SANOFI

NCT03660839

STATISTICAL ANALYSIS PLAN

A Randomized, Open label, Parallel-group, Single Dose Regimen, Phase 2a Study, to Investigate the Clinical and Parasiticidal Activity and the Pharmacokinetics of 3 dose levels of Artefenomel (OZ439) given in combination with Ferroquine (FQ) and FQ alone, in African Patients with Uncomplicated Plasmodium falciparum Malaria

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V3.0 (Dated 29MAY2020) for Protocol ACT14655

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACPR:	Adequate Clinical and Parasitological Response
AESIs:	Adverse Event of special Interest
ALP:	Alkaline phosphatase
ALT:	Alanine aminotransferase
AST:	Aspartate Aminotransferase
ATC:	Anatomic category
AV:	Atrioventricular conduction
BILDIR:	Direct bilirubin
BMI:	Body Mass Index
CRF:	case report form
DBL:	Data Base Lock
e-CRF:	electronic case report form
ETF:	Early Treatment Failure
FCT:	Fever Clearance Time
FQ:	Ferroquine
HAV:	Hepatitis A virus
HAV IgM:	hepatitis A immunoglobulin M
HBsAg:	hepatitis B surface antigen
HCG:	human chorionic gonadotropin
HCV:	Hepatitis C Virus
HCV Ab:	hepatitis C virus antibody
HCV RNA:	hepatitis C virus ribonucleic acid
HLGT:	High Level Group Term
HLT:	High Level Term
ICF:	Informed Consent Form
IMP:	Investigational Medicinal Product
IRT:	Interactive Response Technology
ITT:	intent-to-treat
IVRS:	Interactive Voice Response System
LCF:	Late Clinical Failure
LLT:	Lower Level Term
LOQ:	Limit of Quantification
LPF:	Late Parasitological Failure
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	modified-intent-to-treat
PCR:	Polymerase Chain Reaction
PCSA:	Potentially Clinically Significant Abnormality
PCT:	parasite clearance time
PP:	per-protocol
PR:	Parasite Reduction
PRR:	Parasite Reduction Ratio

PT:	Preferred Term
qPCR:	quantitative polymerase chain reaction
RT-qPCR:	quantitative reverse transcription polymerase chain reaction
SAEs:	Serious Adverse Events
SMQ:	standardized MedDRA query
SOC:	System Organ Class
TBILI:	Total bilirubin
TEAE:	Treatment emergent Adverse Event
TPC50:	Time until reduction by 50% of parasitemia
TPC99:	Time until reduction by 99% of parasitemia
TPGS:	alpha tocopherol polyethylene glycol 1000 succinate
WHO-DD:	World Health Organization-Drug dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

A phase 2a, randomized, open label, parallel-group study, single-dose regimen, testing 3 dose levels of OZ439 given in combination with FQ and FQ alone in participants with uncomplicated P. falciparum malaria.

After a screening phase of up to 1 day before the single dose administration, patients are randomized (stratified by investigative site) via Interactive Response Technology (IRT) in a 1:1:1:1 ratio to 1 of the 4 treatment groups.

Balance across a group of blocks will be achieved by considering a Latin square design feature during the generation of the randomization schedule. This approach is being used to provide better balance of study level treatment assignments as compared to conventional random of sampling for blocks.

12 blocks size (of size 8) will be attributed to each site and will be balanced across the group block entries, as well as within each block. The full randomization list will be comprised of the records which make up twelve 8 x 8 Latin squares (12 x 8 x 8 = 768 records in total). The sequence of treatment groups within each block will be random.

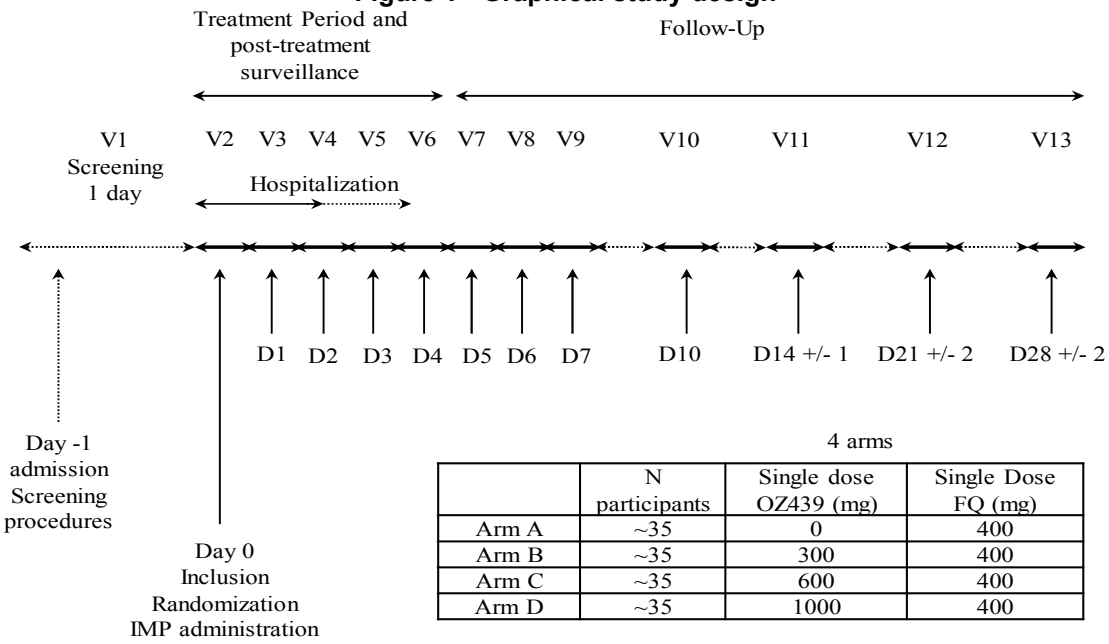
Approximately 140 patients (35 patients per treatment group) will be recruited and randomized in order to have 120 evaluable patients (30 patients per treatment group) from approximately 8 to 10 sites.

Adults up to 69 years old and adolescents as of 14 years old will be included in 4 parallel arms in a 1:1:1:1 randomization ratio. Randomization will occur the day of or up to 1 day after screening procedures.

Participants will receive one of the 4 treatments: FQ 400 mg alone or combined with OZ439 300 mg, 600 mg, or 1000 mg.

The graphical presentation of the study design on the single-dose treatment is provided in Figure 1.

Figure 1 - Graphical study design



4 arms

	N participants	Single dose OZ439 (mg)	Single Dose FQ (mg)
Arm A	~35	0	400
Arm B	~35	300	400
Arm C	~35	600	400
Arm D	~35	1000	400

Note: Visits 1 & 2 can occur on the same day ; Visit 13 : assessment of primary endpoint

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to show the contribution of OZ439 to the clinical and parasiticidal effect of OZ439/FQ combination by analyzing exposure-response of OZ439 measured by Day 28 PCR-corrected ACPR for the effect and the AUC of OZ439 as PK predictor

1.2.2 Secondary objectives

The secondary objectives of this study are:

- To evaluate the dose response of OZ439 combined with FQ on PCR-corrected and crude Day 28 ACPR
- To evaluate the dose-response of OZ439 combined with FQ on selected secondary endpoints
- To evaluate the safety and tolerability of different dosages of OZ439 in combination with FQ and FQ alone
- To characterize the PK of OZ439 in plasma, and of FQ and its active metabolite SSR97213 in blood

1.2.3 Tertiary/exploratory objectives

The exploratory objectives of this study are:

- To explore the impact of study treatment on functional gametocytemia
- To evaluate the relationship between parasitemia and concentration of OZ439/FQ
- To evaluate the relationship between QTc and concentration of OZ439/FQ

1.3 DETERMINATION OF SAMPLE SIZE

The strategy for selecting fixed FQ dose, baseline parasitemia, and sample size was composed of two parts:

1. Estimated efficacy (Day 28 PCR-corrected ACPR) of FQ 200, 400, 600 and 900 mg administrated in presence of OZ439 TPGS for different levels of baseline parasitemia

2. Estimated power for various sample size of an OZ439 exposure-effect analysis, considering the fixed FQ dose, the 4 selected OZ439 dose levels (0, 300, 600, 1000 mg) and the selected baseline parasitemia

Part 1: Estimated efficacy (Day 28 PCR-corrected ACPR) of FQ 200, 400, 600 and 900 mg administrated in presence of OZ439 TPGS for different levels of baseline parasitemia

Clinical trial simulations were used, consisting of simulating FQ concentrations at Day 7, baseline parasitemia, and then PCR-corrected ACPR at Day 28 using a model linking ACPR at Day 28 probability to FQ concentration at Day 7 and baseline parasitemia.

The model (eq 1) was a logistic regression modeling PCR-corrected ACPR at Day 28 probability (p) as a function of FQ concentration at Day 7 ($Conc_{D7,FQ}$), Artesunate (AR) indicator (no/yes) and baseline log_{10}-parasitemia. It was developed from DRI10382 data: African patients, Per Protocol population, excluding patients with reinfections, using the 4 arms of the DRI10382 (FQ 4 mg/kg or AR + FQ 2, 4 or 6 mg/kg, repeated doses). Two types of analyses were done, classifying as failure or excluding patients with rescue therapy before/without failure, and finally the results of the analysis excluding patients were favored, to compensate for the possible underestimation of FQ single dose effect (model built on repeated doses). In this analysis based on 223 patients, the FQ efficacy was estimated to be ACPR28corr=80.9% (95% Confidence Interval [CI]: 66.7% to 90.9%) in arm FQ 600 mg.

(eq 1) $\log(p/(1-p)) = \alpha + \beta_{FQ}.Conc_{D7,FQ} + \beta_{AR}.\ (AR=yes) + \beta_{BasePar}.\log_{10}(BasePar)$

FQ concentrations at Day 7 (168 h post dose) were simulated from the FQ PopPK model updated from DRI12805 (POH0456) for TPGS formulation and single dose administration, in an African adult population (weights resampled from 194 profiles of African adults of DRI10382 and DRI12805 cohort 1A and 1B, of median weight 55 kg and median age 21 years). Log-normal distributions were fitted to these simulated concentrations and then used for simulation.

Baseline parasitemia was simulated for different scenarii, using truncated log-normal distributions. The base assumption was a baseline parasitemia greater than 1000 parasites/µL and of median about 10,000 parasites/µL. Some other scenarii were considered: baseline parasitemia greater than 3000, 5000, or 10,000 parasites/µL, with a maximum fixed at 5.5 $\log_{10}$ parasites/µL. In the following, the baseline parasitemia greater than 3000 parasites/µL scenario was selected to ensure a better enrollment of patients during the study.

Based on N=10,000 simulations/arm and S=1000 simulations for the model parameters uncertainty, the results showed a PCR-corrected ACPR at Day 28 estimated at 72% (90%CI: [57% to 84%]) for FQ 400mg alone and 79% (90%CI: 67% to 87%) for FQ 600 mg alone for a baseline parasitemia greater than 3000 parasites/µL. Finally the FQ fixed dose of 400 mg was selected.
Results estimated that 30 evaluable participants per treatment arm will yield a power around 90% to detect an OZ439 concentration effect relation (in a population of patient with a baseline parasitemia greater than 3000 parasites/µL, for 4 arms FQ 400 mg + OZ439 at 0, 300, 600, and 1000 mg).

Part 2: Estimated power for various sample size of an OZ439 exposure-effect analysis, considering the fixed FQ dose, the 4 selected OZ439 dose levels (0, 300, 600, 1000 mg) and the selected baseline parasitemia

Simulation of clinical trials

Clinical trial simulations were used to simulate trials of 4 arms with a fixed dose of 400 mg FQ and 4 dose levels of OZ439 (0, 300, 600, and 1000 mg) for a baseline parasitemia greater than 3000 parasites/µL. FQ and OZ439 concentrations at Day 7 (168 h post dose) were simulated using log-normal distributions that were corrected to concentrations obtained from the FQ PopPK model and from the OZ439 PopPK model in an African adult population (as in part 1), and were assumed to be slightly correlated. Truncated log-normal distributions were used to simulate baseline parasitemia greater than 3000 parasites/µL in $\log_{10}$Par/µL by a normal distribution:

mean=4, SD=0.55, minimum=3.48; maximum=5.5 (minimum and maximum for the truncation).
Day 28 PCR-corrected ACPR was simulated using a "hypothetical" model linking ACPR at Day 28 probability to FQ and OZ439 concentration at Day 7 and baseline parasitemia.

