AMENDED CLINICAL TRIAL PROTOCOL NO. 03

COMPOUND: SSR97193 / ferroquine in association with artefenomel

A randomized, double-blind, Phase IIb study to investigate the efficacy, safety, tolerability and pharmacokinetics of a single dose regimen of ferroquine (FQ) with artefenomel (OZ439) in adults and children with uncomplicated *Plasmodium falciparum* malaria

STUDY NUMBER: DRI12805

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NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	Sanofi-aventis recherche & développement 1 Avenue Pierre Brossolette 91385 CHILLY-MAZARIN CEDEX France
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: **SSR97193 - ferroquine in association with artefenomel**	**STUDY No: DRI12805**
TITLE	A randomized, double-blind, phase IIb study to investigate the efficacy, safety, tolerability and pharmacokinetics of a single dose regimen of ferroquine (FQ) with artefenomel (OZ439) in adults and children with uncomplicated *Plasmodium falciparum* malaria
INVESTIGATOR/TRIAL LOCATION	Africa and previously in Asia (recruitment in Asia is closed)
STUDY OBJECTIVES	**Primary objective** • To determine whether a single dose combination of OZ439/FQ is an efficacious treatment for uncomplicated *Plasmodium falciparum* (*P. falciparum)* malaria in adults and children **Secondary objectives** • To evaluate the efficacy of OZ439/FQ: - To determine the incidence of recrudescence and re-infection - To determine the time to relief of fever and parasite clearance • To evaluate the safety and tolerability of OZ439/FQ • To evaluate the pharmacokinetics of OZ439/FQ: - To characterize the pharmacokinetics of OZ439 in plasma, FQ and its active metabolite SSR97213 in blood - To determine the blood/plasma ratio for FQ and SSR97213 in some patients at limited time points in selected sites. • To further explore efficacy of OZ439/FQ: - To evaluate the proportion of patients with gametocytes at each parasitological assessment - To characterize gametocyte carriage - To evaluate the relationship between Adequate Clinical & Parasitological Response (ACPR) and exposure to OZ439/FQ - To explore the relationship between Kelch-13 genotype and parasite clearance kinetics • To explore in vitro drug resistance of *P. falciparum* infecting patients >14 years old in Vietnamese sites.
STUDY DESIGN	A randomized, double-blind single-dose treatment, 3 to 4 dose-regimen study in patients with uncomplicated *Plasmodium falciparum* malaria. Adults and children will be included sequentially in four cohorts through a progressive age step-down procedure and FQ dose step-up procedure (pre-defined data of patients >14 years and body weight ≥35 kg exposed to the 3 first lowest doses in parallel will be reviewed before testing 1200 mg FQ dose in association with 800 mg OZ439). At the end of each cohort (or sub-Cohort 1a and 1b), a safety review of adverse events, potentially clinically significant abnormalities (PCSAs) for clinical laboratory test results, vital signs, and 12-lead ECGs will be performed. For patients >14 years (Cohort 1), FQ/active metabolite (SSR97213) blood concentration/QTc effect modelling will be done by a Sponsor's independent unblinded statistician and reviewed by an independent Data Monitoring Committee (DMC). This PK/QTc analyses may or may not be reviewed by the

	DMC at the same time as the safety data review and therefore may or may not be considered by DMC for DMC decision rule to proceed to the 1200 mg FQ dose in association with 800 mg OZ439 in that age category. The DMC will further determine if the range of 3 or 4 FQ doses in association with 800 mg OZ439 can be assessed in the lower age cohorts. The DMC could also decide to enroll additional patients in a same age cohort for collecting more safety data. In addition, interim futility analyses on polymerase chain reaction (PCR)-adjusted ACPR at Day 28 will be performed using Bayesian methodology when approximately 50 patients per treatment arm and thereafter every time another 25 patients per treatment arm have completed Day 28 assessment. The decision to step down with age cohorts will be based on safety.
STUDY POPULATION **Main selection criteria:**	**Inclusion criteria** • Male or female patient aged >6 months old and <70 years old: - Cohort 1 = 14 years <age <70 years and body weight ≥35 kg, - Cohort 2 = 5 years <age ≤14 years; - Cohort 3 = 2 years <age ≤5 years; - Cohort 4 = 6 months <age ≤2 years. • Body weight ≥5 kg and ≤90 kg. • Presence of mono-infection by *P. falciparum* with: Fever, as defined by axillary temperature ≥37.5°C or oral/rectal/tympanic temperature ≥38°C, or history of fever in the previous 24 hours (history of fever must be documented) and, microscopically (blood smear) confirmed parasite infection, ranging from 1000 to 100 000 asexual parasites/µL of blood. • Informed Consent Form signed by the patient or parent or legally acceptable representative of the minor patient. **Main exclusion criteria** • Presence of severe malaria (according to WHO definition). • Anti-malarial treatment: - With piperaquine -based compound, mefloquine, naphthoquine or sulphadoxine/pyrimethamine (SP) within the previous 6 weeks (after their inhibition of new infections has fallen below 50%). - With amodiaquine or chloroquine within the previous 4 weeks. - With quinine, halofantrine, lumefantrine-based compounds and any other anti-malarial treatment or antibiotics with antimalarial activity (including cotrimoxazole, tetracyclines, quinolones and fluoroquinolones, and azithromycin) within the past 14 days. - With any herbal products or traditional medicines, within the past 7 days. • Known history or evidence of clinically significant disorders. • Previous treatment within 5 times the half-life or within the last 14 days, whichever the longest which are: P-gp substrates, CYP2D6 main substrates and/or strong CYP2C or CYP3A inhibitors and/or moderate inhibitors but inhibiting both CYP2C and CYP3A and/or CYP inducers. • Mixed *Plasmodium* infection. • Severe vomiting. • Severe malnutrition.

	• Laboratory parameters with clinical significant abnormalities and/or reaching critical values. For Liver Function Test: (LFT) aspartate transferase [AST >2 upper limit of normal (ULN)], or alanine transferase [ALT >2 ULN] or total bilirubin [>1.5 ULN]. • Presence of Hepatitis A IgM (HAV-IgM), Hepatitis B surface antigen (HBs Ag) or Hepatitis C antibody (HCV Ab). • Previous participation in any malaria vaccine study or received malaria vaccine in any other circumstance. • Female patient of child bearing potential or male patient having a partner of child bearing potential not willing to use an effective contraceptive(s) method(s) for the duration of the study. • Positive pregnancy test at study screening for female participants of childbearing potential. • Known history of hypersensitivity, allergic or anaphylactoid reactions to ferroquine or other - aminoquinolines or to OZ439 or OZ277 or to any of the excipients. • Family history of sudden death or of congenital prolongation of the QTc interval or known congenital prolongation of the QTc-interval or any clinical condition known to prolong the QTc interval eg, patients with a history of symptomatic cardiac arrhythmias or with clinically relevant bradycardia. • QTcF >450 ms at screening or pre-dose. • Hypokalemia (<3.5 mmol/L), hypocalcemia (<2.0 mmol/L) or hypomagnesemia (<0.5 mmol/L) at screening or pre-dose. • Any treatment known to induce a lengthening of QT interval.
Total expected number of patients:	Approximately 495 (in case of 3 treatment arms, scenario A) or 662 (in case of 4 treatment arms, scenario B) African patients (approximately 165 per treatment arm), plus 21 Asian patients.
Expected number of sites:	Approximately 18 sites in Africa and Asia
STUDY TREATMENTS	
Investigational Products Formulation	Ferroquine (FQ): Capsules of 5, 30, 100 and 200 mg and matching placebo Artefenomel (OZ439): Individual sachets containing 150, 200, 300, 400, 600 and 800 mg OZ439 + TPGS granules for oral suspension.
Route of administration:	Oral route, fasted conditions (3 hours)
Dose regimen:	3 to 4 treatment arms for the combination of FQ and OZ439. For patients ≥35 kg, 3 to 4 treatment arms of FQ will be assessed along with a fixed dose of OZ439: - Treatment arm #1: OZ439 800 mg and FQ 400 mg in single dose; - Treatment arm #2: OZ439 800 mg and FQ 600 mg in single dose; - Treatment arm #3: OZ439 800 mg and FQ 900 mg in single dose; - Treatment arm #4: OZ439 800 mg and FQ 1200 mg in single dose will be assessed, if the DMC gives green light to proceed with this dose. Patients <35 kg will receive weight-adjusted doses for OZ439 predicted to achieve exposure (based on AUC) not exceeding 1.5-fold that of a 60 kg adult and not exceeding that of the lightest adult (35 kg) for the lightest patient in each weight band. Patients <35 kg will receive weight adjusted doses for FQ, predicted to achieve FQ and SSR97213 exposure (based on mean C_{max} and AUC) not exceeding 1.3-fold that of a lightest adult (35 kg) for the lightest patient in each weight band.

PRIMARY AND SECONDARY ENDPOINTS	**Primary endpoint:** PCR-adjusted Adequate Clinical and Parasitological Response (ACPR) at Day 28 **Secondary endpoints** **Efficacy endpoints** • PCR - adjusted ACPR at Day 42 and 63. • PCR - crude ACPR at Day 28, 42 and 63. • Kaplan Meier analysis for: - Time to re-emergence; - Time to recrudescence; - Time to re-infection. • Parasite clearance time (PCT). • Fever clearance time (FCT). • Parasite reduction rate (PRR). **Safety endpoints** • Adverse events, including Serious Adverse Events (SAE), Adverse Event of Special Interest (AESI) and Treatment Emergent Adverse Event (TEAE). • Clinical laboratory tests, vital signs and ECG, including: - Liver Function test (LFT); - QTc assessment. • Physical examination and clinical signs and symptoms related to uncomplicated *P. falciparum* 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). **Pharmacokinetic (PK) endpoints** • Pharmacokinetic parameters (mainly CL/F, Vss/F, C_{max}, AUC as relevant) of OZ439 in plasma, FQ and SSR97213 in blood and plasma • Blood/plasma ratio for FQ and SSR97213 (some patients in selected sites). **Exploratory endpoints** • Time to clearance of gametocytemia on blood smear for patients with gametocytes at baseline. • Time to appearance of gametocytemia on blood smear for patients with no gametocytes at baseline and time to clearance. • RT-PCR to measure gametocyte maturation stage (expression of *Pfs*25 mRNA) in patients >5 years. • Correlation between Kelch-13 genotype status and parasite clearance kinetics. • Define phenotypic and genotypic resistance pattern to conventional ACT of *P. falciparum* infecting patients aged >14 years old in Vietnamese sites. • In vitro susceptibility testing of *P. falciparum* infecting patients aged >14 years old in Vietnamese sites to OZ439, FQ and both drugs.
ASSESSMENT SCHEDULE	Refer to study flow chart

STATISTICAL CONSIDERATIONS	**Analysis population:** The primary efficacy analysis population will be the Per-Protocol (PP) population defined as “lower" naturally acquired immunity (NAI) population”, children ≤5 years in Africa. **Sample size determination:** This protocol is adaptive allowing futility at pre-specified interim points during the conduct of the study. At each interim time point, tests for futility will be performed. Recruitment will cease to a particular treatment arm if the pre-specified criterion for futility is reached. Interim assessment of futility will occur after recruitment of approximately 50 evaluable patients per treatment arm for the 1st futility analysis and every 25 patients per treatment arm thereafter for the 3 other interim analyses (including 75, 100 and 125 evaluable patients per treatment arm, respectively). Recruitment continues until each treatment arm is deemed to be futile or until 150 evaluable patients per treatment arm for the final analysis is reached. Given the adaptive nature of the study design, the total number of patients to be recruited can only be estimated. Simulations for different PCR-adjusted ACPR responses at Day 28 showed that a sample size of 150 evaluable patients per treatment arm will provide ≥80% probability to reject the null hypothesis (H0: probability of PCR-adjusted ACPR at Day 28 ≤0.90) at the final analysis, for the true rate ≥96.4%. In addition, a minimum of 15 African patients older than 5 years per treatment arm (likely to have higher NAI and therefore not included in the efficacy analyses) will be included for the DMC safety review. **Primary analysis:** Within each treatment arm, the following null hypothesis will be tested: H0: $p \leq 0.90$ Against the one sided alternative: H1: $p > 0.90$ where p is the probability of PCR-adjusted ACPR at Day 28. The study will follow a group sequential design with up to 4 interim futility analyses, the first one when approximately 50 evaluable patients per treatment arm have reached Day 28 and thereafter every time another 25 evaluable patients per treatment arm (until the final analysis including 150 evaluable patients) have reached Day 28. At each interim analysis, one of the following potential decisions is to be made: • The treatment arm is stopped for futility if the posterior probability of H0 (that is, response rate is below 90%) given the data accumulated at the look for the treatment arm in question is too large, that is, $Pr(H0|data) \geq 0.30$. • The treatment arm advances to the next stage if the above conditions is not met (even if the observed response rate is 95% or greater). A Beta (9.5, 0.5) distribution will be used as prior distribution for the response rate and combined with a binomial likelihood to get a Beta posterior distribution and calculate the posterior probability. At the final analysis, providing the treatment arm has not been stopped for futility, the null hypothesis will be rejected and efficacy of the treatment arm demonstrated if the lower limit of the exact 95% confidence interval using Clopper-Pearson method is >90%.

	Analysis of secondary endpoints Secondary efficacy variables will be summarized descriptively with incidence rates or standard descriptive methods, including 95% confidence intervals, as appropriate and using PCSAs criteria for relevant safety parameters. Time to event variables will be summarized with Kaplan-Meier estimates of the survival function. The relationship between QTc and FQ & SSR97213, respectively and OZ439 concentrations will be explored graphically and by mixed effect modeling. Prediction (estimate and 90% CI) at the observed geometric mean of C_{max} will be presented for each treatment arm. Three PK/QTc analyses are planned (one for Cohort 1a and a second based on the pool of Cohort 1a & 1b for DMC review, the last one will take into account all cohorts for the final analysis). Standard descriptive statistics on OZ439, FQ and SSR97213 concentration data and PK parameters, blood/plasma ratio for FQ and SSR97213. Relationship between PCR-adjusted ACPR and dose, concentration or exposure to OZ439/FQ will be explored through logistic regression. **Safety:** The on-treatment phase will be defined as the start time of investigational medicinal product (IMP) administration up to end of study (EOS). All TEAEs will be summarized (counts and percent) by primary system organ class, preferred term and treatment group. Potentially Clinically Significant Abnormalities (PCSAs) for clinical laboratory test results, vital signs, and 12-lead ECGs (manual readings, mean values of the 3 replicates) will be listed, flagged and summarized for treatment group. In addition, raw data and changes from baseline for some relevant parameters (ECGs, vital signs and laboratory parameters) will be summarized in descriptive statistics and summary plots if relevant.
DURATION OF STUDY (per patient)	Screening or predose on Day -1. Treatment with OZ439/FQ single dose on Day 0. Hospitalization at minimum for 48 hours post-dose (African patients greater than 5 years) or 72 hours post -dose (all Asian patients and African patients ≤5 years) or for a maximum of 7 days, depending on age, parasite and fever clearance, clinical judgment and patient convenience. Note: those patients discharged at 48 or 72 hours or later but prior to D7 will need to return to the investigational site for scheduled assessments up to Day 7. In case the patient is discharged after Day 3, patient has to perform the Day 3 discharge examinations. Following discharge, patients will return for further assessment up to Day 63. Total duration will be up to 67 days for each patient.

1 FLOW CHARTS

1.1 STUDY FLOW CHART

Table 1 - Schedule of assessments: screening to Day 63 (Times are post-dose)

Evaluation	Screen/ Predose	Treatment Period and post-treatment surveillance														Follow-Up (FU)									
Visits (V)	**V1**	**V2**									**V3**			**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15 (EOS)**
Day[a]	**-1**	**0**									**1**			**2**	**3**	**5**	**7**	**10**	**14**	**15-18**[g]	**21 +/- 2**	**24-25**[g]	**28 +/- 2**	**42 +/- 3**	**63 +/- 3**
Hours		**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**18**	**24**	**30**	**36**	**48**	**72**										
Informed consent	X																								
Demography, medical history	X																								
Inclusion/ exclusion criteria	X																								
IVRS/IWRS call	X	X																							X
Randomization		X																							
Hospitalization[b]		→	→	→	→	→	→	→	→	→	→	→	→	→	- - →										
Visit at clinical site															X	X	X	X	X	(X)	X	(X)	X	X	X
<u>Treatment</u>																									
OZ439[c]		X																							
FQ[c]		X																							
Prior and concomitant medication	X	X									X			X	X	X	X	X	X	X	X	X	X	X	X

Evaluation	Screen/ Predose	Treatment Period and post-treatment surveillance														Follow-Up (FU)									
Visits (V)	**V1**	**V2**									**V3**			**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15 (EOS)**
Day[a]	**-1**	**0**									**1**			**2**	**3**	**5**	**7**	**10**	**14**	**15-18**[g]	**21 +/- 2**	**24-25**[g]	**28 +/- 2**	**42 +/- 3**	**63 +/- 3**
Hours		**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**18**	**24**	**30**	**36**	**48**	**72**										
Efficacy																									
Physical exam & malaria signs & symptoms	X								X		X		X	X	X		X						X	X	X
Weight[j]	X													(X)	(X)										X
Temperature (single)[d]	X			X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Asexual & sexual count (thick & thin blood films) >14 y and ≥35 kg (Cohort 1)[d]	X[e]						X		X	X	X	X	X	X	X	X	X	X	X	(X)	X	(X)	X	X	X
Asexual & sexual count (thick & thin blood films) ≤14 years (Cohorts 2 to 4)[d]	X[e]						X			X	X		X	X	X	X	X	X	X	(X)	X	(X)	X	X	X
qPCR, parasite genotyping & RT-PCR gametocyte detection sampling >14 y and ≥35 kg (Cohort 1)[f]	X[e]						X		X	X	X	X	X	X	X	X	X	X	X	(X)	X	(X)	X	X	X

Evaluation	Screen/ Predose	Treatment Period and post-treatment surveillance														Follow-Up (FU)								
Visits (V)	**V1**	**V2**									**V3**			**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15 (EOS)**
Day[a]	**-1**	**0**									**1**			**2**	**3**	**5**	**7**	**10**	**14**	**15-18**[g]	**21 +/- 2**	**24-25**[g]	**28 +/- 2**	**42 +/- 3**	**63 +/- 3**
Hours		**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**18**	**24**	**30**	**36**	**48**	**72**										
Parasite genotyping sampling >6M & ≤14 y (Cohorts 2 to 4)[f]	X[e]									X	X		X	X	X	X	X	X	X	(X)	X	(X)	X	X	X
qPCR & RT-PCR gametocyte detection sampling >5 y & ≤14 y (Cohort 2)[f]	X[e]														X		X						X	X	X
Malaria RDT (taken 'in field')																				(X)		(X)			
Kelch-13 analysis[f]	X																								
Susceptibility testing in patients >14 y in Vietnamese sites[f]	X										(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Safety																									
12-Lead ECG[i]	X	X			X	X	X	X	X		X			(X)	(X)		X								
Vital signs[i]	X						X		X		X			(X)	(X)		X	X	X		X		X	X	X
AEs	→																						→		
Laboratory testing																									
Clinical laboratory safety >5 y[j]	X													(X)	(X)		X		X		X		X		

Evaluation	Screen/ Predose	Treatment Period and post-treatment surveillance													Follow-Up (FU)								
Visits (V)	**V1**	**V2**									**V3**			**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15 (EOS)**
Day[a]	**-1**	**0**									**1**			**2**	**3**	**5**	**7**	**10**	**14**	**15-18**[g]	**21 +/- 2**	**24-25**[g]	**28 +/- 2**	**42 +/- 3**	**63 +/- 3**
Hours		**0**	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**18**	**24**	**30**	**36**	**48**	**72**										
Clinical laboratory safety ≤5 y[j]	X													(X)	(X)		X		X				X		
Hepatitis Serology[k]	X																								
Pregnancy test[l]	X																						X		X
OZ PK >14 y[m]					P00	P01	P02		P03		P04			P05	P06	P07	P08	P09	P10						
OZ PK >2 y to ≤14 y[m]					P00		P02				P04						P08		P10						
OZ PK >6 m to ≤2 y[m]					P00		P02				P04						P08								
FQ PK >14 y[m]			BP00		BP01, PP00	BP02	BP03	BP04	BP05		BP06			BP07			BP08, PP01		BP09				BP10, PP02	BP11	BP12
FQ PK >5 y to ≤14 y[m]					BP01, PP00		BP03				BP06						BP08		BP09				BP10, PP02	BP11	
FQ PK Group 1 >2y to ≤5 y[m]					BP01, PP00		BP03				BP06						BP08		BP09						
FQ PK Group 1 >6 m to ≤2 y[m]					BP01		BP03				BP06						BP08		BP09						
FQ PK Group 2 >2 y to ≤5 y[m]					BP01		BP03				BP06						BP08						BP10, PP02		
FQ PK Group 2 >6 m to ≤2 y[m]					BP01		BP03				BP06						BP08						BP10		
FQ PK Group 3 >2 y to ≤5 y[m]					BP01		BP03				BP06						BP08, PP01							BP11	
FQ PK Group 3 >6 m to ≤2 y[m]					BP01		BP03				BP06						BP08							BP11	

a At each patient visit/contact post dose, antimalarial rescue therapy conditions will be assessed and rescue therapy may be given accordingly.

b Discharge at 48 hours (African patients > 5 years) or 72 hours (all other patients) (or up to Day 7) depending on age, parasite and fever clearance, clinical judgment and patient convenience. If discharged prior to Day 7, will return to Investigational site for further assessment on all scheduled times up to Day 7.

c Patients should have fasted from food and milk for 3 hours before administration. Neither food nor milk should be taken within 2 hour after the end of IMP dosing.

d Blood films (thick and thin, performed locally) and temperature measurements need to be confirmed as follows: when 1st parasite clearance or 1st temperature <37.5 °C, measurements need to be confirmed with second reading 6 to 12 hours after the 1st measurement (ie, to determine Parasite Clearance or Fever Clearance). The first measurement (if confirmed) will be considered the 'Clearance Time'. Only asexual count will be used as parasitemia for evaluation of study endpoints. If parasites have not cleared by 72 hours after IMP administration and criteria for rescue medication are not met at 72 h, 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 8.9). If these additional blood smears are taken they should be recorded as unscheduled visits in the CRF.

Note: Axillary temperature should be recorded. If the axillary method is not possible, an alternative route (tympanic, oral, rectal) may be used. Within an individual patient the same method of temperature measure should be used throughout the study.

e Measurement required within 4 hours prior to dosing. Local thick and thin blood films performed at the site, before Informed Consent signature, according to local standard procedures, can be used as screening / Pre-dose parasitaemia assessments (Section 9.3.1.1) provided that a standard procedure is in place at site and blood films stainings are performed according to Study Parasitology Procedures Manual.

f Blood spots or blood sample for qPCR (patients >5 y only), blood spot for parasite genotyping and Kelch-13 analysis; blood sample for RT-PCR gametocyte detection (patients >5 y only). To be collected, according to the schedule and the instructions reported in the Study Laboratory Procedures 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). Sample for Kelch-13 analysis at baseline only. All of these tests will be performed in central lab. During the intervening periods between V10 and V12, blood for RT-PCR gametocyte detection and qPCR (patients >14 years and ≥35kg only) will only be taken if the patient returns to the site for assessment. (see *g*). An additional blood sample (susceptibility testing) will be taken in patients >14 years old in Vietnamese sites at screening (6 mL) and when criteria for rescue treatment for malaria is met (6 mL). These samples will be used for in vitro research of drug resistance (see Section 9.4.2).

g Patients will have one additional safety check at V10 and V12. Patients may either return to the Investigational site or tests can be performed in the field by trained persons. If returning to the Investigational site, a blood film (thick and thin), a genotyping sample and temperature should be taken. Sample for qPCR and, RT-PCR should be taken for patients >14 years and ≥35 kg only. For patients remaining in the field, a malaria RDT and temperature should be taken. Patients feeling unwell, with increased temperature (axillary temperature ≥37.5 °C) and/or a positive RDT should return to the Investigational site for assessment including blood films, parasite genotyping.

h Deleted.

i Patients should rest supine prior to measurement for a minimum of 10 minutes (or at least 5 minutes for blood pressure measurement).

Single ECG will be taken at screening. Triplicate ECGs will be taken at T0 (before IMP administration) and at all time-points thereafter. Depending on discharge date, triplicate ECG to be performed at D2 or D3. For all African patients of Cohort 1, triplicate ECG to be performed at D2 (PK/QTc purpose). For all patients discharged after D3, triplicate ECG should be performed at D3.

Body weight at screening, discharge (D2 or D3) and EOS. For all patients discharged after D3, body weight and vital signs should be performed at D3. Height at screening for BMI calculation.

j Laboratory safety: hematology (local), clinical chemistry (screening: one local lab sample for inclusion criteria and one central lab sample for baseline values; central lab samples at all time-points thereafter), and urinary dipstick (performed locally; if any parameter on the dipstick is abnormal, a urine sample should be sent to the central lab for microscopic analysis) (See Table 4 for details). Depending on discharge date, laboratory safety at D2 or D3. For all patients discharged after D3, sample should be taken at D3. No sample will be taken at V11 (D21+/-2) for children ≤ 5 years.

k Serology: Test for hepatitis by rapid spot test: HAV IgM, HBs Ag and HCV Ab.

l Urine HCG is the minimum acceptable test. It will be performed locally. Result must be confirmed negative prior to dosing and must be consistent with menstrual history.

m Where time points coincide, PK sampling should be performed after vital signs, temperature and ECG measurement. Blood samples will be collected within ± 15 minutes of nominal time until 48 h after administration. The exact date and time should be recorded at all PK sampling time points.

For FQ PK samplings, blood will be collected by venipuncture for Dried Blood Spot (DBS) assay (all sites). In selected sites, plasma (Dried Plasma Spot, DPS) assay will also be performed in a sub-set of patients.

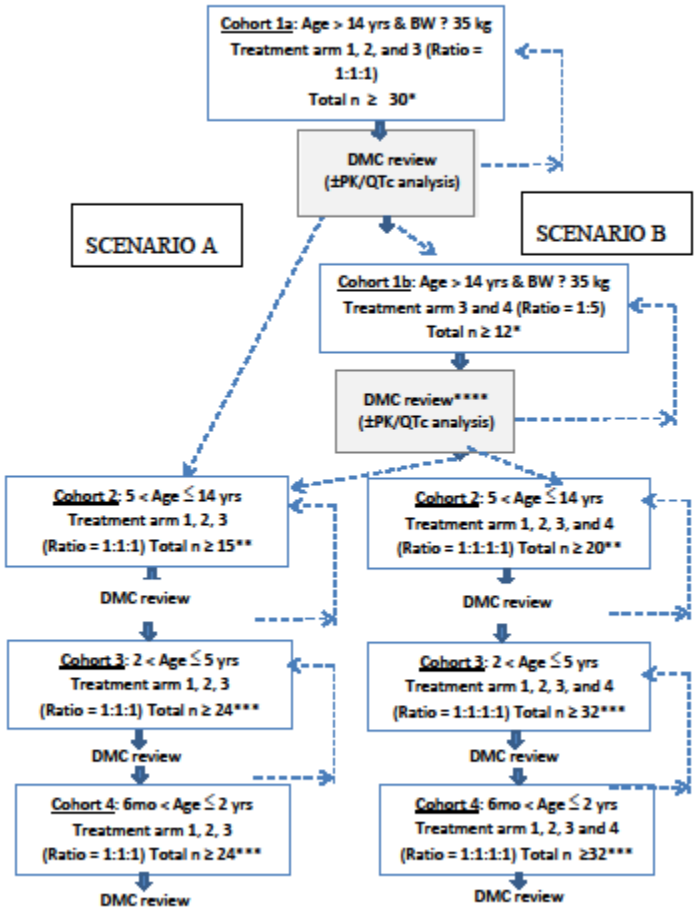
Note: For FQ PK samplings, “BPXX” indicate DBS sample, “PPXX” indicate DPS sample. For OZ PK samplings, "PYY" indicates a plasma OZ PK sample.

For patients > 6 months and ≤5 years, FQ PK sampling will consist of 3 different sampling schedules (Group 1, Group 2, Group 3) attributed at random by the IVRS/IWRS. PP00, PP01 and PP02 only for children >2 years. In addition, for all patients where possible, a PK (OZ and FQ) sample should be obtained when a rescue treatment for malaria is given or when QTcF>500 ms or QTcF prolongation >60 ms from baseline or when ALT increase (see Section 10.4.1.4). Those additional samples will be identified as “BPA01” for DBS of FQ and as “PA01” for plasma sample of OZ.

Note: Visit 1 & Visit 2 can occur on the same day, provided that all baseline assessments and biology (including parasitemia and laboratory safety) results are obtained, before patient randomization. Visits or examinations presented in brackets have to be performed when applicable.

1.2 STEP-DOWN AND STEP-UP PROCEDURES

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



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

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

- Patients ≥35 kg:
  - Treatment arm 1 = OZ439 800 mg - FQ 400 mg,
  - Treatment arm 2 = OZ439 800 mg - FQ 600 mg,
  - Treatment arm 3 = OZ439 800 mg - FQ 900 mg,
  - Treatment arm 4 = OZ439 800 mg - FQ 1200 mg

- Patients <35 kg will receive
  - Weight-adjusted doses for OZ439 predicted to achieve exposure (based on AUC) not exceeding 1.5-fold that of a 60 kg adult and not exceeding that of the lightest adult (35 kg) for the lightest patient in each weight band.
  - Weight adjusted doses for FQ predicted to achieve FQ and SSR97213 exposure (based on mean C_{max} and AUC) not exceeding 1.3-fold that of a lightest adult (35 kg) for the lightest patient in each weight band.

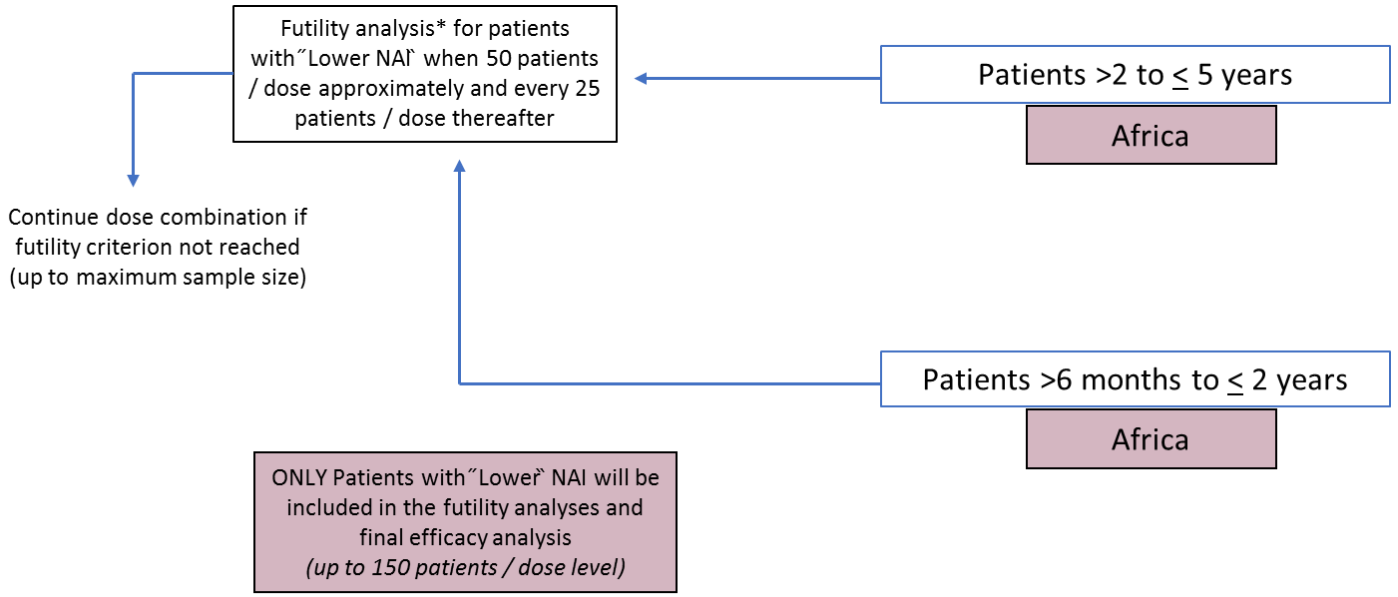
*: A minimum number of 10 patients (Cohort 1) per treatment arm for DMC safety & PK/QTc evaluation
**: A minimum number of 5 patients (Cohort 2) per treatment arm for DMC review
***: A minimum number of 8 patients (Cohorts 3 & 4) per treatment arm for DMC review
After all these age step-down stages, the recruitment will be fully open. Approximately 62 patients will be recruited in Cohorts 1 and 2 for Scenario B. The remaining patients will comprise Cohorts 3 and 4. At least 10% of the lower NAI population will come from African patients of Cohort 4.
****: DMC review before starting Cohort 2 recruitment will be made on pooled data (Cohorts 1a & 1b) with a total number of patients N ≥42.

Notes:

- **Patients likely to have higher NAI (African patients >5 years old to <70 years old) and Asian patients will only be considered for safety review.**
- **African patients likely to have lower NAI (children ≤5 years) will be considered for safety review, and also futility and efficacy analyses**.

For DMC safety review, no predefined ratio between African and Asian patients is requested to move forward from one group of age to the next one. Patients will be included following a "competitive recruitment" process.

Figure 2 - Futility interim analysis



* Futility analysis will be conducted by the DMC statistician

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3 LIST OF ABBREVIATIONS

°C:	degrees Celsius
ACPR:	adequate clinical and parasitological response
ACT:	artemisinin-based combined therapy
AESI:	adverse event of special interest
AS:	artesunate
BP:	blood pressure
CRF:	case report form
DBS:	dry blood sample
DMC:	data monitoring committee
DPS:	dry plasma sample
DRF:	discrepancies resolution form
e-CRF:	electronic case report form
ETF:	early treatment failure
FCT:	fever clearance time
FQ:	ferroquine
GCP:	good clinical practices
HR:	heart rate
IA:	interim analysis
ICH:	International Conference of Harmonization
IMP:	investigational medicinal product
IRB/IEC:	institutional review board/independent ethics committee
LCF:	late clinical failure
LFT:	liver function test
LOQ:	limit of quantification
LPF:	late parasitological failure
MMV:	Medicines for Malaria Venture
MPC:	minimum parasiticidal concentration
ms:	millisecond
NAI:	naturally acquired immunity
OZ439:	artefenomel
P. falciparum:	Plasmodium falciparum
PCR:	polymerase chain reaction
PCT:	parasite clearance time
PK:	pharmacokinetic
PRR:	parasite reduction rate
RDT:	rapid diagnostic test
SAE:	serious adverse event
SUSAR:	suspected unexpected serious adverse reaction
TEAE:	treatment emergent adverse event
TPGS:	alpha tocopherol polyethylene glycol 1000 succinate
WHO:	World Health Organization

GLOSSARY OF TERMS

qPCR (quantitative polymerase chain reaction)
A polymerase chain reaction procedure is used to quantify the amount of *Plasmodium falciparum (P. falciparum)*-specific DNA present and is transformed into number of parasites/µL.

RT-PCR (reverse transcriptase polymerase chain reaction)
Gametocytes are differentiated from asexual forms by targeting RNA transcripts of gametocyte-specifically expressed genes (Pfs25).

Recrudescence
Recrudescence is defined as the appearance of asexual parasites after clearance of initial infection with a genotype identical to that of parasites present at baseline. Recrudescence must be confirmed by microscopy (positive blood smear) and polymerase chain reaction (PCR) analysis.

Re-infection
Re-infection is defined as the appearance of asexual parasites after clearance of initial infection with a genotype that differs from that of parasites present at baseline. Re-infection must be confirmed by microscopy (positive blood smear) and PCR analysis. Confirmed new infection will not be regarded as treatment failure or recrudescence.

Re-emergence/Recurrence
Re-emergence (recrudescence and re-infection) is defined as the appearance of asexual parasites after clearance of initial infection irrespective of genotype.

PCR crude
PCR-crude adequate clinical and parasitological response (ACPR) does not distinguish between re-infection (by a new clone of parasite) and recrudescence (re-emergence of the original clone of parasite that is present at baseline).

PCR-adjusted
PCR-adjusted ACPR applies only to recrudescence (re-emergence of the original clone of parasite that is present at baseline). Recrudescence is distinguished from re-infection by genotyping the parasite clone.

SSR97213
N-demethyl derivative, active metabolite of ferroquine (FQ)

CLASSIFICATION OF TREATMENT OUTCOMES (ADAPTED FROM WHO, 2009) (1)

Parasitemia will be evaluated locally with blood smear.

Early treatment failure (one the following)

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

Late clinical failure

- Danger signs or severe malaria on any day between Day 4 and Day 63 in the presence of parasitemia, without previously meeting any of the criteria of early treatment failure;
- Presence of parasitemia and axillary temperature ≥37.5 degrees Celsius (°C) (or history of fever) on any day between Day 4 and Day 63, without previously meeting any of the criteria of early treatment failure.

Late parasitological failure

- Presence of parasitemia on any day between Day 7 and Day 63 and axillary temperature <37.5°C, without previously meeting any of the criteria of early treatment failure or late clinical failure.

Adequate clinical and parasitological response (ACPR)

- Absence of parasitemia on Day 28 (or Day 42 or Day 63), irrespective of axillary temperature, without previously meeting any of the criteria of early treatment failure or late clinical failure or late parasitological failure.

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Plasmodium falciparum (*P. falciparum*) malaria is a parasitic disease that kills over 600 000 people and results in up to 200 million cases annually affecting mainly young children in Sub Saharan Africa (2). The economic consequences of malaria are enormous in endemic regions including gross domestic product loss and productive life loss due to deaths and disability (3). Malaria is curable and preventable: principal control strategies including rapid diagnosis, effective treatment and personal protection with bed nets.

World Health Organization guidelines (WHO 2015) recommend the use of artemisinin-based combination therapies (ACT) to treat uncomplicated *P. falciparum* malaria (1, 4)

Artemisinin (AS) produces a rapid parasitemia clearance with resolution of malaria symptoms.

A 7-day course was reduced to 3 days when given in combination with long half-life anti-malarial drugs such as 4-aminoquinoline drugs (5). Evidence suggests that compliance to a 3-day treatment course is low, reducing the effectiveness of the treatment. In addition, evidence of emergence of potential plasmodial resistance to artemisinin may become an issue in the coming years (1, 6, 7). Thus new drug combinations are required, and effective single exposure combination treatments in particular are likely to lead to significant improvement in treatment efficacy.

Sanofi and Medicines for Malaria Venture (MMV), are co-developing a fixed dose combination of Ferroquine (FQ;IND 115 244) and Artefenomel (OZ439;IND 104 549) for a single day-single dose treatment of uncomplicated malaria in adults and children with the objective of limit the risk for selecting organisms resistant to either or the two partner drugs. Currently OZ439/FQ is intended to be used for investigational purpose.

Detailed information for both products are described in the related Investigator's brochures, reference document of each product updated regularly or at any time, as needed.

Artefenomel

Artefenomel (OZ439) is a novel, synthetic trioxolane that shows promise as a peroxidic anti-malarial agent. Trioxolanes are closely related to artemisinin in that their chemical structure contains the peroxidic pharmacophore that leads to the potent anti-malarial activity of these agents.

Based upon evidence to date, OZ439 demonstrates an acceptable safety profile, with continued close monitoring for hepatic and cardiac conduction effects recommended in the further clinical development.

OZ439 is studied in combination with FQ in the present Phase IIb DRI12805 FALCI study.

Ferroquine

Ferroquine (FQ) is a new 4-aminoquinoline analogue active against chloroquine-resistant and sensitive *P. falciparum* strains with a promising antimalarial therapeutic potential in humans.

FQ is a ferrocenyl derivative of chloroquine. Incorporation of a ferrocene core in the lateral side chain of chloroquine confers lipophilicity, rigidity, and redox potential to the molecule. A multifactorial mechanism of action of FQ has been proposed: inhibition of hemozoin formation, improved compared to chloroquine, and probably due to preferential location of FQ at the lipid-water interface, and generation of reactive oxygen species.

Ferroquine is a racemic compound with both enantiomers showing an antimalarial activity similar to that of the parent compound, in vitro and in vivo. Ferroquine is metabolized into 1 major metabolite (N-demethyl derivative, SSR97213), equally active in vitro.

Additional information can be found in FQ and OZ latest versions investigator's brochure.

The risk assessment of FQ alone and in combination with OZ439 is based on current available results from nonclinical data and clinical data (12 completed Phase I and Phase 2 studies), including an additional human challenge study (Q3CP14) with FQ alone in healthy subjects. The primary adverse events reported were mainly gastrointestinal (nausea, vomiting) and nervous system (headache, dizziness) events. Hepatic effect (elevated liver enzymes) and pro-arrhythmic effect (QTc prolongation) are the identified risks for the individual components FQ and OZ439 given alone or in combination.

4.2 RATIONALE

4.2.1 Study Rationale

The aim of the phase 2b DRI12805 is to investigate the efficacy, safety, tolerability and pharmacokinetics of a single dose regimen of FQ with OZ439 in adults and children with uncomplicated P. falciparum malaria. Based on predicted efficacy and safety data, this study will determine which single dose combination of OZ439 /FQ once daily is an efficacious and safe treatment for uncomplicated P. falciparum malaria in adults and children. The primary endpoint being evaluated is PCR adjusted ACPR at Day 28. A dose effect of FQ when combined with a defined dose of OZ439 may be demonstrated.

4.2.2 Dose Rationale

Doses for DRI12805 were selected based on clinical data obtained in Human Challenge Model studies for OZ439, Phase IIa data for OZ439 (MMV_OZ439_10_002), Phase IIb FQ/AS (DRI10382 results) and predicted QTc prolongation for FQ as discussed below.

Based on modeling and simulation of the parasite clearance kinetics of OZ439, the MPC (minimum parasiticidal concentration) for OZ439 was estimated to be 3-6 ng/mL. Time above MPC for 800 mg OZ was estimated to be approximately 200 h.

This was confirmed in a Phase IIa study of the acute efficacy (up to 36 hours post-dose) of OZ439 against *P. falciparum* and *P. vivax* malaria in a PoC study in Asian adult patients (MMV_OZ439_10_002) leading to a 97.9% reduction in parasite concentration by 36 hours for *P. falciparum* for all doses investigated (200 to 1200 mg).

Assuming an 11-fold reduction in log10 parasitemia is sufficient for effective therapy of patients (malaria patient parasitemia is between 10^{11} and 10^{12} parasites) PK/PD modeling suggests that a single dose of OZ439 at 800 mg can be considered as effective therapy when administered alone with around 11-fold decrease in log 10 parasitemia.

In DRI10382, PCR-adjusted Day 28 cure rate was 93.3, 97.1 and 96.8% after 100, 200 & 300 mg (2, 4 & 6 mg/kg) of FQ respectively when given in combination with AS over 3 days in children. A dose effect was observed for secondary criteria (uncorrected Day 28 cure rate) with values of 50.0%, 60.0% and 74.2% after 2, 4 and 6 mg/kg x 3 days respectively, in pediatric population (8, 9).

After simulations using POP PK model in children and 55 kg adults, FQ and SSR97213 Day 28 concentrations obtained after 600 mg single dose (or equivalent dose in children, see Table 2) are similar as compared to Day 28 concentration obtained in children after 4 mg/kg x 3 days (corresponding to 200 mg x 3 days). Thus assuming that OZ439 800 mg single dose performs at least as well as AS 200 mg x 3 days (internal MMV data show that OZ439 800 single dose performs better than 150 mg x 3 days di-hydro artemisinin) efficacy expected after 600 mg FQ /800 mg OZ (expressed in adult dose) single dose should be similar in children and in 55 kg adults to efficacy after 200 mg FQ/ 200 AS x 3 days (expressed in adult dose) with PCR-adjusted Day 28 cure rate of 97% in pediatrics.

Considering both corrected and uncorrected Day 28 cure rate from DRI10382, it was deemed relevant to test also doses higher than 600 mg and target the highest possible dose that is considered safe (see below).

The choice of the maximal FQ dose of 900 mg as the high dose (first intention) in adult cohort derives from the predictive QTc effect in the TDU12511 study in the time interval $T_{0h30} - T_{48h}$. The predicted mean ΔΔQTcF at FQ maximum peak observed concentration (Cmax) Day 1 (284 and 618 ng/mL after 900 and 1200 mg, respectively) of 1.3 ms with a 90% upper bound of 3.7 ms and 2.9 ms with a 90% upper bound of 8.0 ms for FQ doses of 900 and 1200 mg in healthy subjects, respectively. Maximum Peak Observed Concentration (Cmax) is expected to be higher in patients (estimated around 1.4-fold higher) with FQ mean values estimated at 388 and 670 ng/mL at 900 mg in 64 kg and 35 kg patients, respectively, thus corresponding to predicted mean ΔΔQTcF of 1.8 ms with a 90% upper bound of 5.0 ms and 3.1 ms with a 90% upper bound of 8.6 ms, respectively (predicted values from the PK/PD ECG model using TDU12511 data in the time interval $T_{0h30} - T_{48h}$). Greater than dose proportional increases in ferroquine exposure (Cmax and AUC) were observed between 900 and 1200 mg in the phase I OZ439/ferroquine combination study when ferroquine was administered with milk. Based on preliminary investigations using Physiologically-Based Pharmacokinetic modeling,(10) the current hypothesis for this non-linearity is an increase in absorbed fraction (estimated at 100%) at high doses in presence of milk. In fasting conditions (as it is recommended for the current DRI12805 study) the PK is believed to be linear between 900 and 1200 mg. In this respect, FQ 900 mg once daily is the highest recommended dose in the Cohort 1a in DRI12805 study (see Section 9.4.1.5).

The expected outcome of this phase 2b study is to document the contribution of FQ to the parasite clearance and long term prevention of recrudescence/re infection, and to select a safe and efficacious dose that will be tested in a large scale Phase 3 trial. It is therefore important to consider increasing level of FQ dose and correctly frame the selected dose.

- The upper limit will most likely be defined on safety aspect and could reasonably be 900 mg or 1200 mg.
- The lower limit should be assessed on efficacy by defining the lowest efficacious dose and the highest non efficacious dose.

Ultimately, we should be able to demonstrate a dose effect of FQ when combined with a defined dose of OZ439, the primary endpoint being evaluated on PCR adjusted ACPR.

Regarding the step-down procedure, the 3 treatment arms (OZ439/FQ 800/400 mg, 800/600 mg and 800/900 mg) will be administered as a single dose in 4 successive cohorts corresponding to 4 age categories evaluated in the following order:

- Cohort 1: adults patients (>14 years and <70 years and body weight ≥35 kg) including, two sub cohorts 1a (highest FQ dose of 900 mg) & 1b (highest FQ dose of 1200 mg),
- Cohort 2: adolescent and toddlers (>5 to ≤14 years),
- Cohort 3: children (>2 years to ≤5 years) and
- Cohort 4: infants and young children (>6 months to ≤2 years).

At the end of the Cohort 1a (OZ439/FQ 800/400 mg, 800/600 mg and 800/900 mg), an interim safety analysis, which may include PK/QTc change analysis will be performed by a Sponsor's unblinded statistician (independent from the study) and reviewed by the Data Monitoring Committee (DMC). This PK/QTc analyses may or may not be reviewed by the DMC at the same time as the safety data review and therefore may or may not be considered by DMC for DMC decision rule. If the 3 treatments up to 800/900 mg OZ439/FQ dose show good tolerability, a 4th treatment arm consisting of OZ439/FQ at 800/1200 mg (Cohort 1b with 2 additional patients receiving OZ439/FQ 800/900 mg for keeping the blinded conditions) will be recruited in the study for assessing the safety of highest FQ dose. A Final PK/QTc change analysis using data from Cohorts 1a and 1b will be performed (details of PK/QTc analysis in Section 11.4.5.3). OZ439/FQ at 800/1200 mg will be first evaluated in adult patients (>14 years and <70 years and body weight ≥35 kg, Cohort 1b) vs OZ439/FQ 800/900 mg in a 5:1 randomization ratio to keep the study blinded.

The transition from one cohort to another will be made upon an interim review of clinical and biological safety data by the DMC (which may include PK/QTc change analysis on pooled Cohorts 1a & 1b) which will continuously monitor safety aspects throughout the study (refer to DMC charter).

For patient <35 kg, the pediatric doses for FQ were weight-adjusted through simulation using POP PK model. The body weight band limits and associated pediatric doses for FQ for treatment arm 2 (600 mg in patient ≥35 kg) were selected in order that D28 concentration of FQ/SSR97213 after single dose of treatment arm 2 are close to corresponding D28 concentration obtained after

3-day treatment of FQ at 4 mg/kg (DRI10382) (as in adult), in order that the lightest subject of a given weight band would not have exposures (based on mean C_{max} and AUC) higher than 1.3-fold the lightest adult (35 kg), and in order to maintain a fixed OZ439/FQ dose ratio across the weight continuum. Pediatric doses for other Treatment groups were selected similarly as regards predicted exposure in pediatrics as compared to the lightest adult and with a fixed OZ439/FQ dose ratio over the weight continuum in each Treatment group. In addition for the first 3 treatment arms (OZ439/FQ 800/400 mg, 800/600 mg and 800/900 mg) mean FQ and SSR97213 exposure are predicted not to exceed the mean exposures achieved in previous studies for any weight band except for FQ C_{max}. For the 900 mg equivalent adult dose, the highest mean FQ C_{max} in pediatric patients is estimated at 756 ng/mL (for a 10 kg child in the 10-15kg weight band); for this C_{max} value, the predicted ΔΔQTcF (change from baseline corrected from placebo) is of 3.52 ms with a 90% upper bound of 9.74 ms.

Up to date, OZ439 has not been studied in a pediatric population. Therefore, in absence of any evidence to the contrary it was assumed that clearance (mainly hepatic) and volume of distribution are related to body weight using the theoretic allometric exponents (0.75 and 1, respectively).

The pediatric doses for OZ439 were selected such that the heaviest patient in each weight band would achieve similar exposures to a 60 kg adult subject in the same treatment arm, and the lightest subject would not have exposures higher than the lightest adult (35 kg) in the same treatment arm. The aim was to ensure adequate efficacious exposures for each body weight band. The lightest patient in each weight band would achieve exposures up to 1.5 times that of a 60 kg adult and not exceeding that of the lightest adult (35 kg).

OZ439 exposures in this study are predicted not to exceed the approximate exposures achieved in previous studies ie, an approximate mean C_{max} of 2000 ng/mL and mean AUC_{inf} of 29000ng.h/mL. These exposures have been demonstrated to have an acceptable safety and tolerability profile (see OZ439 investigator's brochure).

The weight bands and pediatric doses for OZ439 and FQ are detailed in Table 2:

Table 2 - Weight bands and pediatric doses for OZ439 (OZ) and FQ

FQ_400 mg group	≥ kg	< kg	FQ	OZ	FQ/OZ
pediatric	35		**400**	800	0.5
dosing	24	35	**300**	600	0.5
	15	24	**200**	400	0.5
	10	15	**150**	300	0.5
	7	10	**100**	200	0.5
	5	7	**75**	150	0.5

FQ_600 mg group	≥ kg	< kg	FQ	OZ	FQ/OZ
pediatric	35		**600**	800	0.8
dosing	24	35	**450**	600	0.8
	15	24	**300**	400	0.8
	10	15	**225**	300	0.8
	7	10	**150**	200	0.8
	5	7	**115**	150	0.8

FQ_900 mg group	≥ kg	< kg	FQ	OZ	FQ/OZ
pediatric	35		**900**	800	1.1
dosing	24	35	**675**	600	1.1
	15	24	**450**	400	1.1
	10	15	**335**	300	1.1
	7	10	**225**	200	1.1
	5	7	**170**	150	1.1

FQ_1200 mg group	≥ kg	< kg	FQ	OZ	FQ/OZ
pediatric	35		**1200**	800	1.5
dosing	24	35	**900**	600	1.5
	15	24	**600**	400	1.5
	10	15	**450**	300	1.5
	7	10	**300**	200	1.5
	5	7	**225**	150	1.5

FQ: ferroquine, OZ: artefenomel

5 STUDY OBJECTIVES

This study will investigate the efficacy exposure-response of OZ439/FQ combination in the target populations and if it meets its efficacy objectives, will inform dose selection for Phase III studies.

5.1 PRIMARY OBJECTIVE

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

5.2 SECONDARY OBJECTIVES

To evaluate the efficacy of OZ439/FQ:

- To determine the incidence of recrudescence and re-infection.
- To determine the time to relief of fever and parasite clearance.

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

To evaluate the pharmacokinetics of OZ439/FQ:

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

5.3 EXPLORATORY OBJECTIVES

To further explore efficacy of OZ439/FQ:

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

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This is a randomized, double-blind single-dose (loose combination) study in patients spanning the age range greater than to 6 months to less than 70 years, with uncomplicated *P. falciparum* malaria.

Adults and children will be included sequentially in four cohorts through a progressive age step-down procedure and FQ dose step-up procedure (pre-defined data of patients >14 years and <70 years and body weight ≥35 kg exposed to the 3 first lowest doses will be reviewed before testing 1200 mg FQ dose in association with 800 mg OZ439).

For patient ≥35 kg, 3 to 4 treatment arms of FQ (depending of DMC safety review of Cohorts 1a & 1b) will be assessed along with a fixed dose of OZ439:

- Treatment arm #1: OZ439 800 mg and FQ 400 mg in single dose.
- Treatment arm #2: OZ439 800 mg and FQ 600 mg in single dose.
- Treatment arm #3: OZ439 800 mg and FQ 900 mg in single dose.
- Treatment arm #4: OZ439 800 mg and FQ 1200 mg in single dose will be assessed, if the DMC gives green light to proceed with this dose.

Patients <35 kg will receive weight-adjusted doses for OZ439, predicted to achieve exposure (based on AUC) not exceeding 1.5-fold that of a 60 kg adult and not exceeding that of the lightest adult (35 kg) for the lightest patient in each weight band.

Patients <35 kg will receive weight adjusted doses for FQ, predicted to achieve FQ and SSR97213 exposure (based on mean C_{max} and AUC) not exceeding 1.3-fold that of a lightest adult (35 kg) for the lightest patient in each weight band.

For each age cohort, once a pre-defined minimal number of patients per treatment arm have been enrolled and completed Day 28 visit, a safety review will be done by an independent Data Monitoring Committee (DMC) who will recommend or not to proceed to the 1200 mg FQ dose in association with 800 mg OZ439 and then to the lower age cohorts. The safety review will be based on adverse event, potentially clinically significant abnormalities (PCSAs) for clinical laboratory test results, vital signs, and 12-lead ECGs; it may also include FQ/SSR97213 blood concentration/QTc effect modelling for Cohort 1a & 1b only.

The DMC could also decide to enroll additional patients in a cohort for collecting more safety data in that cohort.

In addition, a first interim futility analysis on PCR-adjusted ACPR will be performed at Day 28 using Bayesian methodology when approximately 50 patients per treatment arm and thereafter every time another 25 patients per treatment arm have completed Day 28 assessment

(ie, 75 patients/treatment arm for the 2nd interim analysis (IA), 100 patients/treatment arm for the 3rd IA, 125 patients/treatment arm for the 3rd IA until 150 patients/treatment arm for the final analysis). Of note, there will be no treatment arm dropped for efficacy, only for futility.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

Screening / predose Day -1.

Treatment with OZ439/FQ single dose on Day 0.

Hospitalization at minimum for 48 hours post-dose (African patients greater than 5 years) or 72 hours post -dose (all Asian patients and African patients ≤5 years) or for a maximum of 7 days, depending on age, parasite and fever clearance, clinical judgment and patient convenience.

After discharge patients will return to the investigational site for further assessment up to Day 63.

Note: those patients discharged at 48 or 72 hours will need to return for scheduled assessment up to Day 7.

Total duration will be up to 67 days for each patient.

6.2.2 Determination of end of clinical trial (all patients)

The end of the clinical trial is defined as the day the last patient completes his/her last visit planned in the protocol (ie, EOS visit).

6.3 INTERIM ANALYSIS

Safety review

Unblinded safety data of each cohort (N = 10 patients/arm for Cohort 1, 5 patients/arm for Cohort 2 and 8 patients/arm for Cohort 3 & 4) will be analyzed by the DMC independent statistician and reviewed by the DMC. Refer to Section 11.5 for details.

Interim futility analysis

Up to 4 interim futility analyses may be planned and will be performed by the Sponsor's unblinded independent statistician and reviewed by DMC: for details, please refer to Section 11.5.

6.4 STUDY COMMITTEES

Data Monitoring Committee (DMC): The Data Monitoring Committee is composed of clinicians and methodologists who are experienced with clinical trials –drug safety and malaria- and can be relied upon to exercise good judgment in weighing the potential risks and benefits to patients as data accumulate in this trial. They will be responsible for monitoring the safety of the patients exposed to study medication on a regular basis as well as reviewing the results of each interim futility analysis. DMC members are listed in the DMC charter.

Using clinical and laboratory safety data and PK/QTc evaluations (the latter may or may not be considered for decision rule), the DMC will provide guidance on inclusion of a 1200 mg FQ group (associated with OZ439-800 mg), moving to lower age cohort or stopping a study group for safety reason or if futility rules are met. Stopping rules are provided in the DMC charter.

The DMC, which includes an associated statistician, will receive safety, laboratory and efficacy data from the Sponsor's unblinded statistician for the safety and futility assessment. The data will be blinded per treatment arm and unblinded review of treatment arms will be done upon DMC members' request to the Sponsor's unblinded statistician. The DMC is independent from pharmaceutical companies, including Sanofi and competitor companies, from other study committees, and from the study investigators.

The chairman of the DMC, in conjunction with the other members, will communicate their recommendations to the Sponsor after each meeting. A DMC charter is displayed in a separate document prepared under the responsibility of the DMC chairman. The procedures used to protect the blind within the Sponsor and the age step-down and FQ dose step-up procedures are described in the DMC charter.

All safety data will be collected throughout the entire duration of the study, in timely fashion. Tabular summaries of these will be provided on a regular basis to the DMC chair who may decide at any time to convene a DMC meeting and analyze safety data and endpoints. On the basis of the totality of these results the DMC may recommend to the Sponsor changes in the protocol or stopping the trial.

7 SELECTION OF PATIENTS

7.1 NUMBER OF PATIENTS

The study will be performed using interim assessments of futility. The number of African patients that will be required for the 'lower' naturally acquired immunity (NAI) per protocol population is 150 patients per treatment arm. However to allow for potentially higher variability, the target number of patients recruited will be 165 per treatment arm consisting of:

- 15 African patients per treatment arm greater than 5 years (ie, considered to have "higher" NAI) who will be evaluated within Cohort 1 & 2 and will not be included in the interim analyses for futility (*of note*,17 patients should be included in treatment arm #3 since, in scenario B, 2 additional African patients would be added to Cohort 1b to maintain the blind); these patients will not be part of the per protocol efficacy population,
- Up to 150 patients per treatment arm from the 'lower' NAI population (ie, African patients ≤5 years old) who will be included in the interim analyses for futility.

Overall, this will give a total maximum number of 495 African patients (scenario A with 3 treatment arms) or 662 African patients (scenario B with 4 treatment arms) assuming no treatment arm is dropped 'early' for futility, ie, up to 165 African patients/treatment arm (except treatment arm #3 in which 167 patients should be included regarding scenario B) (see Section 1.2, Figure 1). Twenty-one Asian patients will also be recruited.

7.2 INCLUSION CRITERIA

I 01. Male or female patient aged >6 months old and <70 years old:

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

I 02. Body weight ≥5 kg and ≤90 kg.

I 03. Presence of mono-infection by P. falciparum with:

a) Fever, as defined by axillary temperature ≥37.5°C or oral/rectal/tympanic temperature ≥38°C, or history of fever in the previous 24 hours (history of fever must be documented) and,

b) Microscopically (blood smear) confirmed parasite infection, ranging from 1000 to 100 000 asexual parasites/µL of blood.

I 04. Informed Consent Form signed by the patient (if the patient is ≥ age defining majority) or parent or by the legally acceptable representative of the minor patient (<18 years of age or < other age locally defining majority). In addition, in accordance with local regulation, minor participants with capacity for writing could sign off on an Assent Form. For those who are able to understand but with no capacity for writing the Assent Form would be read. In that case, an impartial witness could certify the document was read to the child.

7.3 EXCLUSION CRITERIA

Patients who have met all the inclusion criteria listed in Section 7.2 will be screened for the following exclusion criteria which are sorted and numbered in the following three sub-sections:

7.3.1 Exclusion criteria related to study methodology

E 01. Presence of severe malaria (according to WHO definition) (see Appendix A).

E 02. Any anti-malarial treatment:

- With piperaquine -based compound, mefloquine, naphthoquine or sulphadoxine/pyrimethamine (SP) within the previous 6 weeks (after their inhibition of new infections has fallen below 50%).
- With amodiaquine or chloroquine within the previous 4 weeks.
- With quinine, halofantrine, lumefantrine-based compounds and any other anti-malarial treatment or antibiotics with antimalarial activity (including cotrimoxazole, tetracyclines, quinolones and fluoroquinolones, and azithromycin) within the past 14 days.
- With any herbal products or traditional medicines, within the past 7 days.

E 03. Known history or evidence of clinically significant disorders such as, respiratory (including active tuberculosis), hepatic, renal, gastrointestinal, immunological, neurological (including auditory), endocrine, infectious, malignancy, psychiatric, history of convulsions or other abnormality (including head trauma).

E 04. Previous treatment within 5 times the half-life or within the last 14 days, whichever the longest which are: P-gp substrates, CYP2D6 main substrates and/or strong CYP2C or CYP3A inhibitors and/or moderate inhibitors but inhibiting both CYP2C and CYP3A and/or CYP inducers (see Appendix B).

E 05. Mixed Plasmodium infection (ie, presence of another Plasmodium species in addition to P. falciparum).

E 06. Severe vomiting, defined as more than three times in the 24 hours prior to enrollment in the study or inability to tolerate oral treatment, or severe diarrhea defined as 3 or more watery stools per day.

E 07. Severe malnutrition (defined for patients aged ten years or less as the weight-for-height being below -3 standard deviation or less than 70% of median of the National Center for

Health Statistics/World Health Organization (NCHS/WHO) normalized reference values, and for patients aged greater than ten years, a body mass index (BMI) of less than 16 (11)

E 08. Laboratory parameters with clinical significant abnormalities and/or reaching critical values. For Liver Function Test: aspartate transferase (AST) >2 ULN, or alanine transferase (ALT) >2 ULN or total bilirubin >1.5 ULN.

E 09. Presence of Hepatitis A IgM (HAV-IgM), Hepatitis B surface antigen (HBsAg) or Hepatitis C antibody (HCV Ab).

E 10. Have received an investigational drug within the past 4 weeks.

E 11. Previous participation in any malaria vaccine study or received malaria vaccine in any other circumstance.

E 12. Measles and yellow fever vaccine injection within the last 15 days or planned for the 28 days after randomization.

E 13. Female patient of child bearing potential not willing to use an effective contraceptive(s) method(s) for the duration of the study (eg, implants, oral contraceptives, some intra-uterine devices or a double barrier method). The need for an efficient method will be reminded to the patient and the patient's legal guardian(s) by the investigator.

E 14. Positive serum or urine beta-human chorionic gonadotropin (ß-HCG) pregnancy test at study screening for female participants of childbearing potential.

E 15. Breastfeeding women.

E 16. Male patient having a partner of child bearing potential not willing to use an effective method of birth control for the duration of the study, or male patient wishing to father a child during study period.

E 17. Splenectomized patients or presence of surgical scar on left hypochondrium.

E 18. Patient unable to drink.

7.3.2 Exclusion criteria related to the current knowledge of Sanofi compound

E 19. Known history of hypersensitivity, allergic or anaphylactoid reactions to ferroquine or other - aminoquinolines or to OZ439 or OZ277 or to any of the excipients.

E 20. Family history of sudden death or of congenital prolongation of the QTc interval or known congenital prolongation of the QTc-interval or any clinical condition known to prolong the QTc interval eg, patients with a history of symptomatic cardiac arrhythmias or with clinically relevant bradycardia.

E 21. QTcF >450 ms at screening or pre-dose.

E 22. Hypokalemia (<3.5 mmol/L), hypocalcemia (<2.0 mmol/L) or hypomagnesemia (<0.5 mmol/L) at screening or pre-dose.

E 23. Any treatment known to induce a lengthening of QT interval (see Appendix C).

7.4 PATIENT POPULATION

7.4.1 Patient sub-populations

7.4.1.1 Higher naturally acquired immunity population

Patients with higher probability of having developed NAI will be recruited (African patients >5 years old to <70 years old). Patients from this population will only be considered for DMC safety review.

- Cohort 1: African Patients >14 years and body weight ≥35 kg (for safety & PK/QTc evaluation only) *:
  - A minimum of 10 patients/arm (30 patients minimum if 3 treatment arms and 42 patients minimum if 4 treatment arms)
- Cohort 2: African Patients of >5 years and ≤14 years old (for safety evaluation only) *:
  - A minimum of 5 patients/arm (15 patients minimum if 3 treatment arms and 20 patients minimum if 4 treatment arms)

** If requested by DMC, additional patients may be included and evaluated for PK/QTc and/or safety.*

7.4.1.2 Lower naturally acquired immunity population

This is the target population of interest. The study aims to recruit predominantly patients with lower probability of having developed NAI defined as:

- children >6 months to ≤5 years in Africa

Only patients from this population will be included in the interim futility analyses and final efficacy analysis.

- Cohort 3: African Patients >2 years and ≤5 years old
- Cohort 4: African Patients >6 months and ≤2 years old:
  - A targeted minimum of 10% of the total number of patients recruited in the lower NAI population ie, approximately 15 patients per treatment arm (if total numbers per arm are 150 for the efficacy analysis).

7.4.2 Age range step-down and FQ dose step-up procedures

Safety (up to Day 28 assessments) in the older age cohort will be assessed before proceeding down to the younger age range (see Section 1.2 and Section 8.4).

Note: For DMC safety review, patients from both higher and lower NAI population will be considered. However, no predefined ratio between Africa and Asia patients are requested to move forward from one cohort of age to the next one. If requested by DMC, additional patients may be included and evaluated for safety.

1. For Cohort 1 (>14 years and <70 years and body weight ≥35 kg), a minimum of 10 patients per treatment arm receiving OZ439/FQ at 800/400 mg, 800/600 mg & 800/900 mg (Cohort 1a, ratio 1:1:1) will be assessed for safety up to Day 28.

   The PK/QTc modeling results will estimate the QT effect of highest FQ plasma concentration before starting the Cohort 1b and may or may not be considered for decision rule. Within the Cohort 1b, the treatment arm OZ439/FQ at 800/1200 mg would be evaluated in a minimum of 10 patients versus 2 patients receiving OZ439/FQ at 800/900 mg (ratio 5:1) to maintain the study blinded. The two highest doses combinations will be assessed for safety up to Day 28 using Cohort 1b data for OZ439/FQ 800/1200 mg and pooled data from Cohorts 1a & 1b for OZ439/FQ 800/900 mg. The PK/QTc modeling results will estimate the QT effect of highest FQ plasma concentration before opening recruitment of the Cohort 2 and may or may not be considered for decision rule.
2. In the Cohort 2 (>5 and ≤14 years), a minimum of 5 patients/arm will be assessed for safety up to Day 28 (ratio 1:1:1 for Scenario A or 1:1:1:1 for Scenario B, see Section 1.2, depending of the safety profile of OZ439/FQ 800/1200 mg) before opening recruitment in the Cohort 3.
3. In the Cohort 3 (>2 and ≤5 year), a minimum of 8 patients/treatment arm will be assessed for safety up to Day 28 before fully opening recruitment.
4. In the Cohort 4 (>6 month to ≤2 year), a minimum of 8 patients/treatment arm will be assessed for safety up to Day 28.

The safety evaluation will be performed by the DMC throughout the study with a frequency defined in the DMC charter.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCTS

The investigational medicinal products (IMPs) will be administered in the following order: FQ then OZ439.

All details regarding the preparation of IMPs, including suspension of FQ and OZ439, will be described in a separate pharmacy manual.

8.1.1 Ferroquine (FQ)

A combination of the following capsules will be used to compose the 4 doses; individual sachets containing sucrose granules are provided:

- 5 mg, 30 mg, 100 mg and 200 mg FQ or matching placebo.
- Placebo capsules are used to keep the same number of capsules in each weight band while keeping the FQ dose blinded. No patient will receive placebo only.
- For young children, capsules will be opened and their content will be diluted in water with sucrose granules in order to make it palatable and given as suspension.
- Oral route.
- Patients should have fasted from food and milk for 3 hours before administration. Neither food nor milk should be taken within 2 hour after the end of IMP dosing.
- Treatment duration: single dose at V2 Day 0.

8.1.2 Artefenomel (OZ439)

Individual sachets containing OZ439 (dose strengths from 150 mg to 800 mg + alpha tocopherol polyethylene glycol 1000 succinate [TPGS]) granules for oral suspension) and individual sachets containing sucrose granules.

- Oral route.
- The sucrose, adjusted to OZ439 dose, is added to the aqueous oral suspension prepared from OZ439 + TPGS granules for oral suspension in order to make it palatable.
- Patients should have fasted from food and milk for 3 hours before administration. Neither food nor milk should be taken within 2 hour after the end of IMP dosing.
- Once prepared, the suspension will have to be drunk within 2 hours and 20 minutes of the start of its preparation.
- The oral suspension should be drunk as quickly as possible and over a maximum of 30-minute period.
- Treatment duration: single dose at V2 Day 0.

8.1.3 Treatment arms

Individual patient treatment kit will be packed according to the weight band. The content of these kits are detailed below:

Table 3 - Treatment kits

Weight band	Compound	Treatment arm 1	Treatment arm 2	Treatment arm 3	Treatment arm 4
≥35 kg	FQ dosage (mg)	400	600	900	1200
	OZ439 dosage (mg)	800	800	800	800
	Sucrose for OZ oral suspension dosage (g)	15	15	15	15
≥24 and <35 kg	FQ dosage (mg)	300	450	675	900
	Sucrose for FQ oral suspension dosage (g)	2.813	2.813	2.813	2.813
	OZ439 dosage (mg)	600	600	600	600
	Sucrose for OZ oral suspension dosage (g)	11,25	11,25	11,25	11,25
≥15 and <24 kg	FQ dosage (mg)	200	300	450	600
	Sucrose for FQ oral suspension dosage (g)	2.813	2.813	2.813	2.813
	OZ439 dosage (mg)	400	400	400	400
	Sucrose for OZ oral suspension dosage (g)	7,5	7,5	7,5	7,5
≥10 and <15 kg	FQ dosage (mg)	150	225	335	450
	Sucrose for FQ oral suspension dosage (g)	2.813	2.813	2.813	2.813
	OZ439 dosage (mg)	300	300	300	300
	Sucrose for OZ oral suspension dosage (g)	5.625	5.625	5.625	5.625
≥7 and <10 kg	FQ dosage (mg)	100	150	225	300
	Sucrose for FQ oral suspension dosage (g)	2.813	2.813	2.813	2.813
	OZ439 dosage (mg)	200	200	200	200
	Sucrose for OZ oral suspension dosage (g)	3,75	3,75	3,75	3,75
≥5 and <7 kg	FQ dosage (mg)	75	115	170	225
	Sucrose for FQ oral suspension dosage (g)	2.813	2.813	2.813	2.813
	OZ439 dosage (mg)	150	150	150	150
	Sucrose for OZ oral suspension dosage (g)	2.813	2.813	2.813	2.813

FQ: ferroquine, OZ439: artefenomel, OZ: artefenomel

The appropriate volume of water needed for the preparation of each specific oral suspension will be mentioned in the Pharmacy Manual.

8.1.4 Re-dosing in the event of vomiting after OZ439 administration

- If a patient vomits within 5 minutes of the start of dosing with OZ439, they can be re-dosed with a freshly prepared new suspension from a new individual patient treatment kit assigned via IVRS/IWRS. No re-dosing of FQ will be performed.
- If vomiting occurs from 5 minutes to 35 minutes post start of OZ439, they should continue to take the OZ439 dose (if any left), but should not be re-dosed.
- If a patient vomits after 35 minutes from the start of OZ439 dosing, they should not be re-dosed.
- No re-dosing of FQ will be performed if a patient vomits 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 8.9.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT

Not applicable.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

For FQ, a double blind design has been set up. Therefore, in each weight band, each patient will receive the same number of capsules, see Section 8.1.1.

Each treatment kit is labeled with a number, which is generated by a computer program from the Sponsor. Investigators do not have access to the randomization (treatment) code except under circumstances described in Section 8.3.2.

- Consequently, the double blinded will be maintained.

  For young children, FQ can be administered as an oral suspension (see Section 8.1). The oral suspension will be prepared by opening the capsules and mixing their content with sweetened water. Depending on the capsules strengths, the color of the content of capsules varies from white to orange. So the oral suspension will be prepared by an unblinded pharmacist. Once ready, there is no difference in color of the oral suspensions within each weight band which can then be administered to the patient by a caregiver (investigator or nurse) maintained blinded
- Study site procedures will be implemented to describe this process and ensure that only well identified and limited personnel will prepare FQ solution.

  OZ439 is under open label design, but it will be included in the FQ treatment kit as described in Section 8.5.

Refer to Section 10.5 for suspected unexpected adverse drug reaction unblinding by the Sponsor.

8.3.2 Randomization code breaking during the study

Please see also Section 8.3.

In case of an adverse event (AE), the code should only be broken in circumstances when knowledge of the IMP is required for treating the patient. If possible, a contact should be initiated with the Monitoring Team before breaking the code.

Code breaking can be performed at any time by using the proper module of the interactive voice response system (IVRS) and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of day and reason for code breaking. As much as possible, patient will continue to be followed up to the End of Study according to study flow-chart (see Table 1).

The DMC will receive blinded by treatment group or unblinded (if necessary) confidential reports from an independent statistician for review, which have to be handled strictly confidentially. None of these reports can be delivered to unauthorized persons.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Centralized randomization and IVRS/IWRS related procedures will be detailed separately (IVRS/IWRS specifications manual).

- A total of 6 randomized treatment kit number lists will be generated centrally by Sanofi corresponding to the weight bands [> 35 kg, 24-35 kg, 15-24 kg, 10-15 kg, 7-10 kg and 5-7 kg].
- Patients will be randomized to one of the treatment arms via a centralized randomization system using an IVRS/IWRS. A patient will be considered randomized when the treatment number has been provided by the IVRS/IWRS, as documented from the IVRS/IWRS log file.
- At the screening visit, Visit 1, the site will contact the IVRS/IWRS to obtain a patient number for each patient for whom an informed consent has been obtained. Each patient will be allocated a patient number associated with the center and allocated in chronological order in each center.

  IVRS will manage 3 patient randomization lists (one for Cohort 1a, a second for Cohort 1b and the third including all 4 cohorts) and allocates the treatment number and the corresponding treatment kit to the patient as follow:

  - In Cohort 1a 30 patients will be randomized to one of the 3 treatment arms of OZ439/FQ. The randomization ratio is 1:1:1 (OZ439/FQ 800/400 mg: OZ439/FQ 800/600 mg: OZ439/FQ 800/900 mg).
  - In Cohort 1b, if DMC has given the green light for proceeding with the 1200 mg dose of FQ, 12 patients will be randomized to one of the 2 treatment arms of OZ439/FQ. The randomization ratio is 1:5 (OZ439/FQ 800/900 mg: OZ439/FQ 800/1200 mg).
  - After Cohorts 1a & 1b DMC review

- if DMC has given the green light for proceeding with the 1200 mg dose of FQ in younger patients according to the age step-down procedure, 155 patients (150 patients for the lower NAI population + 5 patients of Cohort 2 for the higher NAI population) will be randomized to one of the 4 treatment arms of OZ439/FQ according to the randomization ratio of 1:1:1:1 (treatment arm 1, treatment arm 2, treatment arm 3, treatment arm 4).
- if DMC does not give the green light for proceeding with the 1200 mg dose of FQ in younger patients according to the age step-down procedure, 155 patients (150 patients for the lower NAI population + 5 patients of Cohort 2 for the higher NAI population) will be randomized to one of the 3 treatment arms of OZ439/FQ according to the randomization ratio of 1:1:1 (treatment arm 1, treatment arm 2, treatment arm 3).

- The third randomization list will be stratified by region, and within Africa, age class (>14 years and <70 years/Asia; 5-14 years/Africa; 2-5 years/Africa; and 6 months-2 years/Africa). Details will be specified in the IVRS/IWRS specifications manual.
- A patient can be randomized only once.

8.5 PACKAGING AND LABELING

The randomized labelled treatment box will contain:

- 1 randomized blinded labelled wallet with 6 or 8 capsules of FQ (5, 30, 100 or/and 200 mg or placebo) depending on the treatment arm and the weight band,
- An open label individual sachet containing sucrose granules for FQ oral suspension only in kits of weight band <35 kg,
- An open label individual sachet containing OZ439 + TPGS granules for oral suspension (150, 200, 300, 400, 600 or 800 mg) depending on the treatment arm and the weight band,
- An open label individual sachet containing sucrose granule for OZ439 oral suspension.

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of IMP storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMPs will be dispensed in accordance with the Investigator's prescription and it is the Investigator’s responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

Measures taken to ensure and document treatment compliance and IMP accountability include:

- Proper recording of treatment kit number or packaging number as required on appropriate electronic case report form (e-CRF) page for accounting purposes.
- The unblinded pharmacist or designee will prepare the kit assigned by IVRS/IWRS, will complete the corresponding treatment log form, and will perform reconciliation by checking the consistency of the treatment number between IVRS/IWRS assignment notification, the treatment number printed on the kit boxes and the treatment log forms.
- IMP will also be recorded and tracked on the site IMP inventory forms.
- The monitor in charge of the study checks the data entered on the e-CRF by comparing them with the IMP that has been retrieved and the treatment log form.

8.7.2 Return and/or destruction of treatments

All partially-used or unused treatment boxes will be destroyed at study site or returned to the Sponsor for destruction according to local regulations.

A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy the unused IMP unless the Sponsor provides written authorization.

8.8 CONCOMITANT MEDICATION

8.8.1 LIST OF FORBIDDEN CONCOMITANT MEDICATION

All drugs other than oral contraceptives, paracetamol (acetaminophen) at the maximum dose of 40 mg/kg/day, metoclopramide if repeated vomiting and beta-lactams for any infection needing an antibiotic treatment are prohibited over the entire study period unless medically justified. The dosage and number of dose(s) will be recorded. The use of other contraceptive methods may be discussed.

Traditional and herbal remedies are not permitted during the study.

8.9 RESCUE TREATMENT FOR MALARIA

The use of a rescue therapy is recommended in the following cases:

- Vomiting during or after FQ dosing or vomiting within 35 minutes after OZ439 re-dosing
- Treatment failure as-per protocol section “Classification of Treatment Outcomes”

The use of established anti-malarial drug combination per WHO recommendations (1) or local guidelines is to be considered as a rescue therapy and the choice of the best therapeutic option is left at Investigator’s decision.

In case of rescue therapy is given, where possible, a PK (OZ439 and FQ) sample should be taken before giving rescue therapy.

Before giving established ACT:

- Blood films and parasite genotyping must be taken for all patients.
- RT-PCR and qPCR for patients >5 years only.

Following administration of established ACT, patients should be managed according to local standard of care practices. Safety data should continue to be collected in the e-CRF, according to the study schedule, and up to the end of the study even if re-emergence is confirmed.

Patients who will have received a rescue treatment after the OZ439/FQ has failed will be part of the Per-Protocol Population (see Section 11.3.2.2) whereas patients who will have received a rescue treatment because of vomiting during IMP administration will be part of the safety analyses only.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

9.1.1 Primary efficacy endpoint

- PCR-adjusted ACPR at Day 28.
  - The ACPR is defined as a negative parasitemia (blood films) at Day 28, irrespective of axillary temperature, without previously meeting any criteria of early treatment failure (ETF) or late clinical failure (LCF) or late parasitological failure (LPF) or having received a rescue treatment for malaria in the conditions defined in Section 8.9.
  - The PCR-adjusted ACPR applies only to recrudescence (re-emergence of the original clone of parasite that is present at baseline). Recrudescence is distinguished from re-infection by genotyping the parasite clone.

9.2 SECONDARY ENDPOINTS

9.2.1 Secondary efficacy endpoints

- PCR - adjusted ACPR at Day 42 and 63.
- PCR - crude ACPR at Day 28, 42 and 63.
- Kaplan Meier for:
  - Time to re-emergence
  - Time to recrudescence
  - Time to re-infection
- Parasite clearance time (PCT).
- Fever clearance time (FCT).
- Parasite reduction rate (PRR): the PRR is calculated as the slope of the linear portion of the regression fit of logarithm parasitemia (per mL) versus time (in hours).

9.2.2 Safety endpoints

- Adverse events, including Serious Adverse Events (SAE), Adverse Event of Special Interest (AESI) and Treatment Emergent Adverse Event (TEAE).
- Clinical laboratory tests, vital signs and ECG, including:
  - Liver Function test (LFT)
  - QTc assessment

- Physical examination and clinical signs and symptoms related to uncomplicated *P. falciparum* 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).

9.2.2.1 Adverse events

Refer to Section 10.4 to Section 10.6 for details.

9.2.2.2 Laboratory safety variables

(see Study Flow-Chart in Section 1.1 for detailed time schedule)

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

Clinical laboratory at screening:

- Hematology: performed in local laboratory.
- Clinical chemistry: performed in local laboratory for screening purpose and an additional sample to be sent to central laboratory for baseline assessment.
- Urinary dipstick: performed locally; if abnormal: urine sample to be sent to central laboratory for microscopy analysis.

Clinical laboratory at all other visits:

- Hematology: performed in local laboratory.
- Clinical chemistry: sample to be sent to central laboratory.
- Urinary dipstick: performed locally; if abnormal: urine sample to be sent to central laboratory for microscopy analysis.

Details will be provided in Laboratory Manual.

Table 4 - Clinical laboratory blood tests

Clinical Chemistry
Total bilirubin (also Direct, when total bilirubin is ≥ULN)
Albumin
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Haptoglobin
Lactate Dehydrogenase (LDH)
Creatine kinase
Alkaline phosphatase (ALP)
Urea
Creatinine and creatinine clearance[a]
Sodium
Potassium
Magnesium (screening)
Calcium (screening)
Glucose
Hematology
Haematocrit
Haemoglobin
Absolute reticulocytes
Erythrocyte count (RBC)
Platelet count
Leukocytes (WBC) with differential count including eosinophils
Urinalysis Dipstick
Specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes and blood
Pregnancy test (urine β-HCG) for females of childbearing potential
Urinalysis Microscopy (if urinalysis dipstick abnormal)
WBC, RBC and casts (if required)

a For patients >18 years old, the creatinine clearance (CrCl) will be calculated from Cockroft and Gault formula: CrCl (mL/min) = 1.23 (for male) or 1.04 (for female) x weight (kg) x (140 - Age) / serum creatinine (µmol/L) with age in years. For patients ≤18 years old, the GFR Bedside Schwartz Formula should be used: eGFR (mL/min/1.73 m²) = 0.413 x height (cm) / serum creatinine (mg/dL)

9.2.2.3 Vital signs

(see Study Flow-Chart in Section 1.1 for detailed time schedule)

Vital signs include:

- Heart rate (HR) and systolic & diastolic blood pressure (BP) measured after at least 5 minutes in supine resting position and prior to any blood sampling.
- Axillary temperature should be recorded in °C and to an accuracy of one decimal place. If the axillary method is not possible, an alternative route (tympanic, oral or rectal) may be used. The alternative route shall be recorded in the e-CRF. Within an individual patient the same method of temperature measurement (axillary, tympanic, oral or rectal) should be used throughout the entire study period.

All vital signs will be assessed according to local procedures.

9.2.2.4 Electrocardiogram variables

(see Study Flow-Chart in Section 1.1 for detailed time schedule).

Heart rate, QRS duration, PR interval, QT interval, ST deviation and T-wave morphology and also U-wave presence or absence are determined using centralized readings of all ECGs. The screening visit ECG will be read by the Investigator and the automatic QTcF calculation will serve as the reference for exclusion criterion E21. All ECG recordings (triplicate) will be centrally read by independent experts. Refer to central ECG reading manual for more details.

9.2.2.5 Physical examination and malaria signs and symptoms

The Physical Examination will include: general appearance, head and eyes, ears, nose and throat, chest and lungs, cardiovascular, abdomen, neurological, lymphatic and musculoskeletal and any additional body system considered of relevance by the Investigator.

A full assessment of malaria signs and symptoms will be made alongside the physical examination.

9.3 MEASUREMENT OF PARASITEMIA

9.3.1 Parasitemia (Thick and thin blood films)

Blood sampling for parasitology can be done usually by means of finger prick except when the timing for parasitology assessments coincide with time for clinical laboratory tests, in which case, blood films can be done using the venous blood collected for clinical laboratory analyses. Blood spot samples will also be prepared for qPCR, genotyping and Kelch-13 analysis and for RT-PCR gametocyte detection (see Section 9.3.2 and Section 9.3.3).

For full details of slide preparation, determination of parasitemia and quality control, refer to the Study Laboratory Procedures Manual.

9.3.1.1 Screening and pre-dose blood films

For parasitology, Screening and pre-dose are to be considered as one time point. Three slides (two thick films and one thin film) should be prepared in this period for this time point and should be prepared using samples taken within 4 hours of dosing. 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 for screening / Pre-dose parasitemia assessment, provided that a standard procedure is in place at site and blood films staining is performed according to Study Parasitology Procedures Manual.

The first thick film slide must be rapidly stained with 10% Giemsa stain for a period of 10 to 15 minutes. The parasite count from this slide will be used to calculate the Screening parasitemia value.

The second thick film slide must be used only if the patient meets all entry criteria and is being recruited into the study. This second thick film slide should be stained with 2.5 to 3% Giemsa stain for a period of 45 to 60 minutes. The slide from this slower but more accurate staining technique should be used to calculate a more accurate pre-dose parasitemia counts (asexual).

The thin film slide is used specifically for parasite speciation. Only patients with *P. falciparum* mono-infection should be recruited in the study.

9.3.1.2 Post-dose blood films

Three slides (two thick films and one thin film) should be prepared at each planned time point (see Study Flow-Chart in Section 1.1 for detailed time schedule). The first thick film slide should be stained with 2.5 to 3% Giemsa stain for a period of 45 to 60 minutes and used to determine parasite counts. The second thick film slide should be kept as contingency and be stained only if the first thick film slide become damaged prior to reading it. The thin film slide is used specifically for parasite speciation which should be recorded at each time point.

Additional unscheduled films may be prepared to confirm Parasite clearance as described below.

Details of slide preparation, staining, examination, calculation methods and quality control are given in the Study Laboratory Procedures Manual. No deviation from the Sponsor guidelines will be accepted.

9.3.1.3 Definition of parasite clearance (by microscopy)

A blood film will be considered 'negative' when the examination of 1000 white blood cells reveals no asexual parasites (see Study Laboratory Procedures Manual for more detail). Parasite clearance time is defined as the time of the first negative film. This negative film must be confirmed by a second negative film, prepared within 6 to 12 hours of the first. Parasite clearance will be concluded following confirmation of the second negative film. Parasite density, expressed as the number of parasites per microliter of blood, for asexual parasite and for gametocyte counts will be recorded separately throughout the study.

If parasites have not cleared by 72 hours after IMP administration and criteria for rescue medication are not met at 72 h, 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 8.9).

Two qualified microscopists should independently read the stained thick and thin films. Parasite densities will be calculated by averaging the two counts. Blood smears with non-concordant results (differences between the two microscopists in species diagnosis, or differences in parasite density of >50%) will be re-examined by a third, independent microscopist: if discordance relates to parasite density, it will be calculated by averaging the two most concordant counts; if discordance relates to species diagnosis, it will be determined by the third microscopist.

9.3.2 Quantitative PCR, parasite genotyping and Kelch-13 analysis

Blood samples to measure parasitemia by qPCR will be taken according to study flow-chart (see Table 1 in Section 1.1), in patients >5 years only, qPCR analysis will be performed by the central laboratory at all scheduled time points.

For patients >14 years and ≥35 kg only, during the intervening periods between Day 15 and Day 18 (ie, V10) and Day 24 and Day 25 (ie, V12), blood for qPCR will be only taken if the patient returns to the Clinical Unit for assessment (no qPCR sample when the patient has a rapid diagnosis test (RDT) “in the field”)

Blood samplings for genotyping will be collected according to the study flowchart (see Table 1 in Section 1.1) and at the time-points when recrudescence or re-infection after initial parasite clearance was shown on the blood slide. 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.

An analysis of the Kelch-13 genotype will be performed at screening on blood samples (pre-dose).

All details concerning processing and technique will be provided separately in the Study Laboratory Procedures Manual.

9.3.3 Gametocyte detection (RT-PCR)

Blood samples for RT-PCR gametocyte detection will be taken according to Study Flow-Chart (see Table 1 in Section 1.1) in patients >5 years only. RT-PCR analysis will be performed by the central laboratory at all scheduled time points to detect submicroscopic gametocytemia and characterize gametocyte maturation stage.

For patients >14 years and ≥35 kg only, during the intervening periods between Day 15 and 18 (ie, V10) and Day 24 and 25 (ie, V12), blood for RT-PCR gametocyte detection will only be taken if the patient returns to the Investigational site for assessment (no RT-PCR sample when the patient has a RDT “in the field”).

All details concerning processing and technique will be provided in the Study Laboratory Procedures Manual.

9.4 OTHER ENDPOINTS

9.4.1 Pharmacokinetics

Plasma levels of OZ439 and blood level of FQ and its metabolite SSR97213 will be measured.

To evaluate blood/plasma ratio for FQ and SSR97213, plasma level of FQ and SSR97213 will be measured at limited time points in selected sites. About 20 to 25 patients per cohort will have this measurement, excluding children ≤2 years for whom no plasma sample will be collected for FQ.

In Cohort 1a and Cohort 1b, FQ PK samples collected during the first 48h should match with ECG time points (except for T0.5h [no ECG at that time point]) for the purpose of the PK/QTc analyses performed at the end of these cohorts.

9.4.1.1 Sampling time

The sampling times for blood collection can be found in the study flow chart (see Table 1 in Section 1.1).

9.4.1.2 Number of pharmacokinetic samples

Table 5 - Number of PK samples

	Blood sample for FQ and OZ439	Total sample volume
Patient >14 years and body weight ≥35 kg	16 x 1 mL	16 mL
Patient >5 to ≤14 years	7 x 1 mL	7 mL
Patient >2 to ≤5 years	5 or 6 x 1 mL	5 or 6 mL
Patient >6 months to ≤2 years	5 x 0.5 mL	2.5 mL

PK: pharmacokinetics, FQ: ferroquine, OZ439: artefenomel

9.4.1.3 Pharmacokinetics handling procedure

The sample handling procedures are summarized in a table (Table 6 and Table 7).

Special procedures for collection, storage, and shipment will be provided in a separate Laboratory Manual.

Table 6 - Summary of handling procedures for FQ and its active metabolite SSR97213 assessment in blood and in plasma

Anticoagulant	K3-EDTA
Handling procedures	Refer to Laboratory Manual
Blood aliquot split	5 spots of 10 µL per card for DBS 3 spots of 20 µL per card for DPS
Blood storage conditions	Room temperature into a Ziploc bag* with desiccant
Blood shipment conditions	Room temperature

FQ: ferroquine, DBS: dry blood sample, DPS: dry plasma sample
*: the Amber Ziploc bag should be used for DPS (about 20 patients per cohort in selected sites)

Table 7 - Summary of handling procedures for OZ439 assessment

Anticoagulant	Potassium K3-EDTA
Handling procedures	Refer to Laboratory Manual
Plasma aliquot split	No (1 aliquot)
Plasma storage conditions	-20°C
Plasma shipment conditions	Dry ice

OZ439: artefenomel

9.4.1.4 Bioanalytical method

Table 8 - Summary of bioanalytical method for FQ and its active metabolite SSR97213

Analyte	Ferroquine and SSR97213
Matrix	Blood (DBS) and plasma (DPS)*
Analytical technique	LC-MS/MS
Lower limit of quantification	5 ng/mL
Assay volume	A punch of whole spot for DBS samples and a punch of 6 mm diameter for DPS samples
Site of bioanalysis	Covance
Method reference	Refer to Laboratory Manual

FQ: ferroquine, DBS: dry blood sample, DPS: dry plasma sample, LC-MS/MS: Liquid chromatography coupled to tandem mass spectrometry
*: A plasma sample will be prepared after blood collection by venipuncture for DPS (about 20 patients per cohort in selected sites).

Table 9 - Summary of bioanalytical method for OZ439

Analyte	OZ439
Matrix	Plasma
Analytical technique	LC-MS/MS
Lower limit of quantification	1 ng/mL
Assay volume	50 µL
Site of bioanalysis	Swissbioquant, Reinach (BL), Switzerland
Method reference	Refer to Laboratory Manual

OZ439: artefenomel, LC-MS/MS: Liquid chromatography coupled to tandem mass spectrometry

Incurred sample reproducibility analysis will be performed on selected samples in order to assess the reliability of all sample concentration data. These analyses will be reported in addition to the final concentration data.

9.4.1.5 Pharmacokinetics parameters

A pharmacokinetic analysis for OZ439 in plasma, FQ and SSR97213 in blood will be performed using nonlinear mixed effect modelling in separate models for OZ439 and for FQ and SSR97213. Data from previously conducted studies might be added for model development. The analysis will involve an estimation of inter-patient PK variability, the population pharmacokinetic parameters estimates and the assessments of patho-physiologic covariate effects on CL and possibly on volume if warranted. Estimation of individual parameters and of individual exposure (AUC) will also be performed. The pharmacokinetic analysis will be described more precisely in the pharmacokinetic analysis plan.

PK parameters:

- PK parameters (mainly CL/F, V_{ss}/F, C_{max}, AUC as relevant) of OZ439 in plasma, FQ and SSR97213 in blood, in addition, Concentration at Day 7, Day 14, Day 21 and Day 28 for FQ and SSR97213.
- Blood/plasma ratio for FQ and SSR97213 (some patients in selected sites).
- Interim analysis:

  In Cohort 1a and Cohort 1b, a pharmacokinetic analysis for FQ and SSR97213 in blood will be performed using linear mixed effect modelling to predict 1200 mg (Treatment arm 4) C_{max} and AUC in patient >14 y (after the Cohort 1a) and to predict C_{max} and AUC for Treatment #4 over the weight continuum (after the Cohort 1b). C_{max} and AUC at 400 mg, 600 mg and 900 mg as secondly predicted parameters will be estimated. This PK analysis will be performed by a Sponsor's unblinded pharmacokineticist independent from the study.

9.4.2 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 patients >5 years.
- Correlation between Kelch-13 genotype status at baseline and parasite clearance kinetics.
- Define phenotypic and genotypic resistance pattern to conventional ACT of *P. falciparum* infecting patients aged >14 years old in Vietnamese sites (blood sample taken at screening).
- In vitro susceptibility testing of *P. falciparum* infecting patients aged >14 years old in Vietnamese sites to OZ439, FQ and both drugs (blood sample taken in case criteria for rescue treatment is met).

9.4.3 Pharmacogenetic assessment

Not applicable.

9.5 FUTURE USE OF SAMPLES

Residual or leftover serum, plasma or blood samples may be used for additional research purposes on malaria, after the patient will have consented to it.

9.6 APPROPRIATENESS OF MEASUREMENTS

The assessments used in this study follow the recommendations from the WHO.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

10.1.1 Visit 1; Day-1: Screening / Predose Visit

- Informed consent/Assent.
- Demography/Previous medical/surgical history/prior and concomitant medication.
- Inclusion/exclusion criteria.
- Temperature.
- Physical examination, height and body weight measurement, malaria signs & symptoms.
- IVRS/IWRS call for screening.
- Asexual and sexual count (thick & thin blood films) and parasite genotyping for all patients.

  Note: 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 for screening / Pre-dose parasitemia assessment, provided that a standard procedure is in place at site and blood films staining is performed according to Study Parasitology Procedures Manual.
- RT-PCR and qPCR for patients >5 years only.
- Kelch-13 analysis sampling (blood spot).
- In Vietnamese sites and for patients >14 years old only: sample for in vitro research of drug resistance.
- A standard 12-lead ECG.
- Vital signs including BP, HR.
- Inquire about AEs.
- Standardized laboratory exam: local hematology, local biochemistry (including LFTs). For biochemistry, a second sample will be drawn and sent to the central laboratory allowing pre-treatment baseline measurement.
- Urinalysis dipstick: specific gravity, pH, glucose, hemoglobin, protein, nitrates, leukocyte esterase, bilirubin. If any parameter on the dipstick is abnormal, an urine sample should be sent to the central laboratory for microscopic analysis.
- HAV IgM, HBs Ag, and HCV Ab.
- Urine pregnancy test (for women of childbearing potential). If negative, discussion as to the most appropriate contraceptive method for the duration of the study.

10.1.2 Visit 2; Day 0 (may be on the same calendar day than Day-1)

- Hospitalization.
- IVRS/IWRS call for randomization and IMP kit allocation at T0.
- Standard 12-lead ECG at T0 (before IMP administration), T2, T4, T6, T8 and T12.
- IMP administration at T0.
- Temperature at T1, T2, T6, T12 and T18.
- Physical examination/malaria signs & symptoms at T12.
- Inquire about AEs at all time-points.
- Report concomitant medication at T0.
- Asexual and sexual count (thick & thin blood films).
  - at T6, T12 and T18, if >14 years and ≥35 kg,
  - at T6 and T18, if ≤14 years.
- qPCR and RT-PCR gametocyte detection at T6, T12 and T18 for patients >14 years and ≥35 kg only.
- Parasite genotyping (blood spot) at T6, T12, T18 for patients >14 years and >35 kg.
- Parasite genotyping (blood spot) at T18 for patients ≤ 14 years.
- Vital signs including BP and HR at T6 and T12.
- OZ439 PK sampling (see Table 1).
- FQ/SSR97213 PK sampling (see Table 1).

10.1.3 Visit 3; Day 1

- Temperature at T24, T30 and T36.
- Physical examination/malaria signs & symptoms at T24 and T36.
- Inquire about AEs at all time-points.
- Report concomitant medication at T24.
- Asexual and sexual count (thick & thin blood films), parasite genotyping (blood spot).
  - at T24, T30, and T36 if >14 years and ≥35 kg,
  - at T24 and T36 only if ≤14 years.
- qPCR and RT-PCR gametocyte detection at T24, T30 and T36 for patients >14 years and ≥35 kg only.
- In Vietnamese sites and for patients >14 years old only and only in case criteria for the use of rescue therapy is met: sample for in vitro research of drug resistance.
- A standard 12-lead ECG.
- Vital signs including BP and HR at T24.
- OZ439 PK sampling (see Table 1).
- FQ/SSR97213 PK sampling (see Table 1).

10.1.4 Visit 4; Day 2

- Temperature at T48.
- Physical examination/malaria signs & symptoms at T48.
- Inquire about AEs and report concomitant medication.
- Asexual and sexual count (thick & thin blood films) and parasite genotyping (blood spot) for all patients.
- At T48, qPCR and RT-PCR gametocyte detection for patients >14 years and ≥35 kg only.
- In Vietnamese sites and for patients >14 years old only and only in case criteria for the use of rescue therapy is met: sample for in vitro research of drug resistance.
- Parasite genotyping sampling at first recurrence of parasitemia after first initial parasite clearance.
- If discharge:
  - Standard 12-lead ECG at T48,
  - Vital signs including BP and HR at T48,
  - Weight,
  - Clinical laboratory safety:
    - Local hematology,
    - Central lab biochemistry (including LFTs),
    - Urinalysis dipstick: specific gravity, pH, glucose, hemoglobin, protein, nitrates, leukocyte esterase, bilirubin. If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for microscopic analysis.
- If African patient from Cohort 1:
  - Standard 12-lead ECG at T48.
- OZ439 PK sampling (see Table 1).
- FQ/SSR97213 PK sampling (see Table 1).
- Discharge from hospital (from T48 to T72).

10.1.5 Visit 5; Day 3

- Temperature at T72.
- Physical examination/malaria signs & symptoms at T72.
- Inquire about AEs and concomitant medication.
- Asexual and sexual count (thick & thin blood films), parasite genotyping (blood spot) for all patients.
- At T72, qPCR , RT-PCR gametocyte detection (for patients >5 years).

- In Vietnamese sites and for patients >14 years old only and only in case criteria for the use of rescue therapy is met : sample for in vitro research of drug resistance.
- Parasite genotyping sampling at first recurrence of parasitemia after first initial parasite clearance.
- If discharge at D3 or if the patient is still hospitalized at Day 3, discharge procedures should be performed at Day 3:
  - Standard 12-lead ECG at T72,
  - Vital signs including BP and HR at T72,
  - Weight,
  - Clinical laboratory safety,
  - Local hematology,
  - Central lab biochemistry (including LFTs),
- Urinalysis dipstick: specific gravity, pH, glucose, hemoglobin, protein, nitrates, leukocyte esterase, bilirubin. If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for microscopic analysis.
- OZ439 PK sampling (see Table 1).

10.1.6 Follow-up: V6 to V15 at Day 5, 7, 10, 14, 15-18, 21+/-2, 24-25, 28+/-2, 42+/-3 and 63+/-3

- Temperature at each visit.
- Physical examination/malaria signs & symptoms at V7-D7, V13-D28, V14-D42 and V15-D63.
- Inquire about AEs and concomitant medication at each visit.
- Asexual and sexual count (thick & thin blood films) and parasite genotyping (blood spot) sampling at each visit for all patients.
- qPCR and RT-PCR gametocyte detection:
  - at each visit for patients >14 years and ≥35 kg,
  - at V7-D7, V13-D28, V14-D42 & V15-D63 for patients >5 years and ≤14 years.
- If visits V10 (D15-18) and V12 (D24-25) are performed "in the field" a RDT will be performed. During those visits, patients feeling unwell, with increased temperature (axillary temperature ≥37.5 °C) and/or a positive RDT should return to the Investigational site for assessment including blood films and parasite genotyping. In addition, if patients belong to Cohort 1 (>14 years and ≥35kg), qPCR and RT-PCR will be taken.

- In Vietnamese sites and for patients >14 years old only and only in case criteria for the use of rescue therapy is met: sample for in vitro research of drug resistance.
- Parasite genotyping sampling at first recurrence of parasitemia after first initial parasite clearance.
- Standard 12-lead ECG at V7-D7.
- Vital signs including BP and HR at each visit from V7-D7 to V15-D63 (except V10 and V12).
- Weight at V15-D63 only.
- Clinical laboratory safety: at V7-D7, V9-D14, V11-D21 and V13-D28 for patients >5 years (Cohorts 1 & 2).
- Clinical laboratory safety: at V7-D7, V9-D14 and V13-D28 for patients ≤5 years (Cohorts 3&4).
- Pregnancy test (for women of childbearing potential) at V13-D28 and V15-D63.
- IVRS/IWRS call for end of study (EOS).
- OZ439 PK sampling (see Table 1.
- FQ/SSR97213 PK sampling (see Table 1).
- PK samples for measuring FQ and SSR97213 concentrations at Post D7 first recurrence of parasitemia.

10.2 DEFINITION OF SOURCE DATA

The results of certain examinations or evaluations recorded in the e-CRF may be considered source data:

- Patient's medical record,
- Local laboratory results including blood smear results.

10.3 HANDLING OF PATIENT STUDY DISCONTINUATION

Due to the mode of administration of IMP (FQ [capsules or suspension] followed by OZ439 suspension) and the dose regimen (single dose), the following may not apply (see Section 8.1 for IMP administration).

10.3.1 Temporary treatment discontinuation with investigational medicinal products

Temporary treatment discontinuation after incomplete treatment (suspension ingestion) may be considered by the Investigator because of suspected AEs. Re-initiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely.

10.3.2 Permanent treatment discontinuation with investigational medicinal products

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time after incomplete treatment (suspension ingestion).

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason:

If possible, the patients are assessed using the procedure normally planned for the end-of-study visit including a pharmacokinetics sample.

For patients who fail to return to the site, the Investigator should make the best effort to recontact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status at the planned D63 date. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter). The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or

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

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
- Allergic bronchospasm
- Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
- Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the Investigators in oncology studies)
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

10.4.1.3 Adverse event of special interest

Adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment.

- Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2).
- Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or non-serious) with IMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.

    Of note, asymptomatic overdose has to be reported as a standard AE.

10.4.1.4 Project specific AESIs

Owing to safety findings for FQ and OZ439 on ECG and hepatic parameters, an appropriate ECG and hepatic monitoring is proposed (see study flowchart, Table 1).

- Increase in alanine transaminase (ALT): ALT ≥3 ULN (if baseline ALT <ULN) or, ALT ≥2 times the baseline value (if baseline ALT ≥ULN) will be reported as AESI.

  Cases of ALT >3 ULN will be monitored according to the procedures indicated in Appendix D.

  Patients with abnormal ALT values at D63 will be followed-up until ALT returns to normal values. A PK sample will be made at time of event for OZ439 and FQ (& SSR97213) concentration measurement.

  An ALT increase >3ULN is reportable as an SAE in any of the following situation:

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

- QTcF ≥500 ms or QTcF prolongation >60 ms from baseline

  In the event of QTcF interval ≥500 ms (automatic measurement) or a QTcF prolongation >60 ms (automatic measurement) from baseline, the patient should be placed under supervision in a specialized setting.

  Subsequent ECG monitoring of the patient should then be performed on a regular and clinically responsible basis until the QTc interval returns to their baseline QTcF value.

  In case of QTcF ≥500 ms (automatic measurement) or QTcF prolongation >60 ms from baseline, patient will have blood drawn for measurement of OZ439 and FQ (& SSR97213) concentration.

  The Investigator will report an AESI only if QTcF ≥500 ms or QTcF prolongation >60 ms from baseline is confirmed by central reading.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the e-CRF.

  Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s). The causal relationship will be assessed either to FQ or OZ439 which are considered as distinct entities.
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

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.

10.4.4 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF. Instructions for AE reporting are summarized in Table 10.

10.4.5 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix D.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia
- Thrombocytopenia
- Increase in ALT
- Acute renal failure
- Suspicion of rhabdomyolysis

NOTE: Increase in ALT is considered as AESI (see Section 10.4.1.4)

Table 10 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Pregnancy	Yes	Yes	Yes
		Symptomatic overdose	Yes	Yes	No
		ALT≥3 ULN (if baseline ALT<ULN) and ALT≥2 x baseline (if baseline ALT ≥ULN)	Yes	Yes	Yes
		QTcF ≥500 ms or ΔQTcF >60 ms from baseline	Yes	Yes	No

SAE: Serious AE, AESI: AE of special interest, ALT: alanine transferase, ULN: upper limit of normal, QTcF: QT interval corrected with Fridericia method, ms: millisecond

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (Suspected unexpected serious adverse reaction [SUSAR]), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

In case of a SUSAR, Sanofi Global Pharmacovigilance and Epidemiology will utilize XGRID to reveal medication assignment for regulatory reporting requirements for the particular case.

The Sponsor will report in the clinical study report all safety observations made during the conduct of the trial.

10.6 SAFETY INSTRUCTIONS

10.6.1 Development of complicated malaria

The development of symptoms suggestive of severe (also defined as complicated) malaria will be investigated throughout the study. Severe malaria is considered in case of clinical features and/or laboratory and other findings as defined in Appendix A.

Any symptom suggestive of severe malaria will be considered life-threatening and reported as unexpected SAE.

The patient will be treated according the local recommendations for severe malaria.

10.6.2 PK sampling in case of QTcF >=500 ms or QTcF prolongation >60 ms and/or ALT >=3xULN

Patients having experienced a QTcF ≥500 ms or QTcF prolongation >60 ms from baseline and/or with ALT ≥3 ULN will be measured for circulating levels for OZ439, FQ and SSR97213 immediately after a QTcF ≥500 ms and/or ALT ≥3xULN is reported to the investigator.

11 STATISTICAL CONSIDERATIONS

The material of Section 11 of the Clinical Trial Protocol is the basis for the Statistical Analysis Plan for the study. This plan may be revised during the study to accommodate Clinical Trial Protocol amendments and to make changes to adapt to unexpected issues in study execution and data that affect planned analyses. These revisions will be based on blinded review of the study and data, and a final plan will be issued at the latest 6 to 8 weeks before final database lock.

11.1 DETERMINATION OF SAMPLE SIZE

This protocol is adaptive allowing futility at pre-specified interim points during the conduct of the study. At each interim time point, tests for futility will be performed. Recruitment will cease to a particular treatment arm if the pre-specified criterion for futility is reached. Interim assessment of futility will occur after recruitment of approximately 50 evaluable patients per treatment arm for the 1st futility analysis and every 25 evaluable patients per treatment arm thereafter for the 3 other interim analyses (including 75, 100 and 125 evaluable patients per treatment arm, respectively). Recruitment continues until each treatment arm is deemed to be futile or until 150 evaluable patients per treatment arm for the final analysis is reached. In case of high recruitment rate (ie, fast recruitment), not all the futility analyses may be performed.

Given the adaptive nature of the study design, the total number of patients to be recruited can only be estimated. Simulations for different PCR-adjusted ACPR responses at Day 28 showed that a sample size of 150 evaluable patients per treatment arm will provide ≥80% probability to reject the null hypothesis (H0: probability of PCR-adjusted ACPR at Day 28 ≤0.90) at the final analysis, for the true rate of 96.4%. Recruitment will therefore continue until each treatment arm is deemed to be futile or until 150 evaluable patients per treatment arm is reached.

In addition, a minimum of 15 African patients older than 5 years per treatment arm (likely to have higher NAI and therefore not included in the efficacy analyses) will be included for the DMC safety review.

Lower numbers of patients per treatment arm may be recruited in the event of a poorly efficacious dose or doses (ie, futility).

Thus the targeted number of African patients recruited to this study will be approximately 495 (in case of 3 treatment arms, scenario A, approximately 165 patients/arm) or approximately 662 (in case of 4 treatment arms, scenario B, approximately 165 patients/arm).

11.2 DISPOSITION OF PATIENTS

Screened patients (counts and percentages) defined as any patient who signed the informed consent and met the inclusion criteria, screen failures and reason of screened failures will be provided for all patients and separately for each cohort.

Randomized patients consist of all patients with a treatment kit number allocated and recorded in IVRS/IWRS database at visit 2 (Day 0), and regardless of whether the treatment kit was used or not.

Patients treated without being randomized by IVRS 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.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

In addition, a summary table (count and percentage) will be provided on the randomized population by treatment arm, country and center. Same summary will be provided also for each cohort (one table per cohort).

Percentages will be calculated using the number of patients randomized as the denominator.

11.3 ANALYSIS POPULATIONS

The analysis populations described below will be summarized by treatment group in a table given numbers and percentages based on randomized population. Same summary tables will be provided by treatment group and by cohort (one table per cohort). Within Cohort 1, data may also be summarized separately for Asian and African patients.

11.3.1 Randomized population

The randomized population is defined as all patients who have given their informed consent and who have been allocated to a randomized treatment regardless of whether the treatment kit was used or not.

11.3.2 Efficacy populations

Two efficacy analysis populations will be considered ie, Modified intent-to-treat (mITT) and Per-protocol (PP) populations focused on the “lower” NAI African population.

For the Asian patients and for the higher NAI population defined as all randomized patients >5 years in Africa (Cohort 1 & 2), with parasitologically confirmed malaria at baseline, who received at least the single administration OZ439/FQ, separate statistical reporting on all efficacy endpoints will be provided as secondary analyses.

The primary efficacy analysis population will be the per-protocol (PP) population defined as African patients of lower NAI; children ≤5 years in Africa (see Section 11.3.2.2).

11.3.2.1 Modified intent-to-treat population

Modified intent-to-treat (mITT) population is defined as all randomized African patients of "lower" NAI population (ie defined as children ≤5 years in Africa) with parasitologically confirmed malaria at baseline, who received at least the single administration OZ439/FQ , ie, who did not need rescue therapy due to vomiting during IMP administration (see Section 8.9).

African patients with age >5 years old, and Asian patients will not belong to the mITT.

Patients in the mITT population will be analyzed according to the treatment arm allocated by randomization.

11.3.2.2 Per-protocol (PP) population

Per-protocol (PP) population is defined as mITT patients who do not qualify for a major deviation, as defined in the statistical analysis plan.

11.3.3 Safety population

The Safety population considered for safety analyses will be the randomized population including lower and higher NAI population who did actually receive at least one dose or part of a dose of the single administration OZ439 800 mg & FQ. Patients will be analyzed according to the treatment actually received (OZ439/FQ).

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

11.3.4 Pharmacokinetic population

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

11.3.5 Pharmacokinetic/pharmacodynamic population

PK/PD analyses using PCR-adjusted ACPR efficacy endpoint will be performed on all patients included in both the pharmacokinetic and the Per-Protocol (PP) populations.

All patients included in the pharmacokinetic population and having at least one post-baseline assessment in QTc evaluation regarding the three PK/QTc analyses (one for Cohort 1a a second polling Cohorts 1a & 1b and final analysis including all cohorts) will be the pharmacokinetic/pharmacodynamic population.

11.4 STATISTICAL METHODS

11.4.1 Demographics and baseline characteristics

Continuous variables (age, weight) and qualitative variables (gender, race and BMI [<30 or ≥30 kg/m^2]) will be summarized in descriptive statistics by treatment arm and for all patients, and separately for each cohort (one table per cohort) for the randomized population. Within Cohort 1, demographics and baseline characteristics will also be summarized separately for Asian and African patients.

Other baseline characteristics like general medical history, previous medications defined as those started before the first intake of study drug and concomitant medications defined as those taken concomitantly to the study drug will be summarized by treatment arm and for all patients, and separately for each cohort (one table per cohort) for the randomized population:

- Summary of all medical history (number and percentage of patients) by primary system organ class (SOC) and high Level Term (HLT).
- Summary of Prior medications taken prior to first IMP intake (number and percentage of patients) by anatomic class and therapeutic class.
- Summary of concomitant medications (number and percentage of patients) by anatomic class and therapeutic class.

11.4.2 Extent of study treatment exposure and compliance

The listing of patients receiving IMP from specified batch will also be provided by cohort, treatment arm and patient. Besides, a listing sorted by site and cohort 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.

11.4.2.1 Extent of investigational medicinal product exposure

Since this is a single dose administration, duration of IMP exposure will not be calculated.

11.4.2.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data. Since this is a single dose administration, treatment compliance, above-planned and under-planned dosing percentages will not be calculated.

11.4.3 Analyses of efficacy endpoints

The primary final analysis will be carried out on the per-protocol (PP) population. Major protocol deviations disqualifying patients for the PP population will be described in the statistical analysis plan.

All statistical analyses on secondary efficacy endpoints will be done on the PP population. However, in case mITT and PP populations differ by more than 5%, statistical analysis of the primary endpoint ACPR at Day 28 will be carried out on the mITT population.

A separate reporting on primary and secondary efficacy endpoints will be provided on "higher" NAI population; (Africans >5 years), and Asian population.

11.4.3.1 Analysis of primary efficacy endpoint

See Section 9.1.1 for primary efficacy endpoint details.

- PCR-adjusted ACPR (4-term composite criterion) at Day 28.

Within each treatment arm, the following null hypothesis will be tested:

H0: $p \leq 0.90$

Against the one sided alternative:

H1: $p > 0.90$ where p is the probability of PCR-adjusted ACPR at Day 28.

The study will follow a group sequential design with up to 4 interim futility analyses, the first one when approximately 50 patients per treatment arm have reached Day 28 and thereafter every time another 25 patients per treatment arm (until the final analysis including 150 patients) have reached Day 28.

At each interim analysis, based on PP population one of the following potential decisions is to be made:

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

A Beta (9.5, 0.5) distribution will be used as prior distribution for the response rate and combined with a binomial likelihood to get a Beta posterior distribution (9.5 + x, 0.5 + N-x) with x is the number of successes out of N patients and calculate the posterior probability.

At the final analysis, providing the treatment arm has not been stopped for futility, the null hypothesis will be rejected and binary endpoints such PCR-adjusted ACPR, ETF, LCF and LPF at Day 28 will be analyzed thanks to a frequency table ie, proportion, percentage and exact binomial 95% confidence intervals (two-sided by using Clopper-Pearson method for calculating binomial confidence intervals) on the per-protocol (PP) population by cohort and treatment arm (one table including all patients and one table per cohort). Efficacy of the treatment arm demonstrated if the lower limit of the exact 95% confidence interval of PCR-adjusted ACPR rate is >90%.

Same frequency table will be provided by treatment arm for children population (ie, including only Cohort 3 & 4).

11.4.3.2 Analyses of secondary efficacy endpoints

See Section 9.2.1 for secondary efficacy endpoints details

- PCR-adjusted ACPR (4-term composite criterion) at Day 42 and Day 63

  PCR-adjusted ACPR, Early Treatment Failure (ETF), Late Clinical Failure (LCF) and Late Parasitological Failure (LPF) will be analyzed at Day 42 and Day 63 separately thanks to a frequency table ie, proportion, percentage and exact binomial 95% confidence intervals (two-sided by using Clopper-Pearson method for calculating binomial confidence intervals) by cohort and treatment arm (one table including all patients and one table per cohort).

- PCR-crude ACPR at Days 28, 42 and 63

  Same analysis using Clopper-Pearson method will be done on PCR-crude ACPR at Days 28, 42 and 63. The dose-response association of single-dose OZ439/FQ for PCR-crude ACPR will also be evaluated.

- Time to re-emergence, to recrudescence, to re-infection, time to parasite clearance (PCT) and time to fever clearance (FCT).

  Time to event variables (like time to re-emergence, time to recrudescence, time to re-infection, [FCT], [PCT]) will be analyzed using Kaplan-Meier estimators. Unless specified otherwise, all survival times will be calculated from the date/hour of first study drug intake to the first time to which the event occurred. For each variable, an overall overview including number of events (frequency and %), 25%, median and 75% quantile with 95% CI (expressed in weeks), cumulative incidence of events with 95% CI will be provided in a summary table for all patients and for each cohort separately. Survival curves will be plotted by representing each treatment arm for all patients and separately for each cohort.

- Parasite reduction ratio (PRR)

  The calculations and modeling for the PRR will be further discussed in the SAP. This will be calculated using microscopic and, when available, qPCR determined parasitemia.

- 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 each post-baseline assessment. Time profile plots (Mean ± SEM) of parasitemia will be provided for each treatment arm, one curve per arm and also for each cohort separately. These analyses will be done using microscopic and qPCR (in patients >5 years) determined parasitemia.

11.4.3.3 Multiplicity considerations

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

11.4.3.4 Analyses of exploratory endpoints

See Section 9.4.2 for exploratory endpoints details.

- Time to gametocytes clearance

  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

  The first appearance of gametocytes will be presented by time after enrollment for all patients, by treatment arm and separately for each cohort and 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.

- Kelch 13 and parasite clearance

  Genotype – phenotype associations in the propeller region of Kelch 13 and parasite clearance kinetics (like half-life) will be explored graphically thanks to scatter plots. Linear mixed models may be used to test associations between parasite genotypes and parasite clearance half-lives following OZ439/FQ treatment arm.

- Gametocyte detection RT-PCR (in patients >5 years only)

  Standard descriptive statistics will be provided by cohort, treatment arm and time of measurement. If relevant, some correlations or modeling will be explored.

- Phenotypic and genotypic resistance pattern to conventional ACT of P. falciparum infecting patients aged >14 years old in Vietnamese sites

  Standard descriptive statistics will be provided by cohort, treatment arm and time of measurement. If relevant, some correlations or modeling will be explored.

- In vitro susceptibility testing of P. falciparum infecting patients aged >14 years old in Vietnamese sites to OZ439, FQ and both drugs.

  Standard descriptive statistics will be provided by cohort, treatment arm and time of measurement. If relevant, some correlations or modeling will be explored.

11.4.4 Analyses of safety data

The summary of safety results will be presented by treatment arm thanks to descriptive statistics (summary tables, graphics) in the following way:

- Summary tables provided separately for “higher NAI” (African patients >5 years) and “lower NAI” populations, and within the“lower NAI” population, separately for African patients ≤5 years and Asian patients, by treatment arm, whatever the cohort.
- A summary table provided for “higher NAI population” by treatment arm and by cohort (Cohort 1 & 2).
- A summary table provided for “lower NAI population” by treatment arm and by cohort (Cohort 3 & 4).

No formal inferential testing will be performed.

All the safety analyses will be performed using the safety population.

For all safety data (see Section 9.2.2.1 for details), the observation period will be divided into three phases:

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

For laboratory, vital signs and ECG parameters, Potentially Clinically Significant Abnormalities (PCSAs) will be analyzed using the last available version of PCSA list before database lock.

The following definitions will be applied to laboratory parameters, vital signs and ECG:

- 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 criteria will determine which patients had at least 1 PCSA during the on-treatment phase, taking into account all evaluations performed during the on-treatment phase, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSA percentage.

Baseline safety parameters

The baseline value is defined as the last available value before first double-blind IMP at Visit 1 (Day-1) for laboratory, vital sign and Visit 2 (Day 0 before IMP administration) for ECG parameters. For ECG parameters, baseline will be the mean of the 3 consecutive measures (triplicate) done before dosing.

Baseline definitions specific to each type of safety parameter will be detailed in corresponding sections.

Baseline safety data will be presented along with subsequent safety values assessed during or after dosing.

Drug-induced liver injury

The liver function tests, namely ALT, AST, 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 arm for each parameter.

A graph of distribution (e-Dish plot) of peak values of ALT versus peak values of total bilirubin will be presented. Note that the ALT and total bilirubin values are presented on a logarithmic

scale. 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.

The normalization (to ≤1 x ULN or return to baseline) of elevated liver function tests will be summarized by categories of elevation (3 x ULN, 5 x ULN, 10 x ULN, 20 x ULN for ALT and AST, 1.5 x ULN for alkaline phosphatase, and 1.5 x ULN and 2 x ULN for total bilirubin), with the following categories of normalization: never normalized, normalized after permanent discontinuation of study drug. Note that a patient will be counted only under the maximum elevation category.

The incidence of liver-related AEs will be summarized by treatment arm. The selection of preferred terms will be based on standardized MedDRA query (SMQ) Hepatic disorder. Time to liver-related treatment discontinuation and time to liver death may also be provided based on hepatic disorder SMQ.

11.4.4.1 Analyses of adverse events

11.4.4.1.1 Definitions

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA, last version available before database lock).

They will be classified into predefined standard categories according to chronological criteria:

- Pre-treatment AEs are defined as AEs that occurred, worsened (according to Investigator opinion) or became serious during the pre-treatment phase
- Treatment emergent AEs (TEAEs) are defined as AEs that occurred or worsened or became serious during the on-treatment phase
- Post-treatment AEs are defined as AEs that occurred worsened or became serious during the post-treatment phase.

11.4.4.1.2 Treatment emergent adverse events

The following frequency tables of TEAEs (incidence tables) will be provided by treatment arm for each population (higher and lower NAI) and separately for each cohort (one table per cohort) during the on-treatment phase:

- Overview of TEAE: Number and percentage of patients with any TEAE, treatment emergent SAE and TEAEs leading to death.
- Summary of TEAEs (number and percentage of patients) by primary system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment arm. 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 arm.

- Summary of TEAEs (number and percentage of patient s) by primary system organ class (SOC) and preferred term (PT).
- Summary of TEAEs (number and percentage of patient s) by maximal intensity, primary system organ class (SOC) and preferred term (PT).

The following frequency tables of treatment emergent SAEs (incidence tables) will be provided by treatment arm for each population (higher and lower NAI and separately for each cohort (one table per cohort) during the on-treatment phase:

- Summary of treatment emergent SAEs (number and percentage of patients) by primary SOC (sorted by internationally agreed order), HLGT, HLT and PT sorted in alphabetical order for each treatment arm.
- Summary of treatment emergent SAEs (number and percentage of patient s) by primary SOC and PT.

Listing of patients presenting treatment emergent SAEs will be provided by treatment arm, patients, primary SOC, PT and onset date and time.

AESIs:

Summary tables of patient count (%) for each AESI (PT or pre-specified grouping) by treatment arm for each population (higher and lower NAI and separately for each cohort (one table per cohort) will be generated:

- Number (%) of patients experiencing torsade de pointes/QT prolongation by Primary SOC and PT.
- Number (%) of patients experiencing hepatic disorders by Primary SOC and PT.

Death:

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study, post-study) summarized on the safety population by treatment received.
- Death in nonrandomized patients or randomized and not treated patients.
- TEAE leading to death (death as an outcome on the AE e-CRF page as reported by the Investigator) by primary SOC, HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

11.4.4.2 Laboratory variables analyses

Baseline definition

The values to be used as baselines will be the values collected on Day -1 for each treatment arm. If any of the scheduled baseline tests are repeated for any patient, the last rechecked values will be

considered as baselines, provided they were done before the start of IMP administration and in the same conditions.

In case of central and local tests performed at the same time, central value will be considered as the baseline value provided it was done before the start of IMP administration. If a central test was not performed but a local value exists at the same date for the same test, the local value will be considered as the baseline.

Abnormalities analyses

For parameters with laboratory ranges and/or abnormality criteria (PCSA), an "on-treatment" analysis will be performed using all post-baseline assessments done during the on-treatment phase, including all unplanned and rechecked values.

Counts of patients with PCSAs at any time during the on-treatment phase will be summarized by treatment arm for each population (higher and lower NAI) and separately for each cohort (one table per cohort) in summary tables showing shifts from normal and abnormal baselines to post-baseline abnormalities. These tables are split by normal/abnormal status and missing value at baseline (if any).

Descriptive statistics and plots

For ALT, AST, ALP, total and conjugated bilirubin, raw data and changes from baseline (including mean, median, quartile (Q1), Q3, standard deviation, minimum and maximum) will be summarized in descriptive statistics, by treatment arm and visit for all patients and separately for each cohort (one table per cohort).

Additionally, time profile plots (mean+/- SD) on raw data and change from baseline will be provided for all patients and separately for each cohort and each of these parameters, using one curve per treatment arm.

Listings

All individual data, for planned hematology and biochemistry including rechecked values, will be listed by biological function, cohort, treatment arm and patient, visit. If any, data from unscheduled laboratory tests will also be listed. In these listings, individual data will be flagged when lower or higher than the lower or upper laboratory limits and/or when reaching the absolute limit of PCSA criteria, when defined. A listing of out-of-normal range definitions will also be provided.

A listing of liver function data for patients experiencing at least one of the following situations will be provided as an in-text table:

- ALT >3 ULN and total bilirubin >2 ULN during the study, with at least one of them being post first dose, irrespective of the definition of the on-treatment phase.
- Direct bilirubin >35% of total bilirubin and total bilirubin >1.5 ULN, on the same sample post first dose, irrespective of the definition for the on-treatment phase.

A separate listing of individual data from patients with post-baseline PCSAs will be provided.

If any, a listing related to increase in ALT ≥2 ULN will be provided, including notably the information on IMP intake, medical and surgical history, alcohol habits, trigger factors, event details with ALT values, associated signs and symptoms.

11.4.4.3 Analyses of vital sign variables

11.4.4.3.1 Heart rate and blood pressure

Heart rate (HR) and systolic and diastolic blood pressure (SBP and DBP) will be analyzed as raw parameter value and change from baseline (for supine position only).

Baseline definition

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

Abnormalities analyses

For all parameters, an "on-treatment" analysis will be performed using all post-baseline assessments done during the on-treatment phase, including all unplanned and rechecked values.

Counts of patients with post-baseline PCSAs will be provided in summary tables regardless of the normal or abnormal status of the baseline. This table will be presented by treatment arm for each population (higher and lower NAI) and separately for each cohort (one table per cohort).

Descriptive statistics

For heart rate and blood pressures, raw data and changes from baseline (for supine position only including mean, median, quartile (Q1), Q3, standard deviation, minimum and maximum) will be summarized in descriptive statistics, for each type of measurement and by treatment arm, visit and time of measurement for all patients and separately for each cohort (one table per cohort).

Listings

Individual data for supine position, including unplanned and rechecked values, will be listed by cohort, treatment arm and patient, visit and time of measurement.

In the listings, values will be flagged when reaching the limits of the PCSA criteria, when defined.

A separate listing of individual data from patients with post-baseline PCSAs will be provided.

11.4.4.3.2 Body temperature

Raw data and changes from baseline will be summarized in descriptive statistics, by type of measurement (axillary [recommended], tympanic, oral or rectal), treatment arm, visit and time of measurement for all patients and separately for each cohort (one table per cohort).

11.4.4.4 ECG parameters analyses

For all ECG parameters the mean of the 3 consecutive measures of ECG (triplicates) at each time of measurement when applicable will be calculated for each parameter, patient and nominal time point and will be used for analyses.

Heart rate, PR-, QRS-, and QT-intervals, corrected QTcF (Fridericia) will be analyzed as raw parameter value and change from baseline, as well as percent change from baseline for selected parameters.

Baseline definition

The value to be used as baseline will be defined as the average of the triplicate assessments done on Day 0 T0 for each treatment arm.

Abnormalities analysis

For all parameters, an "on-treatment" analysis will be performed using all post-baseline assessments done during the on-treatment phase, including all unplanned and rechecked values. Counts of patients with post-baseline PCSAs will be provided in summary tables regardless of the normal or abnormal status of the baseline. This table will be presented by treatment arm for each population (higher and lower NAI) and separately for each cohort.

A summary of ECG morphological assessments (for all high level types of comments) will be provided by cohort and treatment arm.

Descriptive statistics and plots

For all parameters, raw data and changes from baseline will be summarized in descriptive statistics, by treatment arm, visit and time of measurement for all patients and separately for each cohort (one table per cohort). Summary plots (mean+/-SD) on raw data and changes from baseline, as well as percent change from baseline for selected parameters will also be generated, separately for each cohort and each of these parameters, using one curve per treatment arm.

Additionally, time profile plots (mean+/- SD) on raw data and change from baseline will be provided on all ECG parameters for all patients and separately for each cohort and each of these parameters, using one curve per treatment arm.

Listings

Individual data, including rechecked values, will be listed by cohort, treatment arm, patient, visit and time of measurement. In the listings, values will be flagged when reaching the limits of the PCSA criteria, when defined. A separate listing of individual data from patient s with post-baseline PCSAs will be provided.

11.4.5 Analyses of pharmacokinetic and pharmacodynamic variables

11.4.5.1 Analysis of pharmacokinetic data

Pharmacokinetic analysis for OZ439, FQ and SSR97213 are described in Section 9.4.1.5.

Blood and plasma FQ (respectively its metabolite [SSR97213]) observed concentrations, plasma OZ439 observed concentrations will be summarized by treatment arm and by time point using descriptive statistics for each cohort. Blood/plasma concentration ratio for FQ and SSR97213 will be provided by treatment arm and by time point using descriptive statistics for each cohort. Additional plots will be prepared, as deemed necessary.

Pharmacokinetic parameters of FQ, 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 treatment arm and each cohort.

The results of population PK modeling will be reported separately from the study report.

11.4.5.2 Analysis of pharmacodynamic data

Not applicable.

11.4.5.3 Analysis of pharmacokinetic/pharmacodynamic data

11.4.5.3.1 Relationship between ACPR and dose or concentrations

For each cohort and for all patients separately, the dose-response association of single-dose OZ439/FQ for PCR-adjusted ACPR will demonstrate how the probability of a response in PCR-adjusted ACPR increases with increasing dose OZ439/FQ thanks to a logistic regression with SAS® PROC LOGISTIC by using ACPR data at Days 28, 42 and 63. Same analysis will be done between PCR-adjusted ACPR and exposure.

Results of logistic regressions of PCR-adjusted ACPR on dose (respectively FQ/SSR97213 blood or OZ439 plasma concentrations) of OZ439/FQ will be provided in a summary table including odds ratio estimates, the corresponding 95% Wald confidence intervals and p-value.

11.4.5.3.2 Relationship between PK concentrations and QTc parameters

Two PK/PD statistical analyses (one for cohort 1a in a first time and then by pooling cohort 1a and 1b in a second time) will be done with ECG parameters (HR, PR, QRS and QTcF) regarding FQ and SSR97213 compounds by combining the two compounds in the same linear direct/indirect model (as covariates or by using the molecular weight formula in order to obtain an “average” concentration). A complementary analysis will be performed pooling Cohort 1a and 1b and including OZ concentrations as PK variable (in addition to FQ and SSR97213). These two analyses will be prepared by a Sponsor’s unblinded independent statistician.

The first PK/QTc analysis will include 30 African patients >14 years (Cohort 1a) receiving the dose levels OZ439/FQ 800/400, 800/600 and 800/900 mg.

The second PK/PD analysis will include a total of 42 African patients >14 years (Cohort 1a & 1b) receiving the dose levels 800/400, 800/600,800/900 and 800/1200.
Concentrations below the limit of quantification (LOQ LOQ), will be replaced with ½ LOQ in the statistical analyses. LOQ is defined as 1 ng/mL for OZ439 and as 5 ng/mL for FQ and SSR97213.

Relationships between change from baseline in ECG parameters by combining the two compounds FQ and SSR97213, using the molecular weight (MW) 433.77 g.mol-1 for ferroquine 419.74 g.mol-1 for SSR97213 or by using ferroquine and SSR97213 blood drug concentrations as covariates in the same model (selection of the best model will depend of fit statistics criteria), on the restricted time window [Day 0 T_{2h} – Day 2 T_{48h}] will be explored using data from OZ439/FQ:

1st step: 800/400, 800/600 and 800/900 mg dose levels from Cohort 1a.

2nd step: 800/400, 800/600, 800/900 and 800/1200 mg dose levels from Cohorts 1a and 1b. (OZ concentration to be added as PK variable in the complementary analysis with the molecular weight (MW) of 469.28 g.mol-1).

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

A third PK/PD analysis will include all patients of all cohorts receiving the dose levels 800/400, 800/600, 800/900 mg and/or 800/1200 mg at the end of the study. Relationships between change from baseline in ECG parameters versus FQ (respectively SSR97213 and OZ439) blood drug concentrations, on the restricted time window [Day 0 T_{2h} – Day 2 T_{48h}].

11.4.5.3.3 Exploratory plots

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

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

- Histogram of distribution of time of smallest change from baseline in HR, PR, QRS and QTcF and largest FQ (respectively SSR97213 and OZ439 [complementary analysis at end of Cohort 1 and final analysis only]) concentrations, respectively.

11.4.5.3.4 Modeling: linear model

A random coefficients linear regression of QTcF (respectively HR, RR) change from baseline vs. concentration will be used from Day 0 T2h to Day 2 T48h, with fixed terms for common intercept and slope, with or without time effect, and with random terms for patient -specific intercept and slope, and using an unstructured variance-covariance structure for random coefficients and a common variance for error, using SAS® PROC MIXED procedure:

Change from baseline $QTcF_{ij} = (\alpha + A_i) + Time_j + (\beta + B_i) \times Concentration_{ij} + error$,
with i = patient and j = Time

Estimates and 90% CIs of coefficients (intercept corresponding to the mean of individual time Intercept in case of time effect is included in the model and slope) of the linear regression model, and the prediction (estimate and 90% CI) in change from baseline of ECG parameters corresponding to the C_{max} value (geometric mean) for each FQ dose group will be provided for FQ and SSR97213 respectively (OZ439 compound for the complementary analysis at end of Cohort 1 and final analysis only), and will be calculated following the formula $\beta_{estimated} \times$ observed geometric mean C_{max}:

- OZ439 800 mg/FQ xxx mg/ at geometric mean of C_{max} for each dose of OZ439/FQ.
- Scatter plots of change from baseline versus FQ and SSR97213 concentrations, respectively, with the regression line overlaid, will also be provided.

11.4.5.3.5 Model Averaging to Concentration-QT analysis

By combining estimates obtained from several competing models (linear, exponential and Emax), Model averaging (MA) will provide estimators which will have good robustness properties compared to the linear model or non-linear model estimates.

The estimated endpoint will be the drug effect on delta QTcF at the Cmax value (geometric mean) observed concentrations at the maximal dose (OZ439 800 mg/FQ 1200 mg).

11.4.6 Analyses of quality of life/health economics variables

Not applicable.

11.5 INTERIM ANALYSIS

Safety review

No interim analysis is planned. However unblinded safety data of each cohort (N=10 patients/arm for Cohort 1, 5 patients/arm for Cohort 2 and 8 patients/arm for Cohort 3 & 4) will be analyzed by the Sponsor's independent unblinded statistician and reviewed by the DMC (see Section 11.4.5.3).

Also, PK/QTc modeling data (Cohort 1a and pooled of Cohort 1a & 1b) will be prepared by a Sponsor's independent unblinded statistician and reviewed by the DMC (See Section 11.4.5.3).

Go/No Go for transition from one cohort to the next and FQ dose step-up procedure toOZ439/FQ-800/1200 mg will be based on DMC's assessment and recommendation.

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

Efficacy review: interim futility analyses

Up to 4 interim futility analyses may be planned and will be performed by the Sponsor's independent unblinded statistician and reviewed by the DMC.

As soon as the first 50 patients/treatment arm have completed the 28-days treatment period, the 1st analysis will be performed by the DMC statistician to assess the primary endpoint (response rate of PCR-adjusted ACPR at Day 28, Section 11.4.3) in order to pursue or not the recruitment of each treatment arm. Thereafter, subsequent interim futility analysis will be performed every time another 25 patients per treatment arm (ie, 75 patients/treatment arm for the 2nd IA, 100 patients/treatment arm for the 3rd IA, 125 patients/treatment arm for the 4th IA until 150 patients/treatment arm for the final analysis) will be enrolled in the study and will have completed the primary endpoint at Day 28. Recruitment continues until each treatment arm is deemed to be futile or until 150 patients per treatment arm for the final per protocol analysis is reached.

The results of each interim futility analysis will be reviewed by the DMC which will recommend continuing or not the recruitment of patients in each treatment arm depending of the cohort age group if the following conditions are met:

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

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Subinvestigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the International Conference of Harmonization (ICH) guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient (and the parent[s] or guardian[s]) of all pertinent aspects of the clinical trial including the written information given approval/favorable opinion by the ethics committee (Institutional Review Board/Independent Ethics Committee [IRB/IEC]). All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the informed consent form should be signed, name filled in and personally dated by the patient, the patient’s parent(s) or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient. When applicable, local law must be observed in deciding whether 1 or both parents/guardians consent is required. If only 1 parent or guardian signs the consent form, the Investigator must document the reason for only 1 parent or guardian’s signature.

In addition, participants will assent as detailed below or will follow the Ethics Committee (IRB/IEC) approved standard practice for pediatric participants at each participating center (age of assent to be determined by the IRB’s/IEC’s or be consistent with the local requirements):

Participants who can read the assent form will do so before writing their name and dating or signing and dating the form.

Participants who can write but cannot read will have the assent form read to them before writing their name on the form.

Participants who can understand but who can neither write nor read will have the assent form read to them in presence of an impartial witness, who will sign and date the assent form to confirm that assent was given.

The informed consent form and the assent form used by the Investigator for obtaining the Patient's Informed Consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

In relation with the population of patients exposed in the trial ie, pediatric/minor patients, the IRB/IEC should ensure proper advice from specialist with pediatrics expertise (competent in the area of clinical, ethical and psychosocial problems in the field of pediatrics) according to national regulations. This should be documented.

12.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure, Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATORS

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Sub-investigators shall be appointed and listed in a timely manner. The Sub-investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

13.3 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of

the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.4 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor’s duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.5 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.6 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Sub-investigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-investigators of the confidential nature of the clinical trial.

The Investigator and the Sub-investigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party’s account.

14.3 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff / Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Sub-investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.4 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party;
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Patient race/ethnic origin (African, Asian) will be collected in this study because these data support the sub-population definition: *higher and lower NAI population* (see Section 7.4.1).

14.5 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.6 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.7 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.7.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio;
- Patient enrollment is unsatisfactory;
- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;
- Non-compliance of the Investigator or Sub-investigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP;
- The total number of patients are included earlier than expected;

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.7.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.8 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.9 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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17 APPENDICES

Appendix A Severe *P. falciparum* malaria definition

Clinical features of severe malaria

- impaired consciousness (including unrousable coma);
- prostration, ie, generalized weakness so that the patient is unable to sit, stand or walk without assistance;
- multiple convulsions: more than two episodes within 24h;
- deep breathing and respiratory distress (acidotic breathing);
- acute pulmonary oedema and acute respiratory distress syndrome;
- circulatory collapse or shock, systolic blood pressure <80 mmHg in adults and <50 mmHg in children;
- acute kidney injury;
- clinical jaundice plus evidence of other vital organ dysfunction; and abnormal bleeding.

Laboratory and other findings

- hypoglycaemia (<2.2 mmol/l or <40 mg/dL);
- metabolic acidosis (plasma bicarbonate <15 mmol/L);
- severe normocytic anaemia (haemoglobin <5 g/dL, packed cell volume <15% in children; <7 g/dL, packed cell volume <20% in adults);
- haemoglobinuria;
- hyperlactataemia (lactate >5 mmol/L);
- renal impairment (serum creatinine >265 μmol/L); and
- pulmonary oedema (radiological).

Appendix B CYPs inducer/inhibitor/substrate, P-gp substrate (non-exhaustive list)

Compound (INN)	Terminal half life	Reason for exclusion
Aliskiren	38h	Pgp substrate
Amiodarone	25 days	CYP2C and CYP3A inhibitor
Atomoxetine	20h	main CYP2D6 substrate
Avasimibe	24h	CYP inducer
Boceprevir	3h	Strong CYP3A inhibitor
Bosentan	7h	CYP inducer
Carbamazepine	15h	CYP inducer
Carvedilol	2h	main CYP2D6 substrate
Chlorpromazine	30h	main CYP2D6 substrate
Clarithromycin	3h	Strong CYP3A inhibitor
Colchicine	31h	Pgp substrate
Conivaptan	5h	Strong CYP3A inhibitor
Dabigatran etexilate	11h	Pgp substrate
Danoprevir/ritonavir	2h/5h	Strong CYP3A inhibitor
Desipramine	28h	main CYP2D6 substrate
Dextromethorphan	3h	main CYP2D6 substrate
Digoxin	36h	Pgp substrate
Efavirenz	3 days	CYP inducer
Elvitegravir/ritonavir	8h/5h	Strong CYP3A inhibitor
Encainide	3h	main CYP2D6 substrate
Enzalutamide	6h	CYP inducer
Etoposide	8h	Pgp substrate
Etravirine	40h	CYP inducer
Everolimus	30h	Pgp substrate
Fexofenadine	15h	Pgp substrate
Flecainide	11h	main CYP2D6 substrate
Fluconazole	32h	Strong CYP2C inhibitor
Fluoxetine	2 days	CYP2C and CYP3A inhibitor
Fluvoxamine	15h	Strong CYP2C inhibitor
Gemfibrozil	1h	Strong CYP2C inhibitor
Genistein	8h	CYP inducer
Grapefruit juice	-	Strong CYP3A inhibitor
Imipramine	16h	main CYP2D6 substrate
Indinavir, Indinavir/ritonavir	2h/5h	Strong CYP3A inhibitor
Itraconazole	21h	Strong CYP3A inhibitor
Ketoconazole	3h	Strong CYP3A inhibitor
Lapatinib	14h	Pgp substrate
Lersivirine	6h	CYP inducer
Linezolide	5h	Pgp substrate
Loperamide	11h	Pgp substrate
Lopinavir, Lopinavir/ritonavir	5h	Strong CYP3A inhibitor, CYP inducer

Compound (INN)	Terminal half life	Reason for exclusion
Maprotiline	45h	main CYP2D6 substrate
Maraviroc	18h	Pgp substrate
Metoprolol	3h	main CYP2D6 substrate
Mibefradil	22h	Strong CYP3A inhibitor
Miconazole	24h	Strong CYP2C inhibitor
Mitotane	18-159 days	Potent CYP inducer
Modafinil	11h	CYP inducer
Nafcillin	2h	CYP inducer
Nebivolol	11h	main CYP2D6 substrate
Nefazodone	4h	Strong CYP3A inhibitor
Nelfinavir	5h	Strong CYP3A inhibitor
Nilotinib	17h	Pgp substrate
Nortriptyline	31h	main CYP2D6 substrate
Paroxetine	17h	main CYP2D6 substrate
Perphenazine	9h	main CYP2D6 substrate
Phenobarbital	4 days	CYP inducer
Phenytoine	24h	CYP inducer
Pimozide	5 days	main CYP2D6 substrate
Posaconazole	35h	Strong CYP3A inhibitor, Pgp substrate
Propafenone	6h	main CYP2D6 substrate
Propranolol	4h	main CYP2D6 substrate
Ranolazine	7h	Pgp substrate
Rifabutine	28-62h	CYP inducer
Rifampin	4h	CYP inducer
Rifapentine	18h	CYP inducer
Risperidone	3h	main CYP2D6 substrate
Ritonavir	5h	Strong CYP3A inhibitor
Saquinavir, Saquinavir/ritonavir	12h/5h	Strong CYP3A inhibitor, Pgp substrate
Semagacestat	2.5h	CYP inducer
Sirolimus	62h	Pgp substrate
St John's wort	-	CYP inducer
Talinolol	9h	Pgp substrate
Talviraline	-	CYP inducer
Telaprevir	11h	Strong CYP3A inhibitor
Telithromycin	12h	Strong CYP3A inhibitor
Thioridazine	24h	main CYP2D6 substrate
Ticlopidine	4 days	Strong CYP2C inhibitor
Timolol	3h	main CYP2D6 substrate
Tipranavir/ritonavir	6h/5h	Strong CYP3A inhibitor
Tolterodine	2h	main CYP2D6 substrate
Tolvaptan	12h	Pgp substrate
Trimipramine	24h	main CYP2D6 substrate
Troleandomycine	3h	Strong CYP3A inhibitor
Venlafaxine	5h	main CYP2D6 substrate
Voriconazole	7h	Strong CYP3A inhibitor

Appendix C Drugs known to modify QT interval (non exhaustive list)

COMBINED LIST OF DRUGS THAT PROLONG QT AND/OR CAUSE TORSADES DE POINTES (TDP)

CREDIBLEMEDS®

Crediblemeds.org is your trusted partner providing reliable information on medicines. This is a combined list of drugs that CredibleMeds has concluded either 1) have a risk of TdP, 2) prolong QT and therefore have a possible risk of TdP or 3) have a risk of TdP under certain conditions such as overdose, drugdrug interactions or when administered to certain high-risk individuals (e.g. congenital long QT syndrome).

Generic Name	Brand Name
Amantadine	Symmetrel® and others
Amiodarone	Cordarone® and others
Amisulpride	Solian® and others
Amitriptyline	Elavil® (Discontinued 6/13) and others
Amoxapine	Asendin® and others
Anagrelide	Agrylin® and others
Apomorphine	Apokyn® and others
Aripiprazole	Abilify® and others
Arsenic trioxide	Trisenox®
Asimizole (Off US mkt)	Hismanal®
Atazanavir	Reyataz®
Azithromycin	Zithromax® and others
Bedaquiline	Sirturo®
Bepridil (Off US mkt)	Vascor®
Bortezomib	Velcade® and others
Bosutinib	Bosulif®
Chloral hydrate	Aquachloral® and others
Chloroquine	Aralen®
Chlorpromazine	Thorazine® and others
Ciprofloxacin	Cipro® and others
Cisapride (Off US mkt)	Propulsid®
Citalopram	Celexa® and others
Clarithromycin	Biaxin® and others
Clomipramine	Anafranil®
Clozapine	Clozaril® and others
Cocaine	Cocaine
Crizotinib	Xalkori®
Dabrafenib	Tafinlar®
Dasatinib	Sprycel®
Desipramine	Pertofrane® and others
Dexmedetomidine	Precedex® and others
Dihydroartemisinin+piperaquine	Eurartesim®
Diphenhydramine	Benadryl® and others
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Dolasetron	Anzemet®
Domperidone (Not on US mkt)	Motilium® and others
Doxepin	Sinequan® and others
Dronedarone	Multaq®
Droperidol	Inapsine® and others
Eribulin	Halaven®
Erythromycin	E.E.S.® and others
Escitalopram	Cipralex® and others
Famotidine	Pepcid® and others
Felbamate	Felbatol®
Fingolimod	Gilenya®
Flecainide	Tambocor® and others
Fluconazole	Diflucan® and others
Fluoxetine	Prozac® and others
Foscarnet	Foscavir®
Fosphenytoin	Cerebyx® and others
Furosemide (Frusemide)	Lasix® and others
Galantamine	Reminyl® and others
Gatifloxacin (Off US mkt)	Tequin®
Gemifloxacin	Factive®
Granisetron	Kytril® and others
Grepafloxacin (Off market worldwide)	Raxar®
Halofantrine	Halfan®
Haloperidol	Haldol® (US & UK) and others
Hydrochlorothiazide	Apo-Hydro® and others
Ibutilide	Corvert®
Iloperidone	Fanapt® and others
Imipramine (melipramine)	Tofranil®
Indapamide	Lozol® and others
Isradipine	Dynacirc®
Itraconazole	Sporanox® and others
Ivabradine (Not on US mkt)	Procoralan® and others
Ketoconazole	Nizoral® and others
Lapatinib	Tykerb® and others
Levofloxacin	Levaquin® and others
Levomethadyl (Off US mkt)	Orlaam®
Lithium	Eskalith® and others
Mesoridazine (Off US mkt)	Serentil®
Methadone	Dolophine® and others
Metronidazole	Flagyl® and many others
Mifepristone	Korlym® and others
Mirabegron	Myrbetriq®
Mirtazapine	Remeron
Moexipril/HCTZ	Uniretic® and others
Moxifloxacin	Avelox® and others
Nelfinavir	Viracept®
Nicardipine	Cardene®
Nilotinib	Tasigna®
Norfloxacin	Noroxin® and others
Nortriptyline	Pamelor® and others
Ofloxacin	Floxin®
Olanzapine	Zyprexa® and others
Ondansetron	Zofran® and others
Oxytocin	Pitocin® and others

If list is printed, check website for updates: www.crediblemeds.org •Please see Disclaimer and list continued

COMBINED LIST OF DRUGS THAT PROLONG QT AND/OR CAUSE TORSADES DE POINTES (TDP)

CREDIBLEMEDS®

Crediblemeds.org is your trusted partner providing reliable information on medicines. This is a combined list of drugs that CredibleMeds has concluded either 1) have a risk of TdP, 2) prolong QT and therefore have a possible risk of TdP or 3) have a risk of TdP under certain conditions such as overdose, drugdrug interactions or when administered to certain high-risk individuals (e.g. congenital long QT syndrome).

Generic Name	Brand Name
Paliperidone	Invega® and others
Pantoprazole	Protonix® and others
Paroxetine	Paxil® and others
Pasireotide	Signifor®
Pazopanib	Votrient®
Pentamidine	Pentam®
Perflutren lipid microspheres	Definity®
Pimozide	Orap®
Piperaperone (Not on US Mkt)	Dipiperon (E.U) and others
Posaconazole	Noxafil® and others
Probucol (Off US mkt)	Lorelco®
Procainamide (Oral off US mkt)	Procesty® and others
Promethazine	Phenergan®
Protriptyline	Vivactil®
Quetiapine	Seroquel®
Quinidine	Quinaglute® and others
Quinine sulfate	Qualaquin®
Ranolazine	Ranexa® and others
Rilpivirine	Edurant® and others
Risperidone	Risperdal®
Ritonavir	Norvir®
Roxithromycin (Not on US Mkt)	Rulide® and others
Saquinavir	Invirase®(combo)
Sertindole (Not on US mkt)	Serdolect® and others
Sertraline	Zoloft® and others
Sevoflurane	Ulane® and others

Generic Name	Brand Name
Solifenacin	VESIcare®
Sorafenib	Nexavar®
Sotalol	Betapace® and others
Sparfloxacin (Off US mkt)	Zagam®
Sulpiride (Not on US Mkt.)	Dogmatil® and others
Sunitinib	Sutent®
Tacrolimus	Prograf® and others
Tamoxifen	Nolvadex®(discontinued 6/13) and others
Telaprevir	Incivek® and others
Telavancin	Vibativ®
Telithromycin	Ketek®
Terfenadine (Off US mkt)	Seldane®
Tetrabenazine (Orphan drug in US)	Nitoman® and others
Thioridazine	Mellaril® and others
Tizanidine	Zanaflex® and others
Tolterodine	Detrol® and others
Toremifene	Fareston®
Trazodone	Desyrel® (discontinued 6/13) and others
Trimethoprim-Sulfa	Septra® and others
Trimipramine	Surmontil® and others
Vandetanib	Caprelsa®
Vardenafil	Levitra®
Vemurafenib	Zelboraf®
Venlafaxine	Effexor® and others
Voriconazole	VFend®
Vorinostat	Zolinza®
Ziprasidone	Geodon® and others

Note: Medicines on this list are reviewed on an ongoing basis to assure that the available evidence supports their continued placement on this list. The list changes regularly and we recommend checkingthe website at crediblemeds.org for the most up-todate information. There may be many additional brand names that are not listed on this form.

Disclaimer and Waiver: The information presented is intended solely for the purpose of providing general information about health-related matters. It is not intended for any other purpose, