Failure	Failure
Prematurely discontinued from the study before Day (D) and received SoC.	Failure	Missing	Failure	Failure

Criteria	PP Population		mITT Population	
	Treatment Outcome Crude ACPR	Treatment Outcome PCR-adjusted ACPR	Treatment Outcome Crude ACPR	Treatment Outcome PCR-adjusted ACPR
Prematurely discontinued from the study before Day (D) and no record of SoC.	Missing	Missing	Failure	Failure

SoC: Standard of care.

Patients included in the mITT population with no post-baseline efficacy data available are to be regarded as failure for both the crude and PCR-adjusted ACPR at Day (D) treatment outcome assignments.
Based on the above definitions and derivations according to the criteria set out in Table F: Derivation Criteria of Treatment Outcome Crude ACPR and PCR-adjusted ACPR at Day (D), crude and PCR-adjusted ACPR at Day (D) are to be derived taking into account analysis visit windows defined in Table B (Section 6.4.1).
Preference is to be given to the actual endpoint Day (D) scheduled visit result, if it falls within the predefined visit window. In cases where there is no endpoint visit, and an unscheduled visit falls within the analysis window of Day (D), the unscheduled data is to be used as the endpoint result. If neither exists, the endpoint result at Day (D) is regarded as missing and subsequently the crude and PCR-adjusted ACPR is to be derived using supporting data as detailed in Table F.

13.4. EFFICACY ANALYSIS AND SUB-POPULATIONS

The following table summarizes the efficacy analyses that will be conducted for the mITT and the PP populations.

			Sub-group Analyses (Cohorts 3 and 4)			
Domain/Variable	**Analysis Population**	**All (Cohorts 3&4) ≥0.5 to ≤5.0 years**	**>2.0 to ≤5.0 years (Cohort 3) ≥0.5 to ≤2.0 years (Cohort 4)**	**Weight**	**Baseline parasitemia**	**Country**
Crude and ACPR-adjusted	mITT & PP	Y	Y (only for the PP)	Y (only for the PP)	Y (only for the PP)	Y
ETF, LCF and LPF	mITT & PP	Y	Y (on for the PP)	Y (only for the PP)	Y (only for the PP)	Y
Kaplan-Meier for re-emergence,	mITT	Y	N	N	N	Y

recrudescence and re-infection						
Fever clearance time	PP excluding patients who received Paracetamol	Y	Y	N	N	N
Parasitemia (microscopy)	mITT	Y	Y	N	N	N
Parasitemia (qPCR, >14 years)	mITT	N	N	N	N	N
Parasite clearance time, Parasite reduction rate, PC half-life	PP	Y	Y	N	Y	Y
Kelch-13 genotype	mITT & PP	Y (all Africans combined, i.e. including African >5 years)	N	N	N	N
Relationship between PC half-life and Kelch-13 genotype	PP	Y (all Africans combined, i.e. including African >5 years)	N	N	N	N
Signs & symptoms of malaria	PP	Y	Y	N	N	N
Gametocyte carriage (microscopy)	mITT	Y	Y	N	Y	Y
Gametocyte carriage (RT-PCR, >14 years)	mITT	N	N	N	N	N

For the African >5 years mITT (A5mITT) and PP (A5PP) and for the Asian mITT (AmITT) and PP (APP) populations the following analysis is planned:

Domain/Variable	**Analysis Population**	**Africans >5 years**	**Asians**
Crude and ACPR-adjusted	AmITT, A5mITT APP, A5PP	Y (summary tables only)	Y (summary tables only)
ETF, LCF and LPF	AmITT, A5mITT APP, A5PP	Y (summary tables only)	Y (summary tables only)
Kaplan-Meier for re-emergence, recrudescence and re-infection	APP, A5PP	Y	Y
Fever clearance time	APP, A5PP excluding patients who received Paracetamol	Y	Y
Parasitaemia (microscopy)	AmITT, A5mITT	Y	Y
Parasitaemia (qPCR, >14 years)	AmITT, A5mITT	Y	Y
Parasite clearance time, Parasite reduction rate, PC half-life	APP, A5PP	Y	Y

Kelch-13 genotype	AmITT, APP	N (combined with African ≤5 years)	Y
Relationship between PC half-life and Kelch-13 genotype	APP	N (combined with African ≤5 years)	Y
Signs & symptoms of malaria	APP, A5PP	Y	Y
Gametocyte carriage (microscopy)	AmITT, A5mITT	Y	Y
Gametocyte carriage (RT-PCR, >14 years)	AmITT, A5mITT	Y	Y

13.5. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

13.5.1. STATISTICAL ANALYSIS

The primary analysis will be the analysis of the PCR-adjusted ACPR at Day 28 in the PP28 population. The PCR-adjusted ACPR at Day 28 is defined in Section 13.3. The PP28 and the population evaluable for the primary efficacy endpoint is defined in Section 5.4.

Let k, the number of treatment arms at the time of final analysis (k = 1, 2, 3 or 4). All treatments will be evaluated separately without adjustment.

The proportion of PCR-adjusted ACPR at Day 28 observed among evaluable patients from the PP population and receiving the treatment arm i (i = 1, …, k) will be seen as an observation from a binomial distribution, with unknown probability of success p_i .

For each treatment arm i (i = 1, …, k), the null hypothesis is that:

H_i0: $p_i \leq 0.90$

And this will be tested against the alternative hypothesis:

H_i1: $p_i > 0.90$, at two-sided α level of 5%, as follows:

Let p_iL, the lower bound of the exact (Clopper-Pearson) 95% two-sided confidence interval for p_i, then:

if $p_iL > 0.9$, then H_i0 will be rejected. Indeed:

Let N_i, the number of evaluable patients in the treatment arm i.
Let n_i, the number of PCR-adjusted ACPR at Day 28 observed in the treatment arm i.
The test statistic is X_i, the number of PCR-adjusted ACPR at Day 28, distributed as $Bin(N_i,p_i)$, binomial

distribution with unknown probability of success p_i. X_i is observed through n_i.

p_iL is obtained from n_i as the Inf{θ: Pθ($X_i \geq n_i$) >α/2}. If p_iL >0.9, then by definition of p_iL: P0.9($X_i \geq n_i$) ≤ α/2.
Under H_i0, the function Pθ($X_i \geq n_i$) being monotone in θ, then Pp_i($X_i \geq n_i$) ≤ P0.9($X_i \geq n_i$).

The probability to wrongly reject H_i0 when p_iL >0.9 is then at most equals to α/2, and is given by P0.9($X_i \geq n_i$).
This p-value will be provided in addition to the exact (Clopper-Pearson) 95% confidence interval for p_i.
No adjustment for multiple testing will be made, therefore the overall type I error when testing the k hypotheses may exceed 5% if k ≥ 2.

The primary analysis is to be performed for the PP population and will be repeated as a sensitivity analysis for the mITT.

For analysis purposes the PCR-adjusted ACPR at Day 28 is to be categorized as:

1 = Cure
0 = Failure

For the PP population

- Only a definite 'Cure' or 'Failure' result as derived per Table F is to be used in the analysis.
- n = Number of patients with the treatment outcome of 'Cure'.
- N = Total number of patients in the relevant analysis population with a definite response of 'Cure' or 'Failure'.
- % = Percentage of patients in each category calculated relative to the total number of patients in the relevant analysis population with a definite response.
- PCR-adjusted ACPR rate at Day 28 = (Number of patients with the treatment outcome 'Cure')/(Number of patients in the relevant analysis population with a definite result) * 100.

For the sensitivity analysis on the mITT population:

- Missing response as derived per Table F is to be set to failure and included in the analysis.
- n = Number of patients with the treatment outcome of 'Cure'.
- N = Total number of patients in the relevant analysis population.
- % = Percentage of patients in each category to be calculated relative to the total number of patients in the analysis population.
- PCR-adjusted ACPR rate at Day 28 = (Number of patients with the treatment outcome 'Cure')/(Number of patients in the mITT population) * 100.

The following by-patient listing is to be presented for the mITT population:

- Crude and PCR-adjusted ACPR

13.5.2. ADDITIONAL ANALYSIS OF PRIMARY VARIABLES

13.5.2.1. CRUDE AND PCR-ADJUSTED ACPR

As noted in Section 13.5.1, the primary analysis will be repeated for the mITT population as a sensitivity analysis.

Summaries will be repeated for each of the following subgroups as detailed in Sections 7.4 and 13.4:

- Age group
- Weight group
- Baseline parasitemia
- Country

In addition, the descriptive statistics for the African >5 years and Asian mITT and PP populations will also be presented as described in Section 13.4.

13.5.2.2. ETF, LCF AND LPF

The following tables are to be presented for the mITT and PP populations:

- The number and percentage (%) of patients with a treatment failure outcome, including ETF, LCF and LPF up to Day 28.
- The number and percentage (%) of patients with crude and PCR-adjusted result following re-emergence of asexual parasites, i.e. recrudescence, re-infection, indeterminate and negative up to Day 28.

These tables will also be repeated separately for each of the following subgroups as detailed in Sections 7.4 and 13.4:

- Age group
- Weight group
- Baseline parasitemia
- Country

In addition, tables will be repeated for the African >5 years and Asian mITT and PP populations as described in Section 13.4.

The following bar charts are to be presented for the mITT and PP populations:

- Separate bar charts of crude and PCR-adjusted cure rate over time.

These bar charts will also be repeated separately for each of the following subgroups as detailed in Sections 7.4 and 13.4:

- Age group
- Weight group
- Baseline parasitemia
- Country

The following by-patient listing is to be presented for the mITT population: treatment failure (ETF, LCF and LPF).

13.6. ANALYSIS OF SECONDARY EFFICACY VARIABLE(S)

13.6.1. PCR-ADJUSTED ACPR AT DAYS 42 AND 63, AND CRUDE ACPR AT DAY 28, 42 AND 63

The PCR-adjusted ACPR at Day 42 and 63, and crude ACPR at Day 28, 42 and 63 are defined, analyzed and presented in a similar manner as for the primary efficacy endpoint PCR-adjusted ACPR at Day 28 (refer to Section13.3: Crude and PCR-adjusted ACPR Outcome Derivation).

13.6.2. KAPLAN-MEIER ANALYSIS FOR TIME TO RE-EMERGENCE, RECRUDESCENCE AND RE-INFECTION

The following time to event variables are to be derived:

- Time to re-emergence (days): Defined as the time to appearance of asexual parasites after clearance of initial infection irrespective of genotype.
- Time to recrudescence (days): Defined as the time to appearance of asexual parasites after clearance of initial infection with a genotype identical to that of parasites present at Baseline.
- The time to re-infection (days): Defined as the time to appearance of asexual parasites after clearance of initial infection with a genotype different to that of parasites present at Baseline.
- Censored: Patients with no event are censored at the time of study completion, premature study discontinuation, including switch to established anti-malarial treatment or start of any other treatment with anti-malarial activity as captured on the Prior and Concomitant Medications eCRF, whichever is earliest.

The time to event is calculated from date of study drug administration to the onset of the event in days:

Time to event (days) = (Date of event – Start date of study drug administration)

The median time to event and 95% confidence interval for each treatment arm is to be estimated using the Kaplan-Meier method.

The following is to be presented for the mITT population overall and by country and repeated for the African >5 years and Asian mITT populations as described in Sections 7.4 and 13.4:

- Kaplan-Meier estimates of time to re-emergence, recrudescence and re-infection of asexual parasites in days.
- Kaplan-Meier estimates of incidence rates until Days 28, 42 and 63.
- Kaplan-Meier plots of the cumulative incidence for each treatment arm (within specified population/ sub-group) is to be presented for time to re-emergence, recrudescence and re-infection of asexual parasites in days.

13.6.3. PARASITE CLEARANCE TIME (PCT) (HOURS)

The following clearance time variables are to be derived:
Defined as the time (in hours) from start of study drug administration until the time of first negative film (no asexual parasites). This negative film is to be confirmed by a second negative film, taken within (≥)6 to (≤)12 hours of the first. Parasite clearance is concluded following confirmation of the second negative film. A deviation of 2 hours is allowed for the time interval. If the second film is performed less than 6 hours after the first, then the parasite clearance will be confirmed or invalidated by a third thick film, whatever the timing of this third film:

- If this third film is negative, then the clearance is confirmed.
- If this third film is positive, then the clearance is invalidated.

Time to clearance (hours) = (Date and time first thick film – Start date and time of study drug administration)

Censored: In the event that there is no second/ third film during the stipulated time period to confirm/not confirm parasite clearance, but the next available film thereafter is negative, the time to parasite clearance will be censored at the time of the first negative film. In the event that parasite clearance is not observed or confirmed before withdrawal (for any reason) or before the start of rescue therapy, the time to parasite clearance will be censored at the time of the last blood film (using the post-dose timing above defined) before withdrawal or start of rescue therapy, whichever is earliest. Blood films performed the day of rescue start are regarded as before rescue.

The parasite clearance time is to be analyzed using Kaplan-Meier estimates. The median and quartiles clearance time is to be presented together with the corresponding 95% confidence interval for the median.

Percentage parasite clearance achieved:

- At 24 hours (Day 1): number of patients with PCT ≤24 hours.
- At 48 hours (Day 2): number of patients with PCT ≤48 hours.
- At 72 hours (Day 3): number of patients with PCT ≤72 hours.

The following is to be presented for the PP population overall and by age, by baseline parasitemia, and country as described in Sections 7.4 and 13.4.

The proportion of patients and the 95% confidence intervals will be calculated for patients who have parasite clearance after study drug administration overall and at 24 hours (Day 1), 48 hours (Day 2) and 72 hours (Day 3) using Kaplan-Meier estimates.

Kaplan-Meier plots of the cumulative incidence for each treatment arm over time to parasites clearance in hours is to be presented.

13.6.4. FEVER CLEARANCE TIME (FCT) (HOURS)

Only patients with measured fever (adjusted body temperature ≥37.5 °C) present at Baseline and who did not receive paracetamol on day of study drug administration until 96 hours after study drug administration are to be included. Patients entered in the study on the basis of history of fever and who do not subsequently have an increased body temperature measurement indicating presence of fever at pre-dose, are not included in the analysis of fever clearance time.

Calculated as the time from start of study drug administration to the first assessment of adjusted body temperature <37.5 °C. This assessment is to be confirmed by a second assessment, taken within (≥)6 to (≤)12 hours of the first. Fever clearance is to be concluded for the first assessment, following confirmation of temperature <37.5 °C on the second assessment.

Time to clearance (hours) = (Date and time of first clearance assessment – Start date and time of study drug administration)

Censored: Patient who did not have second assessment during the stipulated time period to confirm/not confirm fever clearance, but were fever-free at the next available assessment time point, are censored at the time of the first assessment of body temperature <37.5 °C. Patients who did not have fever clearance are censored at premature study discontinuation, including switch to established anti-malarial treatment or start of any other treatment with anti-malarial activity as captured on the Prior and Concomitant Medications eCRF, whichever is earliest.

The proportion of patients who have fever clearance after study drug administration are to be calculated and the 95% confidence intervals for the single binomial proportion is to be calculated according to Clopper-Pearson method.

The fever clearance time is to be analyzed using Kaplan-Meier estimates. The median and quartiles clearance time is to be presented together with the corresponding 95% confidence intervals for the median (expressed in weeks). The table is to be presented for the PP population overall and by age, as described in Sections 7.4 and 13.4.

The following figures are to be presented for the PP population overall and by age group:

- Kaplan-Meier plots of the cumulative incidence for each treatment arm over time for patients with

measured fever at Baseline to parasites clearance in hours, excluding patients receiving paracetamol during the first 96 hours after study drug administration.

13.6.5. PARASITE REDUCTION RATIO

The following method will be used for estimating slopes:

A Tobit regression model (SAS PROC LIFEREG) will be used in order to take into account for censored observations (i.e. negative parasitemia) however only the first zero sustained (i.e. followed by negative slides only) will be included in the analysis. In addition, a linear regression model starting from the second parasite measurement will be fitted if this second measurement exceeded the first measurement (baseline) by more than 25%. The Tobit model is a censored regression model, where the response variable Y_i is related to a latent (or unobservable) variable Y*i by:

$Y_i = Y^*i$ if $Y^*i > YL$, $Y_i = YL$ if $Y^*i \leq YL$.

The latent variable is then modelled in the standard way: $Y^*i = Xi\beta+\varepsilon$. And the regression model is solved using maximum likelihood techniques, however the likelihood function is now a truncated normal distribution in the case when $Y^*i \leq YL$.

13.6.5.1. PARASITE CLEARANCE PARAMETERS

The following parasite clearance parameters are to be estimated using the WWARN parasite clearance estimator (PCE) based on the linear part of the individual natural log parasitemia-time profiles for both microscopic and qPCR determined parasitemia.

- Clearance rate constant (1/hours)
- PC half-life
- Time to 50%, 90% and 99% parasite reduction (PC50, PC90 and PC99)

Analyzable data: Identifies the data per scheduled timepoint to be used for the PCE especially in view of patients switching to established anti-malarial treatment or start of any other treatment with anti-malarial activity as captured on the Prior and Concomitant Medications eCRF. This flag excludes those test results obtained whilst on alternative treatment and only data up to 168 hours post study drug administration are to be included for the parasite parameter analysis.
Analyzable result: Identifies the parasite clearance parameter results to be used in the summary tables. Results from patients with a poor fit to the linear model ($r^2 < 0.75$) or with <3 data points are excluded from the analysis. For asexual parasite assessments equal to 'Absent', the WWARN calculator use 8 /µL as the limit of detection.

Parasite reduction rate (PRR) at 24 and 48 hours derivations:

- The clearance rate constant (1/hours) obtained from the WWARN PCE calculator and defined as the minus slope of the final model fitted after exclusion of outliers, lag phase and tail are to be used to calculate PRR24 and PRR48. Hence PRR24 and PRR48 is the drop in log units over 24 and 48 hours.
    - PRR24 = ln (clearance rate constant [1/hours]*24 hours).
    - PRR48 = ln (clearance rate constant [1/hours]*48 hours).

The following table is to be presented for the PP population overall and by age, by baseline parasitemia and country as described in Sections 7.4 and 13.4.

- Descriptive statistics (n, minimum, 25th percentile, median, 75st percentile, maximum) for the parasite clearance parameters, i.e. PRR24, PRR48, PC half-life, PC50, PC90 and PC99 as estimated with the use of the PCE developed by WWARN.

The following result are to be presented in a by-patient listing for the PP population:

- The parasite clearance parameters, i.e. clearance rate constant (1/hours), PC half-life, PC50, PC90 and PC99, including the calculated PRR24 and PRR48 results.

13.6.6. PARASITAEMIA

The following tables are to be presented for the mITT population overall and by age as described in Section 13.4.

- Descriptive statistics (n, mean, geometric mean, SD, median, Q1, Q3, minimum, and maximum) for parasitemia data (number of parasites/µL) (raw data and absolute change from baseline) using microscopic determined parasitemia will be displayed at each post-baseline assessment.

The following tables are to be presented for the African >5 years population and Asian population as described in Section 13.4.

- Descriptive statistics (n, mean, geometric mean, SD, median, Q1, Q3, minimum, and maximum) for parasitemia data (number of parasites/µL) (raw data and absolute change from baseline) using microscopic determined parasitemia and qPCR (quantitative polymerase chain reaction) (in patients >14 years) determined parasitemia, will be displayed at each post-baseline assessment.
- qPCR: A polymerase chain reaction method is used to quantify the amount of *Plasmodium falciparum (P. falciparum)*-specific DNA present and is transformed into number of parasites/µL.

13.7. ANALYSIS OF PHARMACOKINETIC PARAMETERS

Blood and plasma FQ (respectively its metabolite [SSR97213]) observed concentrations, plasma OZ439 observed concentrations will be summarized by treatment arm and by time point using descriptive statistics (mean, geometric mean, median, standard deviation, standard error of mean, coefficient of variation, minimum, maximum and number of available observations) for each cohort.

Blood/plasma ratio for FQ and SSR97213 will be provided by treatment arm and by time point using above descriptive statistics for each cohort. Blood and plasma concentrations will be kept for the descriptive statistics if sampling occurs within ± 15% of theoretical time. Additional plots will be prepared, as deemed necessary.

The population PK analysis for both OZ439 and FQ/ SSR97213 will be performed using non-linear mixed effect modeling. Subsequently, for each patient the individual OZ439, FQ and SSR97213 exposures (Cmax, AUCs, CDay 7, CDay 14, CDay 21 and CDay 28) will be estimated using each patient's estimated individual PK parameters. These will be summarized by various subgroups. Data from previously conducted studies might be added for model development. More details will be provided in a separate pharmacokinetic analysis plan. The pharmacokinetic analyses will be reported separately from the main CSR. A summary of the methods and results will be reported in the main CSR.

13.8. ANALYSIS OF PHARMACODYNAMIC PARAMETERS

13.8.1. RELATIONSHIP BETWEEN ACPR AND EXPOSURE TO OZ439/FQ

An exploratory objective of this study is to evaluate the relationship between ACPR and exposure to OZ439/FQ. More details will be provided in a separate analysis plan. A summary of the methods and results may be reported in the main CSR.

13.8.2. RELATIONSHIP BETWEEN OBSERVED PK CONCENTRATIONS AND ECG PARAMETERS

Two PK/PD statistical analyses (one for Cohort 1a in a first time and then by pooling Cohort 1a and 1b in a second time) will be done with ECG parameters (HR, PR, QRS, QTcB and QTcF) regarding FQ and SSR97213 compounds by combining the two compounds in the same linear direct/indirect model (as covariates or by using the molecular weight formula in order to obtain a "total" concentration). A complementary analysis will be performed pooling Cohort 1a and 1b and including OZ concentrations as PK variable (in addition to FQ and SSR97213). These two analyses will be prepared by a Sponsor's unblinded independent statistician.
The first PK/QTc analysis will include 30 African patients >14 years (Cohort 1a) receiving the dose levels OZ439/FQ 800/400, 800/600 and 800/900 mg.
The second PK/PD analysis will include a total of 42 African patients >14 years (Cohort 1a & 1b) receiving the dose levels 800/400, 800/600, 800/900 and 800/1200 mg.
Post-dose concentrations below the lower limit of quantification (LLOQ), will be replaced with ½ LLOQ in the statistical analyses. LLOQ is defined as 1 ng/mL for OZ439 and as 5 ng/mL for FQ and SSR97213.

Relationships between changes from baseline in ECG parameters with FQ/OZ439 concentrations on the restricted time window [Day 0 T2h – Day 2 T48h] will be explored in two ways by combining the two compounds FQ and SSR97213, using the molecular weight (MW) 433.77 $g.mol^{-1}$ for ferroquine and 419.74 $g.mol^{-1}$ for SSR97213, in order to obtain a "total" concentration separately from OZ439 [mol/L] = C_FQ/433.77 + C_ SSR97213/419.74 Total concentration (FQ+SSR97213) [µmol/L] = Concentration (µg/L)/433.77 (µg/µmol) + Concentration_SSR97213 (µg/L)/419.74 (µg/µmol), by using ferroquine and SSR97213 blood drug concentrations as covariates in the same model.

For the complementary analyses, when OZ439 will be included in the model, the concentrations will be converted to µmol/L using its molecular weight (469.28 $g.mol^{-1}$) for the first approach and will be used unchanged for the second approach.
The selection of the best model will depend of fit statistics criteria.

The PK/PD analysis will be performed in three successive steps:

- 1st step: 800/400, 800/600 and 800/900 mg dose levels from Cohort 1a.
- 2nd step: 800/400, 800/600, 800/900 and 800/1200 mg dose levels from Cohorts 1a and 1b. (OZ concentration to be added as PK variable in the complementary analysis).

These PK/QTc analyses may or may not be reviewed by the DMC at the same time as the safety data review and therefore may or may not be considered by the DMC for DMC decision rule.

- A third PK/PD analysis will include all patients of all cohorts receiving the dose levels 800/400, 800/600, 800/900 mg and/or 800/1200 mg at the end of the study.

13.8.3. EXPLORATORY PLOTS

The relationship between change from baseline in HR, PR, QRS, QTcB and QTcF and FQ (respectively SSR97213, their total concentrations using MW and OZ439 [complementary analysis at end of Cohort 1 and final analysis only]) concentrations, respectively, from Day 0 T2h to Day 2 T48h will be first explored graphically, in order to investigate any potential delayed or sustained effects and the type of PK/PD modelling to be done, using the following plots:

- Plot of Mean (± SEM) change from baseline in HR, PR, QRS, QTcB and QTcF with FQ (respectively SSR97213, their total concentrations using MW and OZ439 [complementary analysis at end of Cohort 1 and final analysis only]) concentrations, versus time (hours post-dose) overlaid onto the same plot; the same plot will be produced on the log concentration;
- Hysteresis plot of individual and mean change from baseline in HR, PR, QRS, QTcB and QTcF and FQ (respectively SSR97213, their total concentrations using MW and OZ439 [complementary analysis at end of Cohort 1 and final analysis only]) concentrations, respectively;
- Histogram of distribution of time of largest change from baseline in HR, PR, QRS, QTcB and QTcF and largest FQ (respectively SSR97213 and OZ439 [complementary analysis at end of Cohort 1 and final analysis only]) concentrations, respectively;
- Histogram of distribution of time of smallest change from baseline in HR, PR, QRS, QTcB and QTcF

and largest FQ (respectively SSR97213, their total concentrations and OZ439 [complementary analysis at end of Cohort 1 and final analysis only]) concentrations, respectively.

A graphical exploration will be performed to assess appropriateness of QT correction methods by plotting baseline individual QTc values on the y-axis and baseline HR (or RR) values on the x-axis. A regression line will be fitted between QTc and HR. These plots will be performed separately by age cohort for the final analysis.

13.8.4. MODELING: LINEAR MODEL

A random coefficients linear regression of QTcF (respectively HR, PR, QRS and QTcB) change from baseline vs. concentration will be used from Day 0 T2h to Day 2 T48h, with fixed terms for common intercept and slope, and with random terms for patient - specific intercept and slope, and using an unstructured variance-covariance structure for random coefficients and a common variance for error, using SAS® PROC MIXED procedure:
For the model with ferroquine and SSR97213 total concentration using MW:
Change from baseline = $(\alpha + A_i) + (\beta + B_i) \times \text{Concentration}_{ij}$ + error, with i = patient and j = time
For the model where ferroquine and SSR97213 blood drug concentrations will be used as covariates simultaneously:
Change from baseline = $(\alpha + A_i) + (\beta_1 + B_{1i}) \times$ Ferroquine $\text{Concentration}_{ij} + (\beta_2 + B_{2i}) \times$ SSR97213 $\text{Concentration}_{ij}$ + error, with i = patient and j = time

When OZ439 will be added to the model [complementary analysis at end of Cohort 1 and final analysis only], a term $(\beta_3 + B_{3i}) \times$ OZ439 $\text{Concentration}_{ij}$ will be added to the model, OZ439 concentrations being used unchanged or converted to µmol/L depending on the model used.

Estimates and 90% CIs of coefficients of the linear regression model, and the prediction (estimate and 90% CI) in change from baseline of ECG parameters corresponding to the observed Cmax value (geometric mean) for each FQ dose group will be provided for FQ and SSR97213 respectively (OZ439 compound for the complementary analysis at end of Cohort 1 and final analysis only), and will be calculated as follows:

- For the models with ferroquine and SSR97213 total concentration using MW:
  - Estimated change from baseline at total concentration Cmax = βestimated x total concentration Cmax geometric mean (GM)
- For the models with ferroquine and SSR97213 concentrations as covariates:
  - Estimated change from baseline at ferroquine Cmax = $\beta_{1\ \text{estimated}}$ x ferroquine Cmax GM + $\beta_{2\ \text{estimated}}$ x (mean of SSR97213 concentrations obtained at individual ferroquine tmax)
  - Estimated change from baseline at SSR97213 Cmax = $\beta_{1\ \text{estimated}}$ x (mean of ferroquine concentrations obtained at individual SSR97213 tmax) + $\beta_{2\ \text{estimated}}$ x SSR97213 Cmax GM
- For the models including OZ439 [complementary analysis at end of Cohort 1 and final analysis only], contribution of OZ439 will be addressed in the same way, that is, by estimating the change from baseline at OZ439 Cmax GM conditioned to mean concentrations for ferroquine, SSR97213 or the total of their concentrations obtained at OZ439 tmax, or by conditioning predictions for ferroquine, SSR97213 or the

total of their concentrations by the mean of OZ439 concentrations obtained at the tmax of interest.

Scatter plots of changes from baseline versus FQ, SSR97213 concentrations and OZ439 (for the complementary analysis at end of Cohort 1 and final analysis only), respectively, with the regression line overlaid, will also be provided.

Goodness-of-fit and residual plots will be provided. In case of lack of fit (i.e., the linear model is not adequate), alternative models like non-linear models (exponential, Emax) and/or Model Averaging) might be explored.

13.8.5. MODEL AVERAGING

By combining estimates obtained from several competing models (linear, exponential and Emax), Model averaging (MA) will provide estimators which will have good robustness properties compared to the linear model or non-linear model estimates.
The estimated endpoint will be the drug effect on delta QTcF at the Cmax value (geometric mean) observed concentrations at the maximal dose (OZ439 800 mg/FQ 1200 mg).

13.9. ANALYSIS OF EXPLORATORY EFFICACY VARIABLES

13.9.1. KAPLAN-MEIER ANALYSIS FOR THE RISK OF HAVING GAMETOCYTES

The following time to event variables are to be derived:

- The time to appearance (days):
  Only patients without gametocytes at Baseline are to be included, i.e. gametocytes equal to 'Absent' at Screening (Baseline).
  Calculated from the start of study drug administration until the appearance of gametocytes.
  Time to appearance of gametocytes (days) = (Date of appearance of gametocytes – Date of study drug administration).
  Censored: Patients who did not have an event of appearance of gametocytes are censored at the time of study completion, premature study discontinuation, including switch to established anti-malarial treatment or start of any other treatment with anti-malarial activity as captured on the Prior and Concomitant Medications eCRF, whichever is earliest.

- Gametocyte clearance time (PCT) (days):
  Only patients with gametocytes present at Baseline are to be included, i.e. gametocytes assessment equal to 'Present' at Screening (Baseline) with a gametocyte count greater than zero.

Calculated as the time from start of study drug administration to the first negative (no gametocytes detected) film. This negative film is to be confirmed by a second negative film, taken within (≥)6 to (≤)12 hours of the first. Gametocyte clearance is concluded following confirmation of the second negative film.
Time to gametocytes clearance (days) = (Date of first negative film – Date of study drug administration).
Censored: Patients who did not have second film within the stipulated time period to confirm/not confirm gametocyte clearance are censored at the time of first negative film if the next available film is negative for gametocytes. Patients who did not have gametocyte clearance are censored at the time of study completion, premature study discontinuation, including switch to established anti-malarial or start of any other treatment with anti-malarial activity as captured on the Prior and Concomitant Medications eCRF, whichever is earliest.

The median time to event and 95% CI for each treatment are to be estimated using the Kaplan-Meier method.
The following tables are to be presented for the mITT population:

- Kaplan-Meier estimates of time to appearance of gametocytes in days, for patients with no gametocytes at Baseline. The percentage of patients in each category are to be calculated relative to the total number of patients in the relevant analysis population without gametocytes at Baseline.
- Kaplan-Meier estimates of gametocyte clearance time in days, for patients with gametocytes at Baseline. The percentage of patients in each category are to be calculated relative to the total number of patients in the relevant analysis population with gametocytes present at Baseline.

The following figures are to be presented:

- Kaplan-Meier plots of the cumulative incidence for each treatment arm is to be presented for time to appearance of gametocytes for patients without gametocytes present at Baseline.
- Kaplan-Meier plots of the cumulative incidence for each treatment arm is to be presented for gametocytes clearance time for patients with gametocytes present at Baseline.

13.9.2. KELCH-13 GENOTYPE

Analysis of Kelch-13 genotype associated with Artemisinin resistance is to be carried out on the pre-dose blood spot samples. If insufficient blood spot samples at Baseline, alternative blood spots collected as specified in the schedule of assessments are to be used.

Binary Classification:

- Per patient: Kelch-13 data is to be categorized as either true wild type or mutation, where:
  - True wild type (WT): Defined for patient with no mutations at any of the tested loci.
  - Mutation: Defined for patient with at least one mutation tested loci.
- The “mixed” infection, meaning sample contained both mutants and wild type, will be considered as “mutant” in the analyses.

The following table is to be presented for the mITT and PP populations grouping all African patients together as described in Section 13.4. In addition, the following table will also be presented for the Asian population:

- Number (n) and percentage (%) of patients carrying WT parasites, and carrying each mutation are to be calculated relative to the total number of patients in the relevant analysis population with an evaluable result ('wild type' or 'mutation') at any of the tested loci per patient overall and per tested loci.

The following data are to be presented in a by-patient listing for the mITT:

- Kelch-13 mutations and wild types.

The following figures are to be presented:

- Stacked bar chart of the frequency of occurrence of Kelch-13 of wild type and each mutation. The percentage (%) of patients in each category are to be calculated relative to the total number of patients in the mITT population (for all African patients together and separately for Asian patients) with an evaluable result ('wild type' or 'mutation') at any of the tested loci.
- Scatter plot of the correlation of parasite clearance half-life and true wild type and Kelch 13 mutations in the PP population for all African patients together and separately for Asian patients).

13.9.3. CLINICAL SIGNS AND SYMPTOMS OF MALARIA

Descriptive statistics of the number (%) of patients experiencing clinical signs or symptoms related to malaria will be provided at each visit and for each sign or symptom, regardless of the presence of the sign/symptom at baseline, and within the subset of patients who has the sign/symptom at baseline. Assessments performed after start of rescue treatment will not be included in above summaries.

The following table is to be presented for the PP population and separately for the PP population by age at randomization subgroup as defined in Sections 7.4 and 13.4:

- Number (n) and percentage (%) of patients having any signs and symptoms of malaria per scheduled visit, calculated relative to the total number of patients at the visit.

The following by-patient listing is to be presented for the mITT population:

- Clinical signs and symptoms of malaria, including information on clinical signs and symptoms of uncomplicated malaria present.

13.9.4. FURTHER EXPLORATORY ANALYSIS

Drug resistance of *P. falciparum* infecting patients >14 years old in Vietnamese sites will be explored further by defining phenotypic and genotypic resistance patterns to conventional ACT of *P. falciparum* infecting patients aged >14 years old in Vietnamese sites (blood sample taken at screening). This data will be reported separately and will not be included in the CSR.

In vitro susceptibility testing of *P. falciparum* infecting patients aged >14 years old in Vietnamese sites to OZ439, FQ and both drugs (blood sample taken in case criteria for rescue treatment is met). This data will be reported separately and will not be included in the CSR.

14. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF population.
There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

All safety analyses described will be presented as follows:

- For all patients in safety population (SAF) by treatment group (pooled cohorts) and overall

And if specified in the relevant sub-sections:

- For the Cohorts 3 and 4 safety population (C3&4SAF) by treatment group (pooled cohorts) and overall
- For Asian patients (ASAF) by treatment group and overall
- For African patients >5 years (A5SAF) by treatment group (pooled cohorts) and overall

14.1. OBSERVATION PERIOD

The **on-study observation period** is defined as the time from start of IMP until the end of the study (defined as last protocol planned visit or the resolution/stabilization of all SAEs and AEs with prespecified monitoring).
The **post-study period** is defined as the time from the last protocol planned visit until database lock.

The observation period will be divided into three phases:

- The **pre-treatment phase** is defined as the time between the patient provides informed consent and the start time of the first double-blind IMP administration (excluded).
- The **on-treatment phase** is defined as the time from the start of the first dose of double-blind IMP administration (included) up to the Day 63 visit (included).
- The **post-treatment phase** is defined as the time after the Day 63 visit (excluded).

The TEAE period is the on-treatment study phase.

14.2. POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITY (PCSA)

The PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG parameters (PCSA version dated May 2014 or as updated thereafter). PCSA definitions

depend on the age, race, or sex of the patient and are detailed in Appendix 3. Specific PCSA criteria for children will use children's age at time of safety assessment.

PCSA criteria will determine which patients had at least one PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including non-scheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSA percentage.

The denominator for the PCSA percentage for a given parameter will be based on the number of patients assessed for that given parameter in the TEAE period on the considered safety population. In addition, the denominator could be adjusted if only adults or children are concerned by the PCSA.

PCSA definitions depending on age, sex or race cannot be displayed within line headers of incidence tables. Therefore, specific tables providing the PCSA definitions for laboratory, vital sign and ECG parameters will be generated.

For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group. Summaries will include the worst value, defined as the nadir and/ or the peak according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list, during the TEAE period.

14.3. ADVERSE EVENTS

The occurrence of all AEs (including SAEs and AESIs) will be recorded from the time of signed informed consent until the end of the study.

14.3.1. ADVERSE EVENT OBSERVATION PERIOD

Pre-treatment AEs are AEs that developed or worsened or became serious during the pre-treatment phase.
Treatment-emergent AEs are AEs that developed or worsened or became serious during the TEAE period (on-treatment phase).
Post-treatment AEs are AEs that developed or worsened or became serious during the post-treatment phase.

The primary focus of adverse event reporting will be on TEAEs.

14.3.2. GENERAL CONVENTIONS

If an AE date/time is missing or partial, the conventions in Appendix 2 will be used to classify the AE as treatment-emergent or otherwise.

All AEs (including SAEs and AESIs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of MedDRA currently in effect at IQVIA three months prior to database lock or data cut-off for interim deliverables.

Adverse event incidence tables will present the number (n) and percentage (%) of patients experiencing an AE by SOC and PT. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase.

Sorting within tables will ensure the same presentation for the set of all AEs within each observation period (pre-treatment, treatment-emergent, and post-treatment). For that purpose, the table of all TEAEs presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting for decreasing frequency of PTs within SOC will be based on results for the pooled treatment groups ("Total" column).

14.3.3. ALL TEAEs

Incidence of TEAEs will be presented by SOC and PT and also broken down further by maximum severity and relationship to study medication.

The following TEAE tables will be generated for the SAF population:

- Overview of TEAEs, summarizing number (%) of patients with at least one
  - TEAE
  - Serious TEAE
  - TEAE leading to death
  - TEAE (other than treatment failure) leading to discontinuation of the study medication.

  Table will be repeated for C3&4SAF, ASAF and A5SAF sub-populations.
- A summary of all TEAEs (number and percentage of patients) by primary SOC and PT.
  Table will be repeated for C3&4SAF, ASAF and A5SAF sub-populations
- A summary of all TEAEs (number and percentage of patients) by maximal severity, primary SOC and PT.
- Summaries of all TEAEs (number and percentage of patients) by relationship to study medications (FQ and OZ439 separately), primary SOC and PT.
- Summaries (number and percentage of patients) of all adverse drug reactions (TEAEs considered related to the study medication FQ or OZ439 separately) by maximal severity, primary SOC and PT.

14.3.3.1. SEVERITY

Severity is classed as mild, moderate, or severe (increasing severity). TEAEs with a missing severity will be

classified as severe.

If a patient reports a TEAE more than once within a primary SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

14.3.3.2. RELATIONSHIP TO STUDY MEDICATION

Relationship to the study medication, as indicated by the Investigator, is classed as related (i.e., 'reasonable possibility that the AE was caused by FQ/OZ') or not related (i.e., 'no reasonable possibility that the AE was cause by FQ/OZ'). TEAEs with a missing relationship to study medication will be classified as related.

If a patient reports the same TEAE more than once within a primary SOC/ PT, the AE with the worst-case relationship to study medication (i.e., "related" if both "related" and "not related" were attributed to the different events) will be used in the corresponding relationship summaries.

14.3.4. TEAES LEADING TO DISCONTINUATION OF STUDY MEDICATION

TEAEs leading to permanent discontinuation of study medication will be identified by using the 'Action taken' question on the AE page of the eCRF. This is specified as 'Drug withdrawn'.

The following incidence table of TEAEs leading to discontinuation of study medication will be presented:

- A summary of all TEAEs leading to discontinuation of either FQ or OZ439 (number and percentage of patients) by primary SOC and PT.

14.3.5. SERIOUS ADVERSE EVENTS

Serious adverse events will be identified as any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/ incapacity, or
- Is a congenital abnormality/ birth defect, or
- Is a medically important event (for further information regarding the definition of medically important events see Section 10.4.1.2 of the Protocol).

An ALT increase >3xULN is also an SAE in any of the following circumstances:

- Possible Hy's law (ALT or AST >3xULN and bilirubin >2xULN and (>35% direct bilirubin) in the absence of a serum alkaline phosphatase level >2xULN. [If fractionation is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury]
- When ALT >10xULN
- When associated with jaundice
- When associated with coagulation disorder (PT<50%)
- In the presence of signs of hepatic encephalopathy

The following incidence tables of treatment-emergent SAEs will be presented:

- A summary of all treatment-emergent SAEs (number and percentage of patients) by primary SOC and PT.

14.3.6. ADVERSE EVENTS LEADING TO DEATH

TEAEs leading to death are those events where the outcome is recorded as "Fatal" on the AE page of the eCRF.

No tables of TEAEs leading to death will be presented, this will be identified in data listings.

14.3.7. ADVERSE EVENTS OF SPECIAL INTEREST

Adverse event of special interest is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required.
Adverse events of special interest will be identified using a dedicated question in eCRF "Does event meet the criteria for AE of special interest per protocol?" and include:

- Pregnancy (occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial)
- Symptomatic overdose with IMP
- Increase in alanine transaminase (ALT): ALT≥3xULN (if baseline ALT<ULN) or, ALT≥2 times the baseline value (if baseline ALT≥ULN)
- QTcF≥500 ms or QTcF increase from baseline >60 ms

Further details regarding AESIs can be found in Section 10.4.1.3 of the study Protocol.

Summary table of AESIs (number and percentage) will be generated for each AESI (PT or pre-specified grouping). This will include:

- Patients (number and percentage) experiencing QTc-interval prolongation
- Patients (number and percentage) experiencing hepatic disorders.

Table will be repeated for C3&4SAF, ASAF and A5SAF sub-populations.

14.3.8. GENERAL AEs LISTINGS

All individual AE data will be listed, including verbatim terms, coded terms, start and stop dates and times, severity, outcome, relationship to study medication, action taken with study medication, seriousness (including criteria met) and whether or not the event was of special interest.

14.4. DEATHS

Deaths during the study will be presented in a data listing.
The observation period for deaths are per the observation periods defined in Section 14.1.

14.5. LABORATORY EVALUATIONS

Clinical laboratory data consists of blood analyses (including hematology and clinical chemistry) and urinalysis. Blood samples for clinical laboratories will be taken as per the schedule of assessments found in Section 1.1 of the Protocol.

Laboratory parameters will be classified according to biological function as follows:

- Hematology:
  - Red blood cells and platelets and coagulation: hematocrit, hemoglobin, absolute reticulocytes, erythrocyte count (RBC), platelet count.
  - White blood cells: leukocytes (WBC) with differential count* including eosinophils.
    (*): in one site, manual counts have been reported due to an issue with the machine to read the results of differential count.
- Clinical chemistry:
  - Metabolism: albumin, creatine kinase, glucose
  - Electrolytes: sodium, potassium, magnesium (Visit 1 only), calcium (Visit 1 only)
  - Renal function: creatinine, creatinine clearance, blood urea nitrogen (BUN)
  - Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), haptoglobin, lactate dehydrogenase (LDH), total bilirubin (also direct, when total bilirubin is ≥ULN)
- Urinalysis dipstick:
  - specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes and blood were evaluated but not recorded in the clinical database and thus will not be reported in the CSR.

- Pregnancy test: urine β-HCG for females of childbearing potential
- Urinalysis microscopy if the dipstick is abnormal: WBC, RBC and casts (if required)

14.5.1. GENERAL CONVENTIONS

Clinical laboratory values will be analyzed in standard international (SI) units after conversion to these as appropriate.

Baseline
The values to be used as baselines will be the values collected on Day -1 for each patient. If any of the scheduled baseline tests are repeated for any patient, the last re-checked values will be considered as baselines, provided they were done before the start of IMP administration and under the same conditions (e.g. fasted) as the original test. In case of central and local tests performed at the same time, the central value will be considered as the baseline value provided it was done before the start of IMP administration. If a central test was not performed but a local value exists at the same date for the same test, the local value will be considered as the baseline.

Quantitative laboratory measurements reported as "<X", i.e. below the lower limit of quantification (LLQ), or ">X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "<X" or ">X" in the listings.

For hematology, only local measures are available and will be used for quantitative summary statistics without normalization of data.

For creatinine clearance: it has to be noted that for African patients more than 14 years old (i.e. Cohorts 1a and 1b), the used assay method for central laboratory based serum creatinine (Jaffre) was not suitable for Schwartz calculation of the creatinine clearance, therefore only Cockroft and Gault formula was used by the central laboratory in this population. For other patients, creatinine clearance is calculated locally and/ or centrally according to formulae specified in the protocol (Cockroft and Gault formula for patients more than 18 years old and GFR Bedside Schwartz formula for other patients).

For glucose, only fasted assessments will be used for quantitative summaries.

14.5.2. DESCRIPTIVE STATISTICS

Summary statistics (including number, mean, SD, median, first and third quartiles, minimum and maximum) of all laboratory variables (values and changes from baseline) will be calculated for each visit or study assessment time point (baseline, each post-baseline time point, worst (as defined by medical team) TEAE period value (as defined in Section 14.1)).

This section will be organized by biological function as specified above. Tables will be repeated by age group for C3&4SAF. Table for liver tests will be repeated for C3&4SAF, ASAF and A5SAF sub-populations.

14.5.3. ANALYSES OF ABNORMALITIES

The incidence of PCSAs (list provided in Appendix 3) at any time during the TEAE period will be summarized by biological function whatever the baseline level and/ or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

Creatinine clearance PCSA definition for adults will be used in African children more than 14 years.

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

Summary tables for liver function will be repeated for C3&4SAF, ASAF and A5SAF sub-populations.

All laboratory abnormalities will be listed.

14.5.4. DRUG-INDUCED LIVER INJURY

The incidence of liver-related AEs will be summarized. The selection of PTs will be based on standardized MedDRA query (SMQ) Hepatic disorder.

A graph of distribution (e-Dish plot) of peak values of ALT versus peak values of total bilirubin will be presented. ALT and total bilirubin values will be presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3xULN for ALT and a horizontal line corresponding to 2xULN for total bilirubin.

A listing will be presented of possible Hy's law cases identified by treatment group (i.e., patients with any elevated ALT>3xULN, and an associated increase in bilirubin >2xULN) with ALT, AST, alkaline phosphatase, total bilirubin, and the following complementary parameters: conjugated bilirubin and prothrombin time/international normalized ratio, creatine kinase, creatinine, full blood count. Other relevant parameters (anti-HAV IgM, anti-HBc IgM, anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies, auto-antibodies: anti-nuclear, anti-DNA, anti-smooth muscle, Epstein-Barr virus, herpes viruses, and anti-LKM) will be presented as available.

A listing will be presented of all patients with increase in ALT≥2xULN, including information on IMP intake, medical and surgical history, alcohol habits, trigger factors, event details with ALT values, associated signs and symptoms.

14.5.5. GENERAL LABORATORY LISTINGS

All individual data, for planned hematology and biochemistry tests, including re-checked and unscheduled values, will be listed by biological function, cohort, treatment group and patient, visit. In these listings, individual data will be flagged when lower or higher than the lower or upper laboratory limits and/or when reaching the absolute limit of PCSA criteria, when defined.

A listing of out-of-normal range definitions will also be provided.

14.6. ECG PARAMETERS

ECG recordings are performed as per the schedule of assessments in Section 1.1 of the Protocol.

Quantitative ECG parameters include:

- Heart rate
- QRS duration
- RR interval
- PR-interval
- QT-interval, QTcF-interval (corrected according to Fridericia formula: QTcF = QT / ($RR^{1/3}$), and QTcB-interval (corrected according to Bazett's formula: QTcB = QT / ($RR^{1/2}$).

Morphological ECG parameters include:

- ST segment deviation
- T-wave morphology
- U-wave presence or absence

14.6.1. GENERAL CONVENTIONS

For all quantitative ECG parameters, the mean of triplicate ECGs at each time point will be used for all analyses including PCSA analyses. As far as at least one record is available from a triplicate, it will be used in the mean calculations for analyses. No time restriction is applied for calculation of mean values from triplicate ECGs performed at the same visit.

For each set of triplicate ECGs, the associated date and time of the assessment is taken as the date and time of the first record of the triplicate.

Baseline

The value to be used as baseline will be defined as the average of the triplicate assessments done on Day 0 T0 or the last available time point prior to first dosing for each treatment group.

14.6.2. DESCRIPTIVE STATISTICS

For all quantitative parameters, raw data and changes from baseline will be summarized using descriptive statistics (including number, mean, SD, median, first and third quartiles, minimum and maximum), by visit and time of measurement (baseline, each post-baseline time point, and worst on-treatment value).
Summaries will be repeated by age group for C3&4SAF. Summaries will be repeated for C3&4SAF, ASAF and A5SAF sub-populations.

14.6.3. ANALYSES OF ABNORMALITIES

The incidence of PCSAs (list provided in Appendix 3) at any time during the TEAE period will be summarized, irrespective of the baseline level and/ or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

Table will be repeated for C3&4SAF, ASAF and A5SAF sub-populations.

If possible, a summary of ECG morphological assessments will be provided by cohort and treatment group.

14.6.4. ANALYSIS OF QTC PROLONGATION

Absolute QTcF and QTcB values will be summarized per post-baseline time point and worst TEAE period value in accordance with the following categories:

- >450 msec
- >480 msec
- >500 msec

QTcF and QTcB prolongations will be evaluated by tabulating the changes from baseline to each post-baseline time point and worst TEAE period value in accordance with the following categories:

- >30 msec
- >60 msec

Table will be repeated for C3&4SAF, ASAF and A5SAF sub-populations.

14.6.5. GENERAL ECG LISTINGS

Individual data, including rechecked values, will be listed by cohort, treatment group, patient, visit and time of measurement. In the listings, values will be flagged when reaching the limits of the PCSA criteria, when defined.

14.7. VITAL SIGNS AND PHYSICAL MEASUREMENTS

Vital signs measurements taken on this study include: heart rate (bpm), systolic and diastolic blood pressure in supine position (mmHg), and body temperature (^{0}C).
Physical measurements include: body weight (kg), height/length (cm) and BMI (kg/m^2).

All assessments are performed as per the schedule of assessments in Section 1.1 of the Protocol.

14.7.1. GENERAL CONVENTIONS

Baseline
The values to be used as baseline will be the Day-1 for each treatment group. If any of the scheduled baseline tests are repeated for any patient, the last rechecked values will be considered as baseline, provided they were done before the start of IMP administration.

14.7.2. DESCRIPTIVE STATISTICS

The summary statistics (including number, mean, SD, median, first and third quartiles, minimum and maximum) of all vital signs variables (values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, and worst on-treatment value).
Summaries will be repeated by age group for C3&4SAF.

14.7.3. ANALYSES OF ABNORMALITIES

The incidence of PCSAs (list provided in Appendix 3) at any time during the TEAE period will be summarized, irrespective of the baseline level and/ or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

14.7.4. GENERAL VITAL SIGN AND PHYSICAL MEASUREMENTS LISTINGS

Individual data (for the supine position only for heart rate, systolic and diastolic blood pressure), including rechecked and unscheduled values, will be listed by cohort, treatment group, patient, visit and time of assessment.
In the listings, values will be flagged when reaching the limits of the PCSA criteria, when defined.

14.8. PHYSICAL EXAMINATION

The physical examination outcome (Normal/Abnormal) will be collected at screening and post baseline visits.
Any abnormal, clinically significant physical examination assessments will be reported as AEs.
A full assessment of malaria signs and symptoms will be made alongside the physical examination.
The following summaries will be provided for physical examination data:

- Incidence of abnormalities at screening
- Incidence of abnormalities post baseline

15. REFERENCES

1. Flegg, J. A., Guerin, P. J., White, N. J., & Stepniewska, K. Standardizing the measurement of parasite clearance in falciparum malaria: the parasite clearance estimator. Malaria journal.2011;10(1): 339

2. Fogarty, C. B., Fay, M. P., Flegg, J. A., Stepniewska, K., Fairhurst, R. M., & Small, D. S. Bayesian hierarchical regression on clearance rates in the presence of "lag" and "tail" phases with an application to malaria parasites. Biometrics. 2015; 71(3):751-759.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

SPELLING FORMAT

English US

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TEAES

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE

		If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR/ CONCOMITANT MEDICATIONS

STARTDATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment

STARTDATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

APPENDIX 3. POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES ARITERIA

PCSA DEFINITION FOR LABORATORY PARAMETERS

Laboratory parameter PCSA criteria	Adults	Children
Hemoglobin		
Low	≤ 115g/L (Male) ≤ 95 g/L (Female)	28 days/1 month to 23 months old : < 90 g/L 24 months/2 years to <16/18 years old : < 100 g/L
Decrease from baseline	≥ 20 g/L	≥2 0 g/L

High (adults)	≥ 185 g/L (Male) ≥ 165 g/L (Female)	
Hematocrit		
Low	≤ 0.37 v/v (Male) ≤ 0.32 v/v (Female)	28 days/1 month to 23 months old: < 0.29 v/v 24 months/2 years to <16/18 years old: < 0.32 v/v
High	≥ 0.55 v/v (Male) ≥ 0.5 v/v (Female)	28 days/1 month to 23 months old: > 0.42 v/v 24 months/2 years to <16/18 years old: > 0.47 v/v
Erythrocyte Count		
High (adults)	≥ 6 Tera/L	
Platelet Count		
Low	< 100 Giga/L	< 100 Giga/L
High	≥ 700 Giga/L	≥ 700 Giga/L
Leukocytes		
Low	< 3.0 Giga/L (Non-Black) < 2.0 Giga/L (Black)	Birth/0 to 23 months old: <4.0 Giga /L 24 months/2 years to <6 years old: <3.0 Giga /L 6 to <12 years old: <5.0 Giga /L
High	≥ 16.0 Giga/L	Birth/0 to 27 days old: >25.0 Giga /L 28 days/1 month to 23 months old: >20.0 Giga /L 24 months/2 years to <6 years old: >16.0 Giga /L 6 to <12 years old: >17.0 Giga /L 12 to 16/18 years old: >13.5 Giga /L
Neutrophils		
Low	< 1.5 Giga/L (Non-Black) < 1.0 Giga/L (Black)	Birth/0 to 27 days old: <4 Giga /L (1 day old) <1.5 Giga /L (2-7 days old) <1.25 Giga /L (>7 day-1 month old) 28 days/1 month to 23 months old: <1.0 Giga /L (1-3 months) <1.2 Giga /L (3-24 months) 24 months/2 years to <16/18 years old: <1.2 Giga /L
High (children)		>1 ULN
Lymphocytes		
Low (children)		Birth/0 to 27 days old: <1.2 Giga /L 28 days/1 month to 23 months old: <2.0 Giga /L 24 months/2 years to <12 years old: <1.0 Giga /L 12 to 16/18 years old: <0.6 Giga /L
High	> 4.0 Giga/L	Birth/0 to 27 days old: >17.0 Giga /L 28 days/1 month to 23 months old: >13.5 Giga /L 24 months/2 years to <6 years old: >9.5 Giga /L 6 to <12 years old: >8.0 Giga /L 12 to 16/18 years old: >6 Giga /L
Monocytes		
High (adults)	> 0.7 Giga/L	
Basophils		
High (adults)	> 0.1 Giga/L	
Eosinophils		

High	> 0.5 Giga/L or > ULN (if ULN ≥ 0.5 Giga/L)	> 0.5 Giga/L or > ULN (if ULN > 0.5 Giga/L)
Glucose		
Low	≤ 3.9 mmol/L and < LLN	<2.7 mmol/L
High	≥11.1 mmol/L (unfasted) ≥ 7 mmol/L (fasted)	≥10.0 mmol/L (unfasted) ≥7 mmol/L (fasted after >12 hours of fast)
Albumin		
Low (adults)	≤ 25 g/L	
Creatine Kinase		
High, all grades	> 3 ULN	≥ 3 ULN
At least grade 1 (adults)	> 3 ULN	
At least grade 2 (adults)	> 10 ULN	
Sodium		
Low	< 3 mmol/L	Birth/0 to 27 days old: ≤3.0 mmol/L 28 days/1 month to 16/18 years old: ≤3.5 mmol/L
High	≥ 5.5 mmol/L	Birth/0 to 27 days old: ≥7.0 mmol/L 28 days/1 month to 23 months old: ≥6.0 mmol/L 24 months/2 years to 16/18 years old: ≥5.5 mmol/L
Creatinine		
High	≥ 150 µmol/L	Birth/0 to <6 years old: >53 µmol/L 6 years to <12 years old: >90 µmol/L 12 years to 16/18 years old: >132 µmol/L
Increase from baseline		
At least grade 1 (adults)	≥ 30% change from baseline	
At least grade 2 (adults)	≥ 100% change from baseline	
Creatinine Clearance		
Low, all grades	< 90 mL/min*	Birth/0 to 27 days old: < 25 ml/min/1.73m² ** 28 days/1 month to 23 months old: < 45 ml/min/1.73m² ** From 2 years old: < 60 ml/min/1.73m² **
Mild (adults)	[60 – 90[mL/min*	
Moderate (adults)	[30 – 60[mL/min*	
Severe (adults)	[15 – 30[mL/min*	
End stage (adults)	< 15 mL/min*	
	*MDRD or Cokcroft-Gault equation	**GFR Bedside Schwartz Formula Based on normal ranges: 20 to 50 (<8 days), 25 to 80 (8 days to 1 month), 30 to 90 (1-6 months), 40 to 115 (6-12 months), 60 to 190 (12-23 months), 90 to 165 (2-12 years), 80-120 (After 12 years)
BUN		

High	≥ 17 mmol/L	Birth/0 to 27 days old: ≥4.3 mmol/L 28 days/1 month to 16/18 years old: ≥6.4 mmol/L
Alanine Aminotransferase		
High, at least grade 1	> 3 ULN	≥ 3 ULN
High, at least grade 2	> 5 ULN	≥ 5 ULN
High, at least grade 3	> 10 ULN	≥ 10 ULN
High, at least grade 4	> 20 ULN	≥ 20 ULN
Aspartate Aminotransferase		
High, at least grade 1	> 3 ULN	≥ 3 ULN
High, at least grade 2	> 5 ULN	≥ 5 ULN
High, at least grade 3	> 10 ULN	≥ 10 ULN
High, at least grade 4	> 20 ULN	≥ 20 ULN
Alkaline phosphatase		
High	> 1.5 ULN	≥ 1.5 ULN
Total Bilirubin		
High, all grades	> 1.5 ULN	≥ 1.3 ULN
At least grade 1 (adults)	> 1.5 ULN	
At least grade 2 (adults)	> 2 ULN	
Alanine Aminotransferase and total bilirubin		
High	ALT > 3 ULN and TBILI > 2 ULN	ALT ≥ 3 ULN and TBILI ≥ 2 ULN
Direct bilirubin and total bilirubin		
High	BILDIR >35% TBILI and TBILI >1.5 ULN	BILDIR >35% TBILI and TBILI≥1.3 ULN

References:
-for adults: Criteria for Potentially Significant Abnormalities – for Phase 2/3 studies (oncology excepted) - Version 3.0 – 21-MAY-2014
-for children: Criteria for Potentially Clinically Significant Abnormalities for Studies in Children - Version 3.0 - 21-MAY-2014

PCSA DEFINITION FOR ECG PARAMETERS

ECG parameter PCSA criteria	Adults	Children
Heart Rate		
Low, at least grade 1 (adults)	<50 bpm	
Low, at least grade 2 (adults)	<40 bpm	
Low, at least grade 3 (adults)	<30 bpm	
Low and decrease from baseline, all grades	<50 bpm and decrease from baseline ≥20 bpm	Birth/0 to 27 days old: ≤ 90 bpm and decrease from baseline ≥20 bpm 28 days/1 month to 23 months old: ≤ 80 bpm and decrease from baseline ≥20 bpm 24 months/2 years to <6 years old: ≤ 75 bpm and decrease from baseline ≥20 bpm 6 to <12 years old: ≤ 50 bpm and decrease from baseline ≥20 bpm

		12 to 16/18 years old: ≤ 50 bpm and decrease from baseline ≥20 bpm
At least grade 1 (adults)	<50 bpm and decrease from baseline ≥20 bpm	
At least grade 2 (adults)	<40 bpm and decrease from baseline ≥20 bpm	
At least grade 3 (adults)	<30 bpm and decrease from baseline ≥20 bpm	
High, at least grade 1 (adults)	>90 bpm	
High, at least grade 2 (adults)	>100 bpm	
High, at least grade 3 (adults)	>120 bpm	
High and increase from baseline, all grades	>90 bpm and increase from baseline ≥20bpm	Birth/0 to 27 days old: ≥ 190 bpm and increase from baseline ≥20 bpm 28 days/1 month to 23 months old: ≥ 175 bpm and increase from baseline ≥20 bpm 24 months/2 years to <6 years old: ≥ 140 bpm and increase from baseline ≥20 bpm 6 to <12 years old: ≥ 120 bpm and increase from baseline ≥20 bpm 12 to 16/18 years old: ≥ 120 bpm and increase from baseline ≥20 bpm
At least grade 1 (adults)	>90 bpm and increase from baseline ≥20bpm	
At least grade 2 (adults)	>100 bpm and increase from baseline ≥20bpm	
At least grade 3 (adults)	>120 bpm and increase from baseline ≥20bpm	
PR		
High, all grades	>200 ms	Birth/0 to 27 days old: ≥ 120 ms 28 days/1 month to 23 months old: ≥ 140 ms 24 months/2 years to <6 years old: ≥ 160 ms 6 to <12 years old: ≥ 170 ms 12 to 16/18 years old: ≥ 180 ms
At least grade 1 (adults)	>200 ms	
At least grade 2 (adults)	>220 ms	
At least grade 3 (adults)	>240 ms	
High and increase from baseline (adults)		
At least grade 1	>200 ms and increase from baseline ≥25%	
At least grade 2	>220 ms and increase from baseline ≥25%	
At least grade 3	>240 ms and increase from baseline ≥25%	
QRS		
High, all grades	>110 ms	Birth/0 to 27 days old: ≥ 85 ms 28 days/1 month to 23 months old: ≥ 85 ms 24 months/2 years to <6 years old: ≥ 95 ms 6 to <12 years old: ≥ 100 ms

		12 to 16/18 years old: ≥ 110 ms
At least grade 1 (adults)	>110 ms	
At least grade 2 (adults)	>120 ms	
High and increase from baseline (adults)		
At least grade 1	>110 ms and increase from baseline ≥25%	
At least grade 2	>120 ms and increase from baseline ≥25%	
QTc Fridericia and QTc Bazett		
Increase from baseline, Grade 1	Increase from baseline]30-60] ms	All age classes: Increase from baseline]30-60] ms
Increase from baseline, Grade 2	Increase from baseline >60 ms	All age classes: Increase from baseline >60 ms

References:
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PCSA DEFINITION FOR VITAL SIGNS PARAMETERS

Vital signs parameter PCSA criteria	Adults	Children
Systolic blood pressure supine		
Low and decrease from baseline	≤95 mmHg and decrease from baseline ≥20 mmHg	Birth/0 to 27 days old: ≤ 60 mmHg and decrease from baseline ≥20 mmHg 28 days/1 month to 23 months old: ≤ 70 mmHg and decrease from baseline ≥20 mmHg 24 months/2 years to <6 years old: ≤ 70 mmHg and decrease from baseline ≥20 mmHg 6 to <12 years old: ≤ 80 mmHg and decrease from baseline ≥20 mmHg 12 to 16/18 years old: ≤ 90 mmHg and decrease from baseline ≥20 mmHg
High and increase from baseline	≥160 mmHg and increase from baseline ≥20 mmHg	Birth/0 to 27 days old: ≥ 85 mmHg and increase from baseline ≥20 mmHg 28 days/1 month to 23 months old: ≥ 98 mmHg and increase from baseline ≥20 mmHg 24 months/2 years to <6 years old: ≥ 101 mmHg and increase from baseline ≥20 mmHg 6 to <12 years old: ≥ 108 mmHg and increase from baseline ≥20 mmHg 12 to 16/18 years old: ≥ 119 mmHg and increase from baseline ≥20 mmHg
Diastolic blood pressure supine		
Low and decrease from baseline	≤45 mmHg and decrease from baseline ≥10 mmHg	Birth/0 to <6 years old: ≤ 34 mmHg and decrease from baseline ≥10 mmHg 6 to <12 years old: ≤ 48 mmHg and decrease from baseline ≥10 mmHg

		12 to 16/18 years old: ≤ 54 mmHg and decrease from baseline ≥10 mmHg
High and increase from baseline	≥110 mmHg and increase from baseline ≥10 mmHg	Birth/0 to 27 days old: ≥ 50 mmHg and increase from baseline ≥10 mmHg 28 days/1 month to 23 months old: ≥ 54 mmHg and increase from baseline ≥10 mmHg 24 months/2 years to <6 years old: ≥ 59 mmHg and increase from baseline ≥10 mmHg 6 to <12 years old: ≥ 72 mmHg and increase from baseline ≥10 mmHg 12 to 16/18 years old: ≥ 78 mmHg and increase from baseline ≥10 mmHg
Heart rate supine (adults)		
Low and decrease from baseline	≤50 bpm and decrease from baseline ≥20 bpm	
Low and decrease from baseline	≥120 bpm and increase from baseline ≥20 bpm	

References:
-for adults: Criteria for Potentially Significant Abnormalities – for Phase 2/3 studies (oncology excepted) - Version 3.0 – 21-MAY-2014
-for children: Criteria for Potentially Clinically Significant Abnormalities for Studies in Children - Version 3.0 - 21-MAY-2014

APPENDIX 4. POWER AND SAMPLE SIZE

The below table shows the power for different sample size and success rate hypotheses.

Sample size	Hypothesis on success rate	Power[a]
140	0.92	6.3%
140	0.94	25.9%
140	0.95	44.6%
140	0.96	67.2%
140	0.964	75.9%
140	0.97	87.1%
150	0.92	8.1%
150	0.94	31.7%
150	0.95	52.3%
150	0.96	74.7%
150	**0.964**	**82.5%**
150	0.97	91.7%
160	0.92	10.0%
160	0.94	37.4%
160	0.95	59.3%
160	0.96	80.7%
160	0.964	87.5%
160	0.97	94.7%

[a] probability that the lower bound of the exact (Clopper-Pearson) 95% two-sided confidence interval for success rate is strictly greater than 0.9.