The "hypothetical" logistic regression model (eq 2, see below) used for simulations was a composite of the "PQP/OZ-ACPR28 model" built by MMV, modeling PCR-corrected ACPR at Day 28 probability (p) as a function of OZ439 and PQP concentrations at Day 7 and baseline $\log_{10}$-parasitemia, and of assumptions made on FQ efficacy, which were based on the results of part 1. Precisely, β_{FQ} was fixed at 0.12 by calibration to get ~ 72% success ACPR at Day 28 for FQ 400 mg alone for a baseline parasitemia greater than 3000 parasites/µL, and the following parameters were extracted from the MMV model: α=3.23, β_{OZ439} = 0.73, and $\beta_{BasePar}$ = -1.27.

(eq 2) $\log(p/(1-p)) = \alpha + \beta_{FQ}.Conc_{D7,FQ} + \beta_{OZ439}.\ Conc_{D7,OZ} + \beta_{BasePar}.\log_{10}(BasePar)$

Using all these assumptions, the PCR-corrected ACPR at Day 28 rates simulated in the 4 arms FQ 400 mg + OZ439 at 0, 300, 600 and 1000 mg were of 72%, 81%, 91%, and 97% for a baseline parasitemia greater than 3000 parasites/µL.

Clinical trials analyses

Exposure-effect analyses of the simulated clinical trials were performed, consisting of a logistic regression model of exposure at Day 7 for both drugs, with baseline parasitemia as covariate, and the Day 28 PCR-corrected ACPR as response variable (as in eq 2 above). Significance of OZ439 concentration effect (βOZ439) was analyzed using a 2-sided alpha Wald test at 5%.

Overall, five thousand trial simulations were performed, and the power was deduced as the percentage of significant simulated trials. Results estimated that 30 evaluable participants per treatment arm will yield a power around 90% to detect an OZ439 concentration effect relation (in a population of patients with a baseline parasitemia greater than 3000 parasites/µL, for 4 arms FQ 400 mg + OZ439 at 0, 300, 600, and 1000 mg).

1.4 STUDY PLAN

A brief description of the study design is provided in Section 1.1. The planned study schedule can be found in Appendix A Schedule of Activities of the protocol.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The statistical section of the protocol was never changed in an amendment.
There are no planned interim analyses.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The primary efficacy population will be the PK/PD population instead of the mITT population stated in the protocol.

A per-protocol [PP] population was added in order to align the analysis population with the primary endpoint of the study. All populations have been further clarified from the protocol definitions

The derivation of the secondary endpoint, Fever clearance time (FCT), has been added. FCT will be assessed by measuring the time from the first dose until the first time that the body temperature dropped and remained <37.5 °C.

Time to 50% parasite reduction (T_{PC50}) will also be calculated in addition to the time to 99% PR.

The evaluation of the relationship between parasitemia (as measured on thick blood film and/or by qPCR) and concentration of OZ439/FQ may be performed in a separate analysis pooling data from different studies and be reported in a separate report.

The terminal half-life (t1/2) for OZ439 and ferroquine will not be estimated as this endpoint does not contribute to the objectives of the study.

The definition of baseline to be used for efficacy analyses has been clarified.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Baseline

Baseline for all efficacy analyses will be defined as the last measurement prior to the study drug administration, i.e., in general the Day 0, pre-dose assessment. Only if the Day 0, pre-dose assessment is missing the screening assessment will be used instead.

For safety analyses baseline is defined as the last available value before first IMP at Visit 1 (screening) for laboratory and vital signs and at Visit 2 (Day 0 before IMP administration) for ECG parameters

2.1.2 Demographic and baseline characteristics

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the on-treatment summary statistics in the efficacy and safety sections (Section 2.4.4 and Section 2.4.5).
The below variables will be summarized by treatment group and, overall.

Demographic characteristics

Demographic variables at baseline:

- Age (years)
- Gender (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported and Unknown)
- Ethnicity (Hispanic, Not Hispanic)
- Body weight (kg)
- Body weight category : [35-40 kg[,[40-50 kg[and > 50 kg
- Body mass index (BMI) (kg/m^2)
- Fever (yes/no) defined with axillary temperature ≥37.5 degree Celsius (°C) or oral/ rectal/ tympanic temperature ≥38°C
- Baseline parasitemia (parasites/µL)
- Baseline parasitemia defined in 4 classes : (< 3000 parasites/µL, [3000-10000] parasites/µL,]10000-50000] parasites/µL and > 50000 parasites/µL)

Medical or surgical history

Medical and surgical history, other than malaria, within the life-time of the patient, will be coded to a preferred term (PT) and associated primary System Organ Class (SOC) using the version of the Medical Dictionary for Regulatory Activities (MedDRA) in use at Sanofi at the time of database lock (DBL).

Disease characteristics at baseline

Clinical signs/symptoms related to uncomplicated malaria and other relevant signs of malaria will be coded to PT using the version of MedDRA in use at Sanofi at the time of DBL.

Any technical details related to computation, dates, and imputations for missing dates are described in Section 2.5.

2.1.3 Prior or concomitant medications

All medications taken within 2 months prior to the screening visit, and during the study until the end of the study (Day 28) are to be reported in the electronic case report form (e-CRF) pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) version in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used prior to screening up until the first investigational medicinal product (IMP). Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from randomization (Day 0) to Day 28. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the post-treatment period (as defined in the observation period in Section 2.1.5).
- Post-treatment medications are those the patient took in the post-treatment period (as defined in the observation period in Section 2.1.5).

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.4 Efficacy endpoints

All efficacy measurements, scheduled or unscheduled, or done out of the time window (see details in the last paragraph of this section), will be assigned to analysis windows defined in Section 2.5.4.1. For all post baseline measurements, the value used for the analyses at a given time point is the value obtained within the corresponding analysis windows.

At screening/pre-dose blood films, three slides (two thick films and one thin film) should be collected using the same blood sample at the site, before Informed Consent signature, according to local standard procedures and within 4 hours prior to dosing, can be used for screening/pre-dose parasitemia assessment.

- The parasite count from the first thick film will be used to calculate the screening parasitemia value.
- The second thick film slide will be used to calculate a more accurate pre-dose parasitemia count (asexual).
- The thin film slide is used for parasite speciation. Only patients with P. falciparum monoinfection should be recruited in the study.

The baseline value for efficacy variables is defined as the last available value on or before randomization. By default, the baseline parasitemia is the parasite count based on the second thick film slide, even if missing value at screening.

Time points and imputation rules

Parasite count (i.e. asexual forms P. falciparum parasite count determined from blood thick films at each planned time point, a second thick film slide is kept as contingency) and concomitant body temperature are the key components of efficacy evaluations. They have to be assessed at predefined time points specified in the study protocol. However, shifts from scheduled timing are expected (especially after discharge from hospital), and this will be managed in analyses by allocating protocol planned time points based on the actual timing of assessments - rather than based on the theoretical timing of the visit they come from, using allowed windows of time around these protocol planned time points. Allowed time windows are defined in Section 2.5.4.1. In this section and other sections related to efficacy, time points will always refer to these allowed time windows, except otherwise specified.

In addition, except where otherwise specified, the following imputation rules will apply in case of missing or out of time window parasite count at a protocol scheduled time point, where the missing count occurs before rescue treatment start, before or on Day 28, or in absence of concomitant fever. In such cases, the missing parasitemia will be considered as:

- positive, if followed or preceded by positive parasitemia,
- negative, if preceded and followed by negative parasitemia,
- missing, if no parasite count available thereafter.

In above bullets:

- positive parasitemia means P. falciparum parasite count from thick film ≥ 1 parasite/μL, otherwise the parasitemia is negative.
- parasite count from thick film performed after rescue treatment start cannot be used for imputation of missing or out of time window parasite count.

- parasite count from thick film performed the day of rescue treatment start can be used for imputation because this is regarded as before rescue treatment.

In case of concomitant fever related to malaria event (fever is defined in Section 2.1.4.2.8), a missing parasitemia will be always considered as positive.

In case of missing (or out of time window) parasite count at successive protocol scheduled time points, the above imputations rules could be extended after endorsement of the imputations by the clinical team, otherwise the case will be classified as a deviation preventing evaluation of ACPR as listed in Section 2.3.2.2. Cases of missing body temperature concomitantly with positive parasitemia (observed, or put in place of a missing parasite count as explained above) will be imputed, according to the same principle as for parasitemia imputations, after endorsement of the imputations by the clinical team, or will be classified as deviation.

Efficacy evaluation

Efficacy evaluation will use Early Treatment Failure (ETF), Late Clinical Failure (LCF), Late Parasitological Failure (LPF), and Adequate Clinical and Parasitological Response (ACPR) definitions given below.

Table 1 - Revised WHO classification of treatment failures in areas of intense malaria transmission

Criterion
ETF is defined as one of the following : - Development of danger signs or symptoms of complicated/severe malaria on Day 1, Day 2 or Day 3, in the presence of parasitemia (reported as Term='Complicated Malaria' by the investigator in the 'Adverse Event' form and reported in the e-CRF dedicated form "Malaria Signs and Symptoms") concomitant to at least one positive parasitemia. Considering that the drug cannot be active before 24h, a severe malaria presenting between 0h and 24h is highly suspect of wrong inclusion of the patient. - Parasitemia on Day 2 higher than baseline parasitemia count (irrespective of body temperature) - Parasitemia on Day 3 with axillary temperature of ≥37.5°C - Parasitemia on Day 3 ≥25% of baseline parasitemia count
LCF is defined as one of the following, without previously meeting any of the ETF criteria : - Development of danger signs or severe malaria after Day 3 in the presence of parasitemia (reported as Term='Complicated Malaria' by the investigator in the 'Adverse Event' form and reported in the e-CRF dedicated form "Malaria Signs and Symptoms") concomitant to at least one positive parasitemia. - Presence of parasitemia and axillary temperature >37.5°C on any day from Day 4 to Day 28, without previously meeting any of the criteria of early treatment failure
LPF - Presence of parasitemia on any day from Day 7 to Day 28, and axillary temperature <37.5°C, without previously meeting any of the criteria of ETF or LCF

Criterion
ACPR - Absence of parasitemia on Day 28 irrespective of axillary temperature without previously meeting any of the criteria of ETF or LCF or LPF, and without previous rescue therapy start. Rescue therapy start without previous WHO criteria can be due to: investigator decision (classified as failure or deviation based on case by case clinical review, see Section 2.3.2.2), major vomiting or severe malaria at Day 0 (both classified as deviation, see Section 2.3.2.2), other species infection.

The following definitions will also be considered regarding efficacy evaluation:

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.

Treatment failure: Any patients who met any of the criteria for ETF, LCF or LPF.

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-corrected 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.

Genotyping adjustment

LCF occurring from Day 7 or LPF will be sub-classified as follows using parasite genotyping results:

- P. falciparum recrudescence, if no other species reported in eCRF and genotyping result is “recrudescence”
- P. falciparum reinfection, if no other species reported in eCRF and genotyping result is “reinfection”

- Other species with P. falciparum recrudescence, if other species reported in eCRF and genotyping result is “recrudescence”
- Other species with P. falciparum reinfection, if other species reported in eCRF and genotyping result is “reinfection”
- Undetermined, negative or missing PCR, if genotyping result is “Undetermined “, “negative”, “undetermined” or “missing”, with or without other species infection.

2.1.4.1 Primary efficacy endpoint

The primary efficacy endpoint is the PCR-corrected ACPR at Day 28. The PCR-corrected ACPR at Day 28 will be derived from the efficacy evaluation at Day 28 defined as follows:

Efficacy evaluation at Day 28	Per Protocol PCR-corrected ACPR at Day 28	mITT PCR-corrected ACPR at Day 28
ACPR	Success	Success
ETF	Failure	Failure
LCF before Day 7	Failure	Failure
LCF on or after Day 7 or LPF		
- P. falciparum recrudescence	Failure	Failure
- P. falciparum reinfection prior to Day 28	Excluded from analysis	Failure
- P. falciparum reinfection on Day 28	Success	Success
- Other species mixed with P. falciparum recrudescence	Failure	Failure
- Other species mixed with P. falciparum reinfection	Excluded from analysis	Failure
- Undetermined, negative or missing PCR	Excluded from analysis	Failure
Rescue therapy start without previous ETF, LCF, LPF, or other species infections, and not classified as a protocol violation	Before Day 7: Failure On/after Day 7: excluded from analysis	Failure
Other species infection without P. falciparum reemergence	Excluded from analysis	Failure
Lost to follow-up	Excluded from analysis	Failure
Withdrawal*	Excluded from analysis	Failure
Protocol violation**	Excluded from analysis	Failure

(*): Patient’s request - Investigator's judgement - Adverse event - Other
(**): protocol violations potentially impacting efficacy assessment at Day 28 for the PP population ar defined in Section 2.3.2.2

2.1.4.2 Secondary efficacy endpoints

2.1.4.2.1 Crude ACPR at Day 28

Derived from the efficacy evaluation at Day 28 defined as follows:

	Per-Protocol	**mITT**
Efficacy evaluation at Day 28	**Crude ACPR at Day 28**	**Crude ACPR at Day 28**
ACPR	Success	Success
ETF	Failure	Failure
LCF before Day 7	Failure	Failure
LCF on or after Day 7 or LPF		
- P. falciparum recrudescence	Failure	Failure
- P. falciparum reinfection prior to Day 28	Failure	Failure
- P. falciparum reinfection on Day 28	Failure	Failure
- Other species mixed with P. falciparum recrudescence	Failure	Failure
- Other species mixed with P. falciparum reinfection	Failure	Failure
- Undetermined, negative or missing PCR	Failure	Failure
Other species infection without P. falciparum reemergence	Excluded from analysis	Failure
Rescue therapy start without previous ETF, LCF, LPF, or other species infections, and not classified as a protocol violation	Failure	Failure
Lost to follow-up	Excluded from analysis	Failure
Withdrawal*	Excluded from analysis	Failure
Protocol violation**	Excluded from analysis	Failure

(*): Patient’ s request - Investigator's judgement - Adverse event - Other
(**): protocol violations potentially impacting efficacy assessment at Day 28 for the PP population are defined in Section 2.3.2.2

2.1.4.2.2 Parasitemia at baseline then every 6 h during the first 36 h then at 48 h and every 24 h until Day 7

Parasitemia is the quantitative content of parasites in the blood. It is used as a measurement of parasite load in the organism and an indication of the degree of an active parasitic infection.

The methods to be used for quantifying parasitemia depend on the parasitic species and its life cycle. The number of plasmodia can be counted using an optical microscope, on a special thick film (for low parasitemias) or thin film blood smear (for high parasitemias).

2.1.4.2.3 Parasite clearance time (PCT)

For a conservative approach, parasite clearance should not be claimed based on negative parasitemia obtained by imputation. Therefore, in this section **no imputation of missing parasitemia** will be used, except in case of concomitant fever where the missing parasitemia will be considered as positive.

Timing to consider

In this section, except otherwise specified, the post-dose timing associated to a parasitemia will refer to:

- its assigned time point as defined in Section 2.5.4.1, if it exists,
- its actual post-dose timing as defined in Section 2.5.4 and expressed in hours, if outside defined time windows. None or very few are expected, otherwise it should be taken into account in the analyses.

Establishing the clearance

A blood thick film is considered negative when asexual forms of P. falciparum are reported as absent on the dedicated e-CRF page, even if other species are reported.

The parasite clearance will be concluded as soon as two consecutive thick films are negative, with second film prepared within 6 to 12 hours of the first (actual times). In case, the second film has been performed less than 6 hours or greater than 12 hours of the first, then the parasite clearance will be confirmed or invalidated by the thick film following the second one, 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 parasite clearance

When the parasite clearance is confirmed, the time to parasite clearance is the post-dose timing associated to the first negative thick film, as defined above.

In case the parasite clearance is not observed or confirmed before withdrawn (for any reason) or before start of rescue therapy, then the time to parasite clearance will be censored at the time of the last blood film (using the post-dose timing above defined) before withdrawn or rescue therapy start, whichever comes first. Blood films (including date and time of recording) performed the day of rescue start are regarded as before rescue.

2.1.4.2.4 Re-emergence time

Timing to consider

In this section, except otherwise specified, the post-dose timing associated to parasitemia will refer to:

- its assigned time point as defined in Section 2.5.4.1, if it exists,
- its actual post-dose timing as defined in Section 2.5.4.1 and expressed in days, if outside defined time windows.

Establishing re-emergence

The re-emergence is defined as the re-appearance of asexual forms of P. falciparum irrespective of genotype after clearance of initial infection. Blood thick films performed before Hour 24 (Day 1) time point will not be considered for re-emergence screened.

Time to re-emergence

The time to re-emergence will be the post-dose timing associated to the first positive - observed or imputed - parasitemia after clearance. For patient not reaching parasite clearance of initial infection, the time to re-emergence will be equal to zero.

In patients having reach parasite clearance of initial infection, in case a rescue therapy would be started without previous re-emergence or other species infection, then the time to re-emergence will be the time point of the rescue therapy start. If the case has been classified as a protocol violation, then the time to re-emergence will be censored at the time of the rescue start.

Otherwise, the time to re-emergence will be censored at the post-dose timing associated to the last available patient's thick film before withdrawn (for any reason), or, on/before start of a rescue therapy for other species infection, whichever comes first.

2.1.4.2.5 Time to recrudescence

The time to recrudescence will be equal to the time to re-emergence (failures or censures), except in case of P. falciparum re-emergence on or after Day 7 where the following rule will apply:

- re-emergence is due to: "Falciparum reinfection" or "Other species with falciparum reinfection". Then the time to recrudescence will be censored from the day of reinfection.
- re-emergence is undetermined, negative or missing PCR. Then the time to recrudescence will be censored from the day of re-emergence.

2.1.4.2.6 Time to reinfection

The time to reinfection will be equal to the time to re-emergence (failures or censures), except in case of P. falciparum re-emergence on or after Day 7 where the following rule will apply:

- re-emergence is due to: “P. falciparum recrudescence” or “Other species with falciparum recrudescence”. Then the time to reinfection will be censored from the day of recrudescence.
- re-emergence is undetermined, negative or missing PCR. Then the time to reinfection will be censored from the day of re-emergence.

2.1.4.2.7 Time elapsed below LOQ of parasitemia

The time elapsed below Limit of Quantification parasitemia (LOQ expressed in parasites/µL will be determined once the assay is validated) is the time for which no parasites are seen i.e time corresponding to PCT up to the time of occurrence of a new malaria infection or recrudescence. If there is no occurrence of new malaria infection or recrudescence, this is the time corresponding to first negative thick film up to the end of study.

2.1.4.2.8 Fever clearance time (FCT)

FCT is the time from start of study drug administration until temperature remained below 37·5°C.

Fever is defined by a body temperature ≥ 37.5°C for axillary temperature or by a body temperature ≥ 38°C for other routes of measurement.

Timing to consider rules will be similar to what it is described in Section 2.1.4.2.3. The FCT is the post-dose timing associated to the first vital sign assessment as defined above.

In case the FCT is not observed or confirmed before withdrawn (for any reason) or before start of rescue therapy, then the FCT will be censored at the time of the last vital sign assessment (using the post-dose timing above defined) before withdrawn or rescue therapy start, whichever comes first.

FCT is not applicable for patients with baseline body temperature < 37.5°C for axillary temperature (or < 38°C for other routes of measurement) or missing.

2.1.4.2.9 Parasite Reduction Ratio (PRR)

Observed Parasite Reduction Ratio (PRR) will be provided at 24 h, 48 h, and 72 h.

The observed PRR_t (where t takes the following values 24h, 48h and 72h after IMP administration) is defined as the ratio of the number of parasites P_0 at time t=0 (before treatment) divided by the parasite count P_t at time t (post-treatment).

$PRR_t = P_0/P_t$

When calculating the observed parasite reduction ratio, if the post dose parasite count is equal to 0 (due to a negative parasitemia) then a value of 1 parasite/µL will be imputed to allow a parasite reduction ratio to be calculated.

2.1.4.2.10 Parasite Clearance Rate

Parasite clearance estimator according to worldwide antimalarial resistance network WWARN will be used to identify the lag phase, tail, clean the data for outliers, and determine the best model (linear, quadratic, cuboidal) to fit the log-transformed parasite data and afterward calculate the following estimate: the parasite clearance rate. The **parasite clearance rate "k"** will be defined as the minus slope of the natural logarithm parasitemia versus time linear relationship, after exclusion of outliers, lag phase and tail, using the WWARN Parasite Clearance Estimator (PCE) method developed by Flegg et al. (2011) (1) through the calculate PCE function of the bhrcr **R** Software Package.

Outliers are defined as parasite counts which are not biologically possible or are highly unlikely based on other parasite measurements in the same individual.

Lag phase is defined as the initial part of the parasite clearance profile which has a much flatter slope that the remaining part of the profile. It is important to note that a lag phase is not observed in all profiles.

Tail is defined as terminal part of the parasite clearance profile when parasitaemia remains close to the detection limit and does not decrease over a number of measurements time-points. Tails are not observed in all profiles.

Two other methods for estimating parasite clearance rate (k) could be explored if deemed useful or if the first method detailed above could not be used:

- 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:

  $$Y_i = Y^*_i \text{ if } Y^*_i > Y_L,\ Y_i = Y_L \text{ if } Y^*_i \leq Y_L.$$

  The latent variable is then modelled in the standard way: $Y^*_i = X_i\beta+\varepsilon$. And the regression model is solved using maximum likelihood techniques, however the likelihood function is now a truncated normal distribution in the case when $Y^*_i \leq Y_L$.
- Using the Bayesian Hierarchical Regression model introduced in Fogarty et al. (2015) (2) through the 'clearance Estimator Bayes' function of the 'bhrcr' R Software Package. As the calculate PCE function , this function estimates parasite clearance rates, through a change point model on the log of the parasite densities to account for three potential phases: (1) a constant phase (the lag phase); (2) a phase with a linear decrease (decay phase); (3) another constant phase (the tail phase). Hence the estimation of the parasite clearance rate is only based on observations within the decay phase. In contrast to the

calculate PCE function, the Bayesian approach in the clearance Estimator Bayes function allows treating the delineation between lag, decay, and tail phases within an individual's clearance profile as being random variables, thus taking into account the additional uncertainty of boundaries between phases. The clearance Estimator Bayes function also allows taking account for covariates (such as laboratory for qPCR), while calculate PCE function does not.

Based on the linear model that is fitted to the linear part of the parasite clearance profile, the time taken for the parasitaemia to be reduced to 50% and 99% of the baselineparasitaemia (PC50 & PC99) will be estimated using the WWARN calculator.

2.1.4.2.11 Time to 50% and 99% parasite reduction

The estimated time in hours it takes for the parasitaemia to decrease by half (50%) and by 99%, independent of the baseline parasitaemia, will be derived. The estimated time to reductions are constants independent of the baseline parasitaemia since reduction in parasitaemia follows the first order process (after excluding tail and lag phase). The estimated time to reductions will be calculated using the below methodology:

The predicted PRR_t is defined as the ratio of the number of parasites P_0 at time $t=0$ (before treatment) divided by the parasitemia at time t using the following equation: $P_t = P_0 e^{-kt}$ (where k is the first-order elimination rate constant).

$PRR_t = P_0/P_t$

$P_0/ P_t = 1/ e^{-kt} \rightarrow PRR_t = 1/ e^{-kt}$. By using logarithmic transformation, the log-linear relationship between the parasite reduction ratio (PRR_t) and the **parasite clearance rate** (k [as defined in section 2.1.4.2.11]) is:

$$\text{Log}(PRR_t) = \mathbf{kt}$$

Time to 50% parasite reduction: the time needed for parasitemia to be reduced by half (called parasite clearance half-life) can be calculated by the following formula:

$T_{PC50} = \log(2)/k = 0.693/k$ where k is the clearance rate constant.

Time to 99% parasite reduction: The time needed for parasitemia to be reduced by 99% can be calculated by the following formula:

$T_{PC99} = \log(100)/k = 4.605/k$ where k is the clearance rate constant.

2.1.4.2.12 Estimated Parasite Reduction Ratio Parameters

After calculating the parasite clearance rate, the parasite reduction ratios (PRR) will be calculated in log10 unit as:

- PRR24 = clearance rate constant [1/hours]*24 hours/ln(10)
- PRR48 = clearance rate constant [1/hours]*48 hours/ln(10)
- PRR72 = clearance rate constant [1/hours]*72 hours/ln(10)

2.1.4.3 Exploratory efficacy endpoints

- Time to clearance of gametocytes on blood smear for patients with gametocytes at baseline.
- Time to appearance of gametocytes on blood smear for patients with no gametocytes at baseline.
- Detection of Pfs25 mRNA by RT-PCR, in order to assess the impact of IP on levels of mature gametocytes up to the asexual parasite clearance, but also later, to check the absence of pernicious effects on gametocytemia and transmision. Time to clearance of gametocytes by RT-PCR for patients with no gametocytes at baseline, and time to appearance of gametocytes by RT-PCR for patients with no gametocytes at baseline will be estimated but may be reported outside of the CSR. (See Section 2.4.4.4).
- Parasitemia determined by blood thick films and by qPCR to evaluate the relationship between parasitemia and concentration of OZ/FQ, at all parasitemia time-points. The relationship between parasitemia by qPCR and concentration of OZ/FQ, if performed will be reported separately.

2.1.5 Safety endpoints

The safety analysis will be based on the reported adverse events (AEs) and other safety information, such as clinical laboratory data, liver function tests, vital signs, ECG (centrally read, triplicate), and physical examination.

Observation period

For all safety data, the observation period will be divided into three segments:

- The **pre-treatment period** is defined as the time from the signed informed consent date up to the start time of first IMP administration (excluded)
- The **on-treatment period** is defined as the time from the start of the first dose of study drug administration up to the Day 28 visit.
- The **post-treatment period** is defined as the time after Day 28 visit (excluded)

The on-study observation period is defined as the time from start of treatment until the end of the study, i.e., last protocol planned visit or the resolution/stabilization of all SAEs.

2.1.5.1 Adverse events variables

Adverse event observation period

- Pre-treatment AEs are AEs that developed or worsened or became serious in the pre-treatment phase
- Treatment-emergent adverse events are AEs that developed or worsened or became serious during the on-treatment period
- Post-treatment adverse events are adverse events that developed or worsened or became serious during the post-treatment period

All adverse events (including serious adverse events) 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 in effect at Sanofi at the time of database lock.

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.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

Adverse event of special interest

All AEs captured on the general AE form, and any specific AE forms (like the "ALT increase", "overdose" and "pregnancy forms") will be searched. The list of Adverse events of special interest (AESIs) will be flagged in the database using search criteria, like standardized MedDRA query (SMQ), as shown in Table 2 below.

Table 2 - AESI and search criteria

AESI	Search criteria
ECG prolongation: QTcF ≥500 ms or QTcF prolongation > 60 ms from baseline	SMQ: Torsade de pointes/QT prolongation
Hepatic disorders: Increase in alanine transaminase (ALT)	SMQ : Drug-related hepatic disorders – comprehensive search
Pregnancy	e-CRF checkbox: Pregnancy
Overdose	e-CRF checkboxes: Symptomatic overdose, Overdose of Ferroquine (FQ), Overdose of Artefenomel (OZ439) and Overdose of NIMP

2.1.5.2 Deaths

The deaths observation period is per the observation periods defined below.

- Death on-study: deaths occurring during the on-study observation period
- Death on-treatment: deaths occurring during the on treatment period
- Death post-study: deaths occurring after the end of the study

2.1.5.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Local clinical laboratory values after conversion will be analyzed into standard international units and international units will be used in all listings and tables.

Blood samples for clinical laboratories will be done locally at Visit 1 (Screening/pre-dose), Visit 4 (Day 2 hour 48), Visit 5 (Day 3 hour 72) only if patient still hospitalized, Visit 6 (Day 3 hour 96) only if patient still hospitalized, Visit 9 (Day 7 hour 168), Visit 11 (Day 14), Visit 12 (Day 21) and Visit 13 (Day 28) unless otherwise specified. The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells and platelets and coagulation**: hemoglobin, hematocrit, reticulocytes (not needed at screening), haptoglobin (not needed at screening), red blood cell count, platelet count.
  - **White blood cells:** white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry
  - **Metabolism:** glucose, albumin, creatine phosphokinase
  - **Electrolytes**: sodium, potassium, calcium, magnesium
  - **Renal function**: creatinine, creatinine clearance, urea

    Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase, total bilirubin (TBILI) and direct bilirubin (BILDIR, not needed at screening)
  - **Pregnancy test (screen)**: Serum or urine β-human chorionic gonadotropin (all female patients)
  - **Viral hepatitis serology (screen):** HAV IgM, HBsAg, HCV Ab, and/or HCV RNA

Urine samples will be collected as follows:

- **Urinalysis** - quantitative analyses: pH, specific gravity, proteins, glucose, blood, ketones, bilirubin, leukocyte esterase by dipstick. Microscopic examination (if blood or protein is abnormal)

Creatinine clearance is calculated locally according to formulae specified in the protocol:

- Cockroft and Gault formula for patients more than 18 y.o.
- GFR Bedside Schwartz formula for patients between 14 y.0 and <18 y.o.

Technical formulas are described in Section 2.5.1.

2.1.5.4 Vital signs variables

Vital signs include heart rate, systolic and diastolic blood pressure (SBP and DBP), temperature and weight. At each visit where blood pressure is scheduled i.e. Visit 1 (Screening/Pre-dose), Visit 2 [hour 6 and 12), Visit 3 (hour 24), Visit 4 (hour 48), Visit 5 (hour 72) only if patient still hospitalized, Visit 6 (hour 96) only if patient still hospitalized, Visit 8 (hour 144), Visit 9 (hour 168), Visit 10 (Day 10), Visit 11 (Day 14), Visit 12 (Day 21) and Visit 13 (Day 28), three assessments, at least 1 minute apart, will be performed and recorded on the e-CRF as the average of the 3 blood pressure readings according to procedures described in the protocol according to supine position.

2.1.5.5 Electrocardiogram variables

A 12-lead ECG recording on Visit 2 (Day 0 hour 0, 2, 4, 6, 8, 12), Visit 3 (Day 1 hour 24), Visit 4 (Day 2 hour 48), Visit 5 (Day 3 hour 72) only if patient still hospitalized, Visit 6 (Day 4 hour 96) only if patient still hospitalized and Visit 9 (Day 7 hour 96), using a 12-lead ECG to extract triplicate measurements at each theoretical time point (each replicate record will be centrally read by a Core Lab Banook group (semi-automatic reading). The parameters that will be received from the ECG reading center are: RR, QT, QTcF, QTcB, PR and QRS (msec) and heart rate (bpm), but also ST deviation, T-wave morphology, U wave presence or absence.

All ECGs (triplicate) will be manually read by independent experts (except Visit 1 (Screen) for which automatic reading will be done).

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.

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.

2.1.6 Pharmacokinetic variables

Concentrations of OZ439 in plasma and of FQ and its metabolite SSR97213 in blood will be evaluated at specific time points.

The PK parameters will be estimated through Bayesian analysis using previously developed population PK models. Please see Appendix C for references.

The Bayesian PK analyses for OZ439 and for FQ and SSR97213 will be described in a separate analysis plan. The detailed pharmacokinetic analyses will be reported separately from the main CSR. A summary of the methods and results will be reported in the main CSR.

The list of pharmacokinetics parameters for OZ439 in plasma, and for FQ and SSR97213 in blood are the following:

- C_{max}, t_{max}, C_{168h}, and AUC
- $AUC_{0\text{-}day28}$ for FQ and SSR97213 only

2.1.7 Further therapy after discontinuation of investigational medicinal product administration during the study

A period of time Day 0 - Day 28, in line with efficacy time points, will be considered for anti-malarial medications other than investigational medicinal product.

Day 0 - Day 28 is defined as the period of time starting the first IMP intake day and ending with the Day 28 time window defined in Section 2.5.4.1.

2.2 DISPOSITION OF PATIENTS

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

Screened patients are defined as any patients who met the inclusion criteria and signed the informed consent form (ICF).

Randomized patients consist of all patients with a signed informed consent form who have had a treatment kit number allocated and recorded in the IRT database (IVRS_H hybrid SDTM dataset), regardless of whether the treatment kit was used. Patients treated without being randomized by Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) will not be considered as randomized and will not be included in any population.

In the unlikely event of any patient being 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.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table by treatment group:

- Randomized and not treated patients

- Randomized and treated patients
- Patients who did not complete the study treatment period as per protocol
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation; (patients who will receive FQ but partially OZ439 or not OZ439 at all regarding FQ+OZ439 groups)
- Reason for treatment discontinuation
- Status at last study contact (Alive/dead)

For all categories of patients (except for the screened) percentages will be calculated using the number of randomized patients as the denominator.

A detailed description of patient recruitment including number of subjects screened, randomized, treated, treated and discontinued will be summarized in a summary table by country/site.

A patient is considered lost to follow-up at the end of the study if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

Additionally, the analysis populations for safety, efficacy, and pharmacokinetics, pharmacokinetics/pharmacodynamics will be summarized in a table by number of patients in the randomized population.

- Safety population
- Modified intent-to-treat population (mITT)
- Per-protocol population (PP)
- Pharmacokinetics population
- Pharmacokinetics/pharmacodynamics efficacy population (Primary efficacy population)
- Pharmacokinetics/pharmacodynamics safety population

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. 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) in a dynamic randomization scheme the treatment assignment is, in fact, not random, due to a computer program error.

   OR

2. 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 nonrandomized 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 clinical study report. 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). Nonrandomized, treated patients will be described separately

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

- Kit dispensation without IRT transaction
- Erroneous kit dispensation
- Kit not available
- Randomization by error
- Patient randomized twice
- Stratification error
- Patient switched to another site

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized will not be considered randomized and will not be included in the PK/PD efficacy population.

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

The primary analysis of the study will be performed using the PKPD efficacy population (see section 2.3.5).

2.3.1 Randomized population

The randomized population (described in Section 2.2) includes all randomized patients and will be analyzed according to the treatment allocated by randomization. Allocation of randomized treatment to included patients will be centrally performed by an IRT. A patient is considered as

randomized as soon as there is a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used or not. Patients allocated outside the IRT will not be taken into account in any of the analyses.

2.3.2 Efficacy populations

2.3.2.1 Modified Intent-to-treat population

The modified intent-to-treat (mITT) population includes all randomized patients who received the single administration of IMP, with parasitologically confirmed P. falciparum malaria at baseline, having parasitemia data post-randomization.

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

2.3.2.2 Per-protocol population

The per-protocol (PP) is the population receiving at least the single administration of FQ 400mg/OZ439, with parasitologically confirmed malaria at baseline, having parasitemia data post-randomization in order to be evaluable for Day 28 ACPR, without major protocol violations possibly affecting efficacy outcome. Note PCR-corrected ACPR applies only to recrudescence i.e. patients with new infections are considered non-evaluable for the analysis of PCR-corrected ACPR see Section 2.1.4).

Parasitemia data for patients with rescue treatment started before the considered time point will be excluded from this time point until Day 28.

In case of vomiting or other reasons interrupting the administration of the complete dose, and if valid parasitemia data post-randomization available, then patients will be included in the PP population.

As defined in Section 2.1.4.1, there are certain criteria that would exclude patients from having an evaluable PCR-corrected ACPR at Day 28:

- Other species infection without P. falciparum reemergence,
- Lost to follow-up,
- Withdrawal,
- Protocol violation.

Protocol violations considered above are those potentially impacting efficacy assessments at Day 28:

- Patients who did not take IMP or who needed rescue treatment due to vomiting during IMP administration. Start of vomiting will be classified in 3 categories (< 5 minutes, [5-35] minutes, > 35 minutes and < 6 hours).
- Patient presenting severe malaria or receiving a rescue treatment due to severe malaria during the first 24 hours following IMP start (i.e. wrong inclusion).
- Start of rescue therapy before Day 28 assessment not due to: vomiting during IMP administration, wrong inclusion, treatment failure (per investigator or per WHO criteria), or other species infections.
- Missing baseline parasitemia, and positive parasitemia at 48 or 72 hours.
- Intermittent missing or out of window post-baseline parasitemia preventing to evaluate ACPR Day 28.
- Missing post-baseline body temperature preventing to evaluate ACPR Day 28.
- Out of Day 28 time window parasitemia preventing to evaluate ACPR Day 28.
- Patients who received treatment that differs from the randomized one.
- Patients re-dosed while they should not according to the protocol.
- Patients not re-dosed while they should have been according to the protocol.
- Patients with at least one enrolment violation among the following:
  - Patients who meet exclusion criteria E 01 which is: “Presence of severe malaria (according to WHO definition)”.
  - Patients violator for inclusion criteria I02 which is: “Presence of P. falciparum malaria, with a fever as defined with axillary temperature ≥37.5 degree Celsius (°C) or oral/ rectal/ tympanic temperature ≥38°C or history of fever in the previous 24 hours (history of fever must be documented), with a mono-infection with P. falciparum and parasitemia (microscopically, blood smear) ≥3,000 and ≤50,000 asexual parasites/µL of blood Microscopically (blood smear) confirmed parasite infection, ranging from 3000 to 50000 asexual parasites/µL of blood”.
  - Patients violator for exclusion criteria E07 who would be treated with anti-malarial treatment:
    - from 6 weeks (with PQP-based compound, mefloquine, naphthoquine or sulphadoxine/pyrimethamine) before IMP administration,
    - 4 weeks (with amodiaquine or chloroquine) before IMP administration,
    - 14 days (quinine, halofantrine, lumefantrine-based compounds and any other anti-malarial treatment or antibiotics with antimalarial activity) before IMP administration,
    - 7 days (herbal products or traditional medicines) before IMP administration.

2.3.3 Safety population

The safety population is defined all patients who actually received at least 1 dose or part of a dose of the IMP. The Safety population will be analyzed according to the treatment actually received.

In addition:

- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population using treatment as randomized
- The OZ439 oral suspension should be discarded if the suspension limit time is exceeded. A new treatment kit box will need to be assigned to the patient via IWRS in order to prepare a new OZ439 oral suspension. The FQ capsules of the new treatment box will not be administered to the patient
- In case of OZ439 re-dosing mistake such as: erroneous kit dispensation at protocol planned re-dosing, protocol planned re-dose not performed, or re-dose performed wrongfully, the treatment group allocation for as-treated analysis will be the one closest to the sum of the administered total dose. Such cases will be tracked through quantitative deviations
- For patients erroneously re-dosed with FQ, the treatment group for as-treated analysis will be the one with the FQ dose the closest to the sum of the FQ dose actually administered to the patient. Such cases can only be tracked through qualitative deviations
- No re-dosing of FQ will be performed in case of vomiting during or after FQ administration but before OZ439 administration. In that case, OZ439 will not be administered and the patient will receive a rescue therapy as per section 7.7.1 of the study protocol. For patients mistakenly re-dosed with FQ, the treatment group for as-treated analysis will be the one with the FQ dose the closest to the sum of the FQ dose actually administered to the patient.

2.3.4 Pharmacokinetics population

The PK population includes all patients in the safety population with at least one evaluable blood sample for PK of either OZ439 orFQ post IMP administration and with adequate documentation of date of dosing and date of sampling.

2.3.5 Pharmacokinetics/pharmacodynamics populations

Two sub-populations will be defined, a PK/PD efficacy population and a PK/PD safety population:

2.3.5.1 PK/PD efficacy population

The PK/PD efficacy population will be the primary efficacy population.

Pharmacokinetic/pharmacodynamics (PK/PD efficacy) population will include those patients in both the PK and mITT populations with additional criteria specified below,..

Patients need at least one evaluable blood sample for PK of both OZ439 and FQ.

Parasitemia data for patients with rescue treatment started before the considered time point will be excluded from this time point until Day 28.

In case of vomiting or other reasons interrupting the administration of the complete dose, and if valid parasitemia data post-randomization available, then patients will be included in the PK/PD efficacy population.

As defined in Section 2.1.4.1, there are certain criteria that would exclude patients from having an evaluable PCR-corrected ACPR at Day 28::

- Other species infection without P. falciparum reemergence
- Lost to follow-up,
- Withdrawal,
- Protocol violation.

Protocol violations considered above are those potentially impacting efficacy assessments at Day 28:

- Patients who needed rescue treatment because they did not take IMP or due to vomiting during IMP administration.
- Patient presenting severe malaria or receiving a rescue treatment due to severe malaria during the first 24 hours following IMP start (i.e. wrong inclusion).
- Start of rescue therapy before Day 28 assessment not due to: vomiting during IMP administration, wrong inclusion, treatment failure (per investigator or per WHO criteria), or other species infections.
- Missing baseline parasitemia, and positive parasitemia at 48 or 72 hours.
- Intermittent missing or out of window post-baseline parasitemia preventing to evaluate ACPR Day 28.
- Missing post-baseline body temperature preventing to evaluate ACPR Day 28.
- Out of Day 28 time window parasitemia preventing to evaluate ACPR Day 28.

- Patients with at least one enrolment violation among the following:
  - Patients who meet exclusion criteria E 01 which is: “Presence of severe malaria (according to WHO definition)”.
  - Patients violator for inclusion criteria I02 which is: “Presence of P. falciparum malaria, with a fever as defined with axillary temperature ≥37.5 degree Celsius (°C) or oral/

rectal/ tympanic temperature ≥38°C or history of fever in the previous 24 hours (history of fever must be documented), with a mono-infection with P. falciparum and parasitemia (microscopically, blood smear) ≥3,000 and ≤50,000 asexual parasites/µL of blood Microscopically (blood smear) confirmed parasite infection, ranging from 3000 to 50000 asexual parasites/µL of blood".

- Patients violator for exclusion criteria E07 who would be treated with anti-malarial treatment:
  - from 6 weeks (with PQP-based compound, mefloquine, naphthoquine or sulphadoxine/pyrimethamine) before IMP administration,
  - 4 weeks (with amodiaquine or chloroquine) before IMP administration,
  - 14 days (quinine, halofantrine, lumefantrine-based compounds and any other anti-malarial treatment or antibiotics with antimalarial activity) before IMP administration,
  - 7 days (herbal products or traditional medicines) before IMP administration.

2.3.5.2 PK/PD safety population

Pharmacokinetic/pharmacodynamic (PK/PD safety) population: all patients included in the PK population and having at least the baseline and one post-baseline ECG assessment.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Parameters described in Section 2.1.2 will be summarized on the randomized population and the PK/PD efficacy population, analyzed in the treatment group to which they were randomized and overall treatment groups. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of that in the primary analysis population for any treatment group.

P-values on demographic and baseline characteristic data will not be calculated.

Summary of baseline clinical signs/symptoms related to uncomplicated malaria and other relevant signs of malaria (Fever, Dizziness, Headache, Nausea, Anorexia, Vomiting, Diarrhea, Itching, Urticaria, Skin Rash, Abdominal Pain, Joint Pain, Muscle Pain, Palpitations, Sleep Problems, Confusion, Hearing Problems, Vision Problems, and Fatigue) by treatment arm.

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.

2.4.2 Prior and concomitant medications

Prior and concomitant medications will be presented for the safety population. All medications taken within 2 months prior the screening visit, and during the study until the end of the study (Day 28), are to be reported in the e-CRF pages.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). 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 several times for the same medication.

The tables for prior, concomitant medications other than anti-malarial treatments and tables for concomitant anti-malarial treatments will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence across all groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories or standardized medications), alphabetical order will be used.

Patients will be counted once in each ATC level linked to the medication, therefore patients may be counted several times for the same medication. The numbers and percentages of patients in each level will be presented by treatment group.

2.4.3 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed and summarized by actual treatment group, overall, using the safety population (Section 2.3.3).

IPs being given as single dose, exposure will be assessed by descriptive summaries of information collected at the time of administration in dedicated eCRFs pages, such as fasting status, total/partial administration and reason for partial administration, occurrence and timing of vomiting, for initial administration of FQ and OZ, and if any, for OZ re-dosing.

Duration of administrations will be also summarized descriptively as quantitative variables (number, mean, SD, median, Q1, Q3, minimum, and maximum) using:

- time between FQ and OZ administration: defined as the start date and time of OZ intake minus start date and time of FQ intake. Not defined in case FQ would be given after OZ.

- duration of OZ administration, for initial administration and, if any, for redose separately: defined as the end date and time of OZ intake minus start date and time of OZ intake.
- overall administration duration for initial administration: defined as the end date and time of OZ intake (initial administration) minus start date and time of FQ intake. Not defined in case FQ would be given after OZ.

Duration of IMP exposure will be summarized categorically by numbers and percentages of patients within each of the following categories:

- Ferroquine (FQ)
    - FQ not administered
    - Partial drug administered
    - All drug administered
    - Reason for not all drug administered (like adverse event, patient request, physician's decision and other reasons)
- Artefenomel (OZ439)
    - OZ439 not administered
    - Partial drug administered
    - All drug administered
    - Reason for not all drug administered (like adverse event, patient request, physician's decision and other reasons)
- Vomiting
    - No
    - Yes
        - After FQ administration, but before OZ439 administration
        - < 5 minutes after start of OZ439 administration
        - 5 – 35 minutes after start of OZ439 administration
        - > 35 minutes after start of OZ439 administration *(but not reported as vomiting since vomiting occurred more than 6 hours after dosing)*
- Re-dose of Artefenomel (OZ439)
    - No
    - Yes
        - OZ439 not administered
        - All drug administered
        - Reason for not all drug administered (like adverse event, patient request, physician's decision and other reasons)
- Vomiting following re-dose of Artefenomel
    - No
    - Yes
        - < 35 minutes after start of OZ439 administration

- > 35 minutes after start of OZ439 administration *(but not reported as vomiting since vomiting occurred more than 6 hours)*

Exploratory analyses studying the relationship between vomiting occurring less than 6 hours from IP start and potential explanatory variables such as baseline parasitaemia level, baseline body temperature, age, center, FQ formulation, durations of administration may be also performed if deemed relevant.

2.4.3.1 Extent of investigational medicinal product exposure

Not applicable (single-dose).

2.4.3.2 Compliance

Compliance is defined as taking the randomized treatment (both OZ439 and FQ) in full. Cases of overdose (defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug) will constitute AESI (serious or non-serious) if symptomatic and will be listed as such. Asymptomatic overdose has to be reported as a standard AE. More generally, dosing irregularities will be listed in Section 2.2.1.

2.4.3.3 Batch number and randomization scheme

The listing of patients receiving IMP from specified batch will also be provided by treatment arm and patient.
Besides, a listing sorted by site will be provided to display the randomization scheme (block number, sequence order with block, treatment arm, date and time of treatment allocation) of the study.

2.4.4 Analyses of efficacy endpoints

The primary analysis detailed in Section 2.4.4.1.1 will be carried out on the PK/PD efficacy population.

All statistical analyses on secondary efficacy endpoints as well as on Section 2.4.4.1.2 and Section 2.4.4.1.3 will be performed on the mITT population only, unless otherwise stated.

2.4.4.1 Analysis of primary efficacy endpoint

2.4.4.1.1 Logistic regression on exposure-response for PCR-corrected ACPR

The exposure-response of single-dose OZ439/FQ for PCR-corrected ACPR at Day 28 will be analyzed using a logistic regression with the probability of a response in PCR-corrected ACPR at Day 28. The following exposure variables will be evaluated: OZ439 AUC,FQ $AUC_{0\text{-}Day28}$ and

SSR97213 $AUC_{0\text{-}Day28}$
Baseline parasitemia (in log_{10}) and age (in years) will be tested as covariates. If needed, some other covariates like sex, weight (in kg), country or site will be tested in the model. The selection of the best fitted model will be done by calculating the fit statistics like AIC, BIC among on all tested models, based on the choice of the predictor variables. The best model detected with the fit statistic chosen by the statistician will be specified in a footnote of the summary table.

The Wald test will be used to test the OZ439 exposure effect on PCR-corrected ACPR at Day 28.

This model will be run utilizing SAS® PROC LOGISTIC or similar using the outcome (response) binary variable (0/1) and the exposure variables (AUC for OZ439, $AUC_{0\text{-}Day28}$ for FQ and SSR97213).
Results of logistic regressions of PCR-corrected ACPR on AUCs parameters of OZ439, FQ and SSR97213 will be provided in a summary table including odds ratio estimates, the corresponding 95% Wald confidence intervals (CI) and p-value for each compound and covariates.

Handling of dropouts or missing data

Patients not classified as failure for ACPR and with missing information on parasitemia at day 28 will be imputed following the criteria defined in Section 2.1.4 (*Time points and imputation rules*) or otherwise will be excluded from the analysis per protocol deviation.

Exposure-response will be done with and without vomiters if relevant.

2.4.4.1.2 Descriptive analyses of Day 28 PCR-corrected ACPR

Frequency table for Day 28 PCR-corrected ACPR, ETF, LCF, LPF or on rescue before Day 7 without WHO criteria, including proportion, percentage and exact binomial 95% CIs (two-sided by using Clopper-Pearson method for calculating binomial CIs) by treatment arm, will also be provided using FREQ procedure in the PP and in the mITT population separately. The number of patients from the PP population and not evaluable for the PCR-corrected ACPR at Day 28 (i.e. patients with re-infection, or undetermined, negative or missing PCR) will be also detailed.

In addition a bar chart of the percentage of subjects meeting ACPR (with two-sided 95 CIs) will be presented.

2.4.4.1.3 Logistic regression on dose-response for Day 28 PCR-corrected ACPR

Dose-response in PCR-corrected ACPR will be done similarly to Day 28 crude-ACPR detailed in Section 2.4.4.2.1.1.

2.4.4.2 Analyses of secondary efficacy endpoints

Apart from Day 28 crude APCR, all other secondary efficacy endpoints will be reported and analysed on the mITT only.

2.4.4.2.1 Day 28 crude APCR

2.4.4.2.1.1 Logistic regression on dose-response

The dose-response association of single-dose OZ439/FQ for Day 28 crude-ACPR will be analyzed using a logistic regression with the probability of a response in Day 28 crude-ACPR and increasing dose of OZ439.

Baseline parasitemia (in $\log_{10}$) and age (in years) will be tested as covariates. If needed, some other covariates like sex, weight (in kg), country or site will be tested in the model. The selection of the best fitted model will be done by calculating the fit statistics like AIC, BIC among on all tested models, based on the choice of the predictor variables (separated AUC vs combined AUC). The best model detected with the fit statistic chosen by the statistician will be specified in a footnote of the summary table.

The Wald test will be used to test the OZ439 dose effect on Day 28 crude-ACPR.

This model will be run using SAS logistic procedure or similar using the outcome (response) binary variable (0/1) and the explicative variable dose susceptible to influence it.

Results of logistic regressions of Day 28 crude-ACPR on OZ439 dose level will be provided in a summary table including odds ratio estimates, the corresponding 95% Wald confidence intervals (CI) and p-value for each dose level and covariates.

Dose-response will be done with and without vomiters if relevant.

2.4.4.2.1.2 Descriptive analysis

Frequency table for Day 28 crude-ACPR, ETF, LCF, LPF or on rescue before Day 7 without WHO criteria, including proportion, percentage and exact binomial 95% CIs (two-sided by using Clopper-Pearson method for calculating binomial CIs) by treatment arm, will also be provided using FREQ procedure. The number of patients from the PP population and not evaluable for the PCR-corrected ACPR at Day 28 (i.e. patients with re-infection, or undetermined, negative or missing PCR) will be also detailed.

2.4.4.2.1.3 Logistic regression on exposure-response

Exposure-response in crude ACPR will be done similarly to Day 28 PCR-corrected ACPR detailed in Section 2.4.4.2.1.1.

2.4.4.2.2 Parasitemia

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

Time profile plots (Mean ± SEM) of parasitemia will be provided for each treatment arm, one curve per arm.

Box-Whisker plots over time of positive parasitemia levels will be provided by treatment arm.

Assessments performed after start of rescue treatment will not be included in above summaries

2.4.4.2.3 Observed Parasite reduction ratio

Descriptive statistics (such as arithmetic mean, geometric mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be provided for each treatment arm.

Relationship between median blood concentrations for FQ (respectively blood concentrations for SSR97213 and plasma concentrations for OZ439) versus time-specific parasite reduction ratios (percent parasite reduction ratio [%PRR]) will be represented thanks to a scatter plot (one curve per treatment arm). Same analysis will be done for parasite clearance rate.

2.4.4.2.4 Parasite clearance rate and derived parameters

The parasite clearance rate, PC50, PC99 and estimated parasite reduction ratios (PRR24, PRR48 PRR72) will be summarized descriptively. However, data from patients with a poor fit to the linear model ($R2<0.75$) will be excluded from the analysis.

2.4.4.2.5 Parasite clearance half-life (time to 50% parasite reduction) and time to 99% parasite reduction

Point estimate and 95% confidence interval for the geometric mean of T_{PC50} and T_{PC99} will be provided pooled across the 4 treatment group and separately for each dose group, using a linear fixed effect model.

Descriptive statistics (such as median, minimum, and maximum) will be provided for each treatment arm.

2.4.4.2.6 Time to parasite clearance

Time to parasite clearance will be analysed using two endpoints:

- Time to confirmed parasite clearance
- Time to parasite clearance (with or without confirmation)

Descriptive statistics (such as median, 25% and 75% percentiles, minimum, and maximum) for each endpoint will be provided for each treatment arm.

2.4.4.2.6.1 Kaplan-Meier method

The time to each parasite clearance endpoint will be estimated by the failure function, F(t)=P(T ≤t), probability that a patient will have parasite clearance before or at time t, using Kaplan-Meier method. The Kaplan-Meier (product-limit) estimate of the failure function for each group will be plotted on a same graph.

Cumulative number of events i.e. parasite clearances - and censures, in addition to quartiles of the survival times with their 95% confidence interval will be provided by treatment arm, and overall. Percentage will be based on the number of patients included in the analysis.
The model will run by using the SAS LIFETEST or ICLIFETEST procedures in order to compute and plot the estimate of the distribution of the survival time.

At t=Hour 24, Hour 48, Hour 72, the number of patients at risk just prior t, the number of events and censures, and the probability that the time to parasite clearance exceeds t, with its 95% confidence interval, will be provided by treatment arm, and overall.

2.4.4.2.7 Time to re-emergence

Incidence of re-emergences will be summarized among patients with complete clearance (i.e those who initially responded). The survival distribution function of the time to re-emergence will be estimated using Kaplan- Meier method. The estimate of the survivor function for each group will be plotted on a same graph. Cumulative number of events (i.e. re-emergence) and censures, in addition to quartiles of the survival times with their 95% confidence interval will be provided by treatment arm. At times t=Day 7, Day 14, Day 21 and Day 28, the number of patients at risk just prior t, the cumulated number of events and censures at t, and the probability that the time to reemergence exceeds t, with its pointwise 95% confidence interval, will be provided.

2.4.4.2.8 Time to recrudescence

Same analyses than those described in Section 2.4.4.2.7 for time to re-emergence.

2.4.4.2.9 Time to reinfection

Same analyses than those described in Section 2.4.4.2.7 for time to re-emergence.

2.4.4.2.10 Elapsed time below LOQ of parasitemia

Same analyses than those described in Section 2.4.4.2.7 for time to re-emergence. All subjects within the associated population will be included.

2.4.4.2.11 Time to fever clearance

Same analyses than those described in Section 2.4.4.2.6 for time to parasite clearance.

2.4.4.3 Multiplicity issues

No adjustment for multiplicity of comparisons was applied for primary or for secondary analyses.

2.4.4.4 Additional efficacy analyses

Additional efficacy analyses will be reported and analysed in the mITT population.

- Disease characteristics post-baseline

Descriptive statistic 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 the sign/symptom at baseline.

- Time to gametocytes clearance (blood smears)

Time to gametocytes clearance will be analyzed using Kaplan-Meier estimators. An overall overview including number of events and cumulative incidence of events with 95% CI will be provided in a summary table, survival curves will be plotted.

- Time to appearance of gametocytes (blood smears)

The first appearance of gametocytes will be presented by time after enrollment for all patients, by treatment arm. The denominator for computation of percentages is the mITT population within each treatment arm. Besides, time to gametocytes clearance will be analyzed using Kaplan-Meier estimators in the same way than time to gametocytes clearance.

- Time to gametocytes clearance (RT-qPCR)

Time to gametocytes clearance will be analyzed using Kaplan-Meier estimators. An overall overview including number of events and cumulative incidence of events with 95% CI will be provided in a summary table, survival curves will be plotted.

- Time to appearance of gametocytes (RT-qPCR)

The first appearance of gametocytes will be presented by time after enrollment for all patients, by treatment arm. The denominator for computation of percentages is the mITT population within each treatment arm. Besides, time to gametocytes clearance will be analyzed using Kaplan-Meier estimators in the same way than time to gametocytes clearance

2.4.5 Analyses of safety data

The summary of safety results will be presented by actual treatment group.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.3, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately.
- The potentially clinically significant abnormality (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.
- PCSA definitions (version dated May 2014) depending on the age, race, or sex of the patient are detailed separately in [Appendix A]. Specific PCSA criteria for children will use children's age at time of laboratory, vital signs and ECG assessments. Age will be collected in the eCRF by the clinical site.
- PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the on-treatment period by treatment group on the safety population.
- For quantitative safety parameters based on local 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 endpoint value and/or the worst on-treatment value. The endpoint value is commonly defined as the value collected at the same day/time of the last administration of IMP. If this value is missing, this endpoint value will be the closest value prior to the last dose intake. The worst value is defined as the nadir and /or the peak on-treatment post-baseline according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list.
- Analyses of the safety variables will be essentially descriptive and no systematic testing between treatment groups is planned.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on the on-treatment period. Pre-treatment and post-treatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pre-treatment, on-treatment, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pre-treatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will presented by SOCand PT, sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pre-treatment, on-treatment, and post-treatment). For that purpose, the table of all treatment-emergent adverse events 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 will be based on results for the experimental arm given with the highest dose.

Analysis of all TEAEs

The following TEAE summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any
  - Treatment-emergent adverse event
  - Serious treatment-emergent adverse event
  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent treatment discontinuation (defined when FQ is taken, not OZ439)
- All TEAEs by primary SOC and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (PT) will be presented in alphabetical order
- All TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified
- All treatment-emergent adverse events regardless of relationship and related to FQ, related to OZ439, by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (PT) will be presented in alphabetical order

- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above

Analysis of all treatment emergent SAEs

- All treatment-emergent SAEs by primary SOC and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (PT) will be presented in alphabetical order
- All treatment-emergent SAEs regardless of relationship, related to FQ, related to OZ439, by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order. The other levels (PT) will be presented in alphabetical order

Analysis of all TEAEs leading to permanent treatment discontinuation

All treatment-emergent adverse events leading to permanent treatment discontinuation, by primary SOC and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (PT) will be presented in alphabetical order

Analysis of adverse events of special interest

All treatment emergent adverse events of special interest, by PT, showing the number (%) of patients, sorted by decreasing incidence of PT within each AESI category (without including the overall number of patients with at least 1 AESI).

In addition summaries of treatment emergent adverse events of the below categories:

- Hepatic disorders
- Torsade de pointes/QT prolongation

will be presented by primary SOC and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (PT) will be presented in alphabetical order.

Analysis of pre-treatment and post-treatment adverse events

If any pre-treatment or post-treatment adverse events lead to death or any pre-treatment adverse events lead to permanent treatment discontinuation, an overview of pre-treatment and/or post-treatment adverse events will be presented as a listing if only a few, otherwise as a summary (presenting number of patients with any pre-/post-treatment adverse events, serious pre-/post-treatment adverse events, pre-/post-treatment adverse events leading to death, pre-treatment adverse events leading to permanent treatment discontinuation) will be presented.

2.4.5.2 Deaths

Listing of deaths will be provided with flags indicating on-treatment, during follow-up or post-study status. Deaths in non-randomized patients or randomized but not treated patients will be listed separately.

2.4.5.3 Analyses of laboratory variables

For clinical chemistry and hematology parameters, measures expressed in local and standard international (SI) units are available. Only values expressed in SI units will be used for quantitative summary statistics.

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all laboratory variables (values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, worst on-treatment value) by treatment group.

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

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

Drug-induced liver injury

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed by treatment group for each parameter.

A graph of distribution (e-dish plot) of peak values of ALT versus peak values of total bilirubin will also be presented. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

Listing of possible Hy's law cases identified by treatment group (eg, patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin ≥2 x ULN) with ALT, AST, alkaline

phosphatase, total bilirubin, and the following complementary parameters: conjugated bilirubin, creatine phosphokinase and serum creatinine.

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all vital signs variables (raw data and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, worst on-treatment value) by treatment group.

The incidence of PCSAs at any time during the on-treatment period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

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

2.4.5.5 Analyses of electrocardiogram variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all ECG variables (central laboratory 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) based on the average of the triplicate assessments by treatment group.

The incidence of PCSAs at any time during the on-treatment period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

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

Listings

Following listings will be produced, using all data, including rechecked or unplanned values, whatever the sources.

- A listing of individual data of subjects with any post-baseline PCSAs will be provided; raw data and absolute or percent change from baseline will be displayed depending on the parameter and values will be flagged when reaching the limits of the PCSA criteria;
- In addition, subjects with QTc/QTcB/QTcF >480 ms and/or change from baseline in QTc/QTcB/QTcF >60 ms will also be listed separately, using all post-dose time points.
- A listing of subjects with at least one abnormality in qualitative assessment (ie, abnormal 12-lead ECG) after the 1st dosing will be also provided.
- A listing of morphological abnormalities (ECG extracted from 12-lead ECG data).

2.4.5.6 Physical Examination

Physical Examination assessments will be listed.

2.4.5.7 Analyses of other safety endpoints

Not applicable.

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

2.4.6.1 Analyses of pharmacokinetic variables

Descriptive statistics and listings

All summaries/plots of PK parameters will be based on the PKPD efficacy population.

Separate summaries based on the PK population may be provided if considered useful (if PK and PKPD efficacy populations are different).

Pharmacokinetic parameters of ferroquine, its metabolite SSR97213 and OZ439 compounds will be summarized by descriptive statistics (such as arithmetic mean, geometric mean, median, SD, SEM, CV, minimum, and maximum) for each group (FQ alone, FQ/OZ439).

Box-and-whisker plots will be provided for each treatment group and compound (FQ, SSR97213 and OZ439), representing mean, median, quartiles and outlying observations.

Individual metabolic ratios (FQ/SSR97193 considering molecular weight of each moiety) will be computed for C_{max}, $AUC_{0\text{-}Day28}$ and AUC listed and summarized for each treatment group.

2.4.6.2 Concentration/parasitemia analyses

The evaluation of the relationship between parasitemia (blood film) and concentration of OZ439/FQ may be performed in a separate analysis pooling data from different studies.

The evaluation of the relationship between parasitemia (measured by qPCR) and concentration of OZ439/FQ may be performed in a separate analysis pooling data from different studies.

These analyses if performed will be described in ad-hoc separate plans and will be reported in separate reports.

2.4.6.3 Concentration/ECG analyses

All the analyses will be performed on the PK/PD Safety population.

Endpoints

The Concentration-ECG analyses will be based on 12-lead ECG method.

The ECG parameters will include heart rate, QTcB, QTcF, PR and QRS intervals, corresponding to the change from baseline value. All post-dose assessments on Visit 2 (Day 0 hour 2, 4, 6, 8 and 12), Visit 3 (Day 1 hour 24), and Visit 4 (Day 2 hour 48) will be included, except Visit 5 (Day 3 hour 72), Visit 6 (Day 4 hour 96) and Visit 9 (Day 7 hour 168).

The pharmacokinetic endpoint will be the PK concentration of SSR97193, its active metabolite SSR97213 and OZ439 compounds. Post-dose concentrations below the lower limit of quantification (LLOQ) will be imputed to LLOQ / 2. LLOQ is defined as 5 ng/mL for FQ and SSR97213, 1 ng/mL for OZ439.

Relationships between concentrations (FQ, SSR97213 and OZ439) and change from baseline in ECG parameters will be analyzed into 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 an "total" concentration, separately from OZ439 (molecular weight of 469.28 g.mol-1)
- by using ferroquine, SSR97213 blood drug concentrations and OZ439 plasma concentrations as covariates in the same model

The relationship will be explored using data from OZ439/FQ on the restricted time window [Day 0, hour 2 – Day 2 hour 48]. Prediction of changes in ECG parameters (with 90% CI) will be obtained for each compound entering the models at each dose $C_{max,}$.

Exploratory plots

The relationship between change from baseline in ECG parameters and FQ (respectively SSR97213, OZ439) concentrations will be first explored graphically, in order to investigate any

potential delayed or sustained effects and the type of modeling to be done, using the following plots, by treatment group:

- Plot of mean (± SEM) change from baseline in ECG data and mean FQ (respectively SSR97213, OZ439) concentration versus time (hours post-dose) overlaid onto the same plot
- Hysteresis plot of mean change from baseline in ECG data and mean FQ (respectively SSR97213, OZ439) concentrations
- Histogram of distribution of time of largest change from baseline in HR, PR, QRS, QTcB and QTcF and largest FQ (respectively SSR97213 and OZ439) 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) concentrations, respectively.

Linear modeling

The linear direct (or indirect depending on the hysteresis plots) model will be carried out for the relationship between concentrations and change from baseline in ECG parameters, with fixed terms for population intercept, and nominal time intercept, with the concentration (slope), and with random terms for individual patient deviation from the population intercept and slope, and using an unstructured variance-covariance structure for random coefficients and a common variance for error, using SAS Proc Mixed®. The analysis model will be the following:

For the model with ferroquine and SSR97213 total concentration using MW:

Change from baseline = $(\alpha + A_i) + (\beta + B_i) \times Concentration_{ij}$ + 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 $Concentration_{ij} + (\beta_2 + B_{2i}) \times$ SSR97213 $Concentration_{ij}$ + error, with i = patient and j = time

with:

- α and β are the fixed population intercept and concentration slope.
- A_i and B_i are the random intercept and concentration slope for the i^{th} patient, with A_i and B_i assumed to be normally distributed with null mean and an unstructured variance-covariance matrix per subject block.

- $Concentration_{ij}$ is the concentration for the i^{th} patient at the j^{th} time point

When OZ439 is added to the model, a term $(\beta_3 + B_{3i}) \times$ OZ439 $Concentration_{ij}$ will be added to the model, OZ439 concentrations being used unchanged or converted to µmol/L depending on the model used.
The influence of time (as factor) could be investigated as covariate if relevant and if it allows to improve the model.
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 Cmax value (geometric mean) for each FQ dose group will be provided for FQ and SSR97213 respectively, 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 = $\beta_{1\ estimated}$ x ferroquine Cmax GM + $\beta_{2\ estimated}$ x (mean of SSR97213 concentrations obtained at individual ferroquine tmax)
  - Estimated change from baseline at SSR97213 Cmax = $\beta_{1\ estimated}$ x (mean of ferroquine concentrations obtained at individual SSR97213 tmax) + $\beta_{2\ estimated}$ x SSR97213 Cmax GM
- For the models including OZ439, 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 change from baseline versus FQ, SSR97213 and OZ439 concentrations, 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 (ie, the linear model is not adequate), alternative models like non-linear models (exponential, E_{max}) and/or Model Averaging (MA, [4]) might be explored.

Model Averaging to Concentration-QT analysis

Model averaging will be used in case it is not possible to determine the best model among 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 C_{max} values (geometric means) observed concentrations at the maximal dose (FQ 400 mg/OZ439 1000 mg).

2.4.6.4 Analyses of quality of life/health economics variables

Not applicable

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

- Body mass index (kg/m²) = (Weight in kg)/ (Height in meters)²
- Time from first diagnosis of current malaria infection: day of randomization - day of diagnosis of current malaria infection
- Prior/concomitant/follow-up medications:

Only the date of medication start/end will be reported in the eCRF (no time), then by convention medication taken the day of randomization will be classified as concomitant.

Renal function formulas

Creatinine clearance value is derived using the equation of Cockroft and Gault: CrCl is calculated using weight assessed at the same visit than creatinine was assessed.

For patients > 18 years old:

CrCl (mL/min) = F × (140 - age(years)) × weight(kg)]/ [serum creatinine (µmol/L)] where F = 1.23 if male, and 1.04 if female

For patients ≤ 18 years old (Bedside Schwartz Formula):

eGFR (mL/min/1.73 m^2) = (0.413 × Height in cm) / [serum creatinine (µmol/L)]

2.5.2 Data handling conventions for secondary efficacy variables

2.5.3 Missing data

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

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the treatment status e-CRF page. If this date is missing, the exposure duration should be left as missing.

The last dose intake should be clearly identified in the e-CRF and should not be approximated by the last returned package date.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

Handling of adverse events with missing or partial date/time of onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

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

The last dose intake should be clearly identified in the e-CRF and should not be approximated by the last returned package date.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

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

Handling of missing* severity *of adverse events

If the severity is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

Handling of potentially clinically significant abnormalities

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 >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 taken into account in the computation of PCSA values.

2.5.4 Windows for time points

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 hours or days from the date and time of IP start as: *date&time of assessment minus date&time of IMP start*.

While the **actual day** of an assessment for which only the date is available (no time) is calculated in days from the date of IP start as: *date of assessment minus date of IMP start*.

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.

In the case where more than one assessment of a 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.

2.5.4.1 Time windows for efficacy evaluation

Before Day 4, time points assigned to scheduled or unscheduled parasitemia and to concomitant - i.e. coming 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 3. In case, the blood thick film is missing at a visit, but body temperature assessment is available (or if missing), 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 3 – Time windows definition before Day 4

Protocol planned time point	Allowed deviation from targeted time	Corresponding window of time for actual blood film timing
Hour 6	-1/+2 hours (included)	5 hours to 8 hours
Hour 12	-1/+2 hours (included)	11 hours to 14 hours
Hour 18	-1/+2 hours (included)	17 hours to 20 hours
Hour 24 (Day 1)	-1/+2 **hours (included)**	**23 hours to 26 hours**
Hour 30	-1/+2 hours (included)	29 hours to 32 hours
Hour 36	-2/+3 hour (included)	34 hours to 39 hours
Hour 48 (Day 2)	**±3 hours (included)**	**45 hours to 51 hours**
Hour 72 (Day 3)	**±4 hours (included)**	**68 hours to 76 hours**

Note: bold font is used when the time point is involved in the ACPR definition.

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

Table 4 – Time windows definition from Day 4

Protocol planned time point	Allowed deviation from targeted time	Corresponding window of time for actual blood film timing
Hour 96 (|Day 4)	0	Day 4
Hour 120 (Day 5)	0	Day 5
Hour 144 (Day 6)	0	Day 6
Hour 168 (Day 7)	**0**	**Day 7**

Day 10	±1 days (included)	9 days to less than 11 days
Day 14	±1 days (included)	12 days to less than 15 days
Day 21	±2 days (included)	19 days to less than 23 days
Day 28	**±2 days (included)**	**26 days to 30 days**

2.5.4.2 Time windows for safety evaluation

2.5.4.2.1 Time windows for laboratory evaluation

Visit	Time window for the actual laboratory assessment timing
Baseline	Before IP start
Hour 48 (Day 2)	36 hours to less than 48 hours
Hour 72 (Day 3)	48 hours to less than 84 hours
Hour 96 (Day 4)	84 hours to less than 5 days
Hour 168 (Day 7)	5 days to less than 11 days
Day 14	11 days to less than 18 days
Day 21	18 days to less than 25 days
Day 28	25 days to less than 32 days

2.5.4.2.2 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 V1 assessments.

Visit	Time window for the actual vital sign assessment timing
Hour 168 (Day 7)	4 days to less than 9 days
Day 10	9 days to less than 12 days
Day 14	12 days to less than 18 days
Day 21	18 days to less than 25 days
Day 28	25 days to less than 35 days

2.5.4.2.3 Time windows for ECG evaluation

Visit	Time window for the ECG assessment timing[a]
Baseline	Before IP start
Hour 2	After IP end to less than 3 hours
Hour 4	3 hours to less than 5 hours
Hour 6	5 hours to less than 7 hours
Hour 8	7 hours to less than 10 hours
Hour 12	10 hours to less than 18 hours
Hour 24	18 hours to less than 36 hours
Hour 48 (Day 2)	36 hours to less than 48 hours
Hour 72 (Day 3)	48 hours to less than 84 hours
Hour 96 (Day 4)	84 hours to less than 5 days
Hour 168 (Day 7)	5 days to less than 9 days

a: using the date and time of the first record from the triplicate ECG.

2.5.5 Unscheduled visits

Unscheduled visit measurements will be used for computation of baseline and PCSAs. All visits will be re-allocated, and re-allocated visits measurements will be included in the by-visit summaries.

2.5.6 Pooling of centers for statistical analyses

Not applicable.

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

No formal interim analysis is planned.

4 DATABASE LOCK

The database is planned to be locked approximately at 4 weeks after last patient last visit.

5 SOFTWARE DOCUMENTATION

The population PK analysis will be performed using the non-linear mixed effect modeling approach as implemented in the Monolix (v.2019R2 or later, Lixoft) software. Data manipulation, additional calculations and graphics will be performed using R (v. 3.5 or later), The R Foundation for Statistical Computing)"

All other summaries and statistical analyses will be generated using SAS version 9.4 or higher.

6 REFERENCES

1. REFBIB000665

2. REFBIB000765

3. REFBIB000865

4. REFBIB000965

5. REFBIB001065

7 LIST OF APPENDICES

Appendix A Flow chart

Appendix B Potentially clinically significant abnormality criteria

Appendix BC References

Appendix A Flow chart

Procedure	Screening (up to 1 day before Day 0)	Treatment Period and post-treatment surveillance (Days)														Follow-up (Days)							Notes
		0*a*							1			2	3	4		5	6	7	10	14 ±1	21 ± 2	28 ±2	
		Hours post-dose																					
		0	1	2	4	6	8	12	18	24	30	36	48	72	96	120	144	168					
Visit	**1***b*	**2**								**3**			**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13***c*	
Informed consent	X																						
Demography, medical history	X																						
Inclusion/ exclusion criteria	X																						
IRTcall	X	X																				X	
Randomization		X																					
Hospitalization	←==========→•••••••••→																						All patients hospitalized for 48 h post dosing or up to 4 days in case malaria symptoms and/or parasitemia persist at the end of day 2 or longer upon investigator's judgment
Treatment																							
FQ		X																					Dosing in fasted condition (see Section 6.3.1 of protocol)
OZ439		X																					
Rescue therapy*d*		←	•••	•••	•••	•••	•••	•••	•••	•••	•••	•••	•• •	•••	•••	•••	•••	•••	•••	•••	•••	••	X	
Prior and concomitant medication	X	X								X			X	X	X	X	X	X	X	X	X	X	X	
Activity																							
Physical exam & malaria signs & symptoms	X							X		X		X	X	(X)	(X)			X				X	Physical exam to be performed at discharge from the hospital
Height	X																						

Procedure	Screening (up to 1 day before Day 0)	Treatment Period and post-treatment surveillance (Days)														Follow-up (Days)							Notes
		0*a*								1			2	3	4	5	6	7	10	14 ±1	21 ± 2	28 ±2	
		Hours post-dose																					
		0	1	2	4	6	8	12	18	24	30	36	48	72	96	120	144	168					
Visit	**1***b*	**2**								**3**			**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13***c*	
Weight	X												(X)	(X)	(X)							X	Weight to be taken at discharge from hospital
Temperature (single)*e*	X		X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Measurement required within 4 hours prior to dosing
Asexual & sexual parasite count (thick & thin blood films)*e*	X					X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
qPCR, parasite genotyping, RT-qPCR gametocyte detection sampling*f*	X					X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety																							
12-Lead ECG*g*	X	X		X	X	X	X	X		X			X	(X)	(X)			X					72 and 96 h post-dose if participant still hospitalized
Vital signs	X					X		X		X			X	(X)	(X)		X	X	X	X	X	X	Vital signs to be taken at discharge from the hospital
AEs	←==========→																						
Laboratory testing																							
Clinical laboratory safety*h*	X												X	(X)	(X)			X		X	X	X	72 and 96 h post-dose if participant still hospitalized
Viral hepatitis serology	X																						rapid spot test (HAV IgM, HBsAg, HCV Ab), and/or HCV RNA (if known)
Pregnancy test	X																					X	Urine beta-HCG is the minimum acceptable test. Result must be confirmed negative prior to dosing.
PK OZ439*i*		X	X	X	X	X		X		X			X	X		X		X		X			Not measured in Arm A; Plasma samples

Procedure	Screening (up to 1 day before Day 0)	Treatment Period and post-treatment surveillance (Days)														Follow-up (Days)							Notes
		0*a*							1			2	3	4	5	6	7	10	14 ±1	21 ± 2	28 ±2	
		Hours post-dose																				
		0	1	2	4	6	8	12	18	24	30	36	48	72	96	120	144	168					
Visit	**1***b*	**2**								**3**			**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13***c*	
PK FQ (+metabolite)*i*		X	X		X	X	X	X		X				X				X		X		X	[redacted]

a Day 0 is defined as the day of single dose treatment to comply with WHO guidelines (5) .

b Visit 1 may occur on the same day as Visit 2 provided that all baseline assessments and biology results (including parasitemia and laboratory safety) are obtained before patient randomization.

c In case of study discontinuation, all assessments planned on Day 28, including rescue therapy administration, should be performed as far as possible.

d Administered at Day 28 for participants who reach Day 28 without having received a rescue medication. At each contact post-dosing, conditions for treatment failure will be assessed and rescue therapy will be given accordingly. See details in Section 7.7.1 of protocol

e Local thick and thin blood films performed at the site, before Informed Consent signature, according to local standard procedures and within 4 hours prior to dosing, can be used as screening/ pre-dose parasitemia assessments (Section 9.1.1.1 of protocol) provided that a standard procedure is in place at site and blood films staining is performed according to the study operational manual. Blood films (thick and thin) and temperature measurements need to be confirmed as follows: when 1st parasite clearance and 1st temperature < 37.5 °C, measurements need to be confirmed with second reading 6 to 12 hours after the first measurement (ie, to determine Parasite Clearance and Fever Clearance). The first measurement (if confirmed) will be considered the 'Clearance Time'. Asexual and sexual counts will be measured separately: only asexual count will be used as parasitemia for evaluation of study endpoints. If parasites have not cleared within 72 hours after IMP administration and criteria for rescue medication are not met at 72 hours post-dose, blood films should continue to be taken according to site standard practice (or at minimum every 8 hours) until parasite clearance is shown or until criteria for rescue medication are met (see Section 7.7.1 of protocol). If these additional blood smears are taken they should be recorded as unscheduled visits in the e-CRF. Axillary temperature should be recorded, if the axillary method is not possible, an alternative route (oral, tympanic, rectal) may be used. Within an individual participant the same method of temperature measure should be used throughout the study.

f RT-qPCR and qPCR will be performed at all parasitemia time-points (To be collected, according to the schedule and the instructions reported in the study operational manual). Parasite genotyping analysis will be performed on previously collected blood spot sample only in case of a positive blood film after initial parasite clearance: one pre-dose sample and one sample at 18 or 24 hours post dosing. A further sample will be analyzed at the time point at which recrudescence/re-infection occurs (if applicable).

g Single local ECG reading for inclusion purpose and triplicate central ECG reading for safety evaluation during study.

h Laboratory safety will be performed locally: hematology, clinical chemistry, and urinalysis (see Appendix 2 of protocol for details).

i Where time points coincide, the PK samples should be taken after measurement of vital signs, temperature, and ECG. A PK sample (OZ439 and FQ) should be obtained if possible when QTcF >500 ms or QTcF is prolonged by >60 ms from baseline, or when increased ALT is measured (see Section 9.2 of protocol). PK samples numbering is detailed in Table 3 of protocol.

AE: adverse event; e-CRF: electronic case report form; ECG: electrocardiogram; FQ: ferroquine; HAV IgM: hepatitis A immunoglobulin M; HBsAg: hepatitis B surface antigen; HCG: human chorionic gonadotropin; HCV Ab: hepatitis C virus antibody; HCV RNA: hepatitis C virus ribonucleic acid; IMP: investigational medicinal product; IRT: Interactive response technology; PK: pharmacokinetics; qPCR: quantitative polymerase chain reaction; RT-qPCR: quantitative reverse transcription polymerase chain reaction; WHO: World Health Organization

Appendix B Potentially clinically significant abnormality criteria

Laboratory parameter PCSA criteria n/N1 (%)	Adults	Children
Haemoglobin		
Low	≤ 115 g/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	≥ 20 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 12 to 16/18 years old : <4,5 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		

Laboratory parameter PCSA criteria n/N1 (%)	Adults	Children
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

Laboratory parameter PCSA criteria n/N1 (%)	Adults	Children
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	≤ 129 mmol/L	≤129 mmol/L
High	≥ 160 mmol/L	≥150 mmol/L
Potassium		
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		

Laboratory parameter PCSA criteria n/N1 (%)	Adults	Children
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	

Laboratory parameter PCSA criteria n/N1 (%)	Adults	Children
At least grade 2 (adults)	> 2 ULN	
Alanine Aminotransferase and tot bilirubin		
High	ALT > 3 ULN and TBILI > 2 ULN	ALT ≥ 3 ULN and TBILI ≥ 2 ULN
Direct bilirubin and total bilirubir		
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

ECG Parameter PCSA criteria n/N1 (%)	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		

ECG Parameter	Adults	Children
PCSA criteria n/N1 (%)		
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		
Increase from baseline, Grade 1	Increase from baseline]30-60] ms	All age classes: Increase from baseline (30-60] ms

ECG Parameter	Adults	Children
PCSA criteria n/N1 (%)		
Increase from baseline, Grade 2	Increase from baseline >60 ms	All age classes: Increase from baseline >60 ms

References:

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Vital signs parameter PCSA criteria n/N1 (%)	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	
High and increase 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

Summary of statistical analyses

EFFICACY ANALYSIS

Endpoint	*Analysis population*	*Primary analysis*	*Supportive analysis*	*Subgroup analysis*	*Other analyses*
PCR-corrected ACPR at Day	PP	Logistic regression on exposure-respo with odds ratio estimates, 2-sided 95 Wald CI and p-value	No	No	Proportion, percentage, 2-sided exact binomial 95 CI by treatment group
PCR crude ACPR at Day 28	PP	Logistic regression on exposure-respo (resp. dose-response) with odds ratio estimates, 2-sided 95% Wald CI and value	No	No	Proportion, percentage, 2-sided exact binomial 95 CI by treatment group
PCR-corrected ACPR at Day 28	PP	Logistic regression on dose-response v odds ratio estimates, 2-sided 95% W CI and p-value	No	No	Proportion, percentage, 2-sided exact binomial 95 CI by treatment group
Parasite Reduction Rate at 24 48 h, and 72 h	PP	Descriptive statistics by treatment grou and time of measurement.	No	No	No
Parasitemia data as a continuous endpoint	PP	Descriptive statistics by visit and treatment group. Time profile plots by treatment grou	No	No	No
Parasite clearance rate	PP	Descriptive statistics by visit and treatment group.	No	No	No
Time to parasite Clearance, to fever clearance, 50% a 99% parasite reduction, recrudescence or re-infection, elapsed below LOQ of parasitemia.	PP	Kaplan Meier estimator and Cox model	No	No	No

SAFETY ANALYSES

Endpoint	*Analysis population*	*Primary analysis*	*Supportive analysis*	*Subgroup analysis*	*Other analyses*
Adverse Events, clinical laboratory data, ECG, vital signs, LFT, Physica examination	Safety	Follow safety guidelines	No	No	No

Appendix C References

Boulu, L. POH0456. Population PK analysis of ferroquine (SSR97193), and its metabolite SSR97213 from a pool of phase I and II studies (TDU5419, TDU5967, TDR5969, INT6856, ACT10420, DRI10382, TDU12511 and DRI12805) Sanofi. Internal Report, 2016

Laurijssens, B. & Cox, E. Pharmacokinetic and PKPD Analyses for Study MMVOZ43913003. Analysis Report Medicines for Malaria Venture. Internal Report, 2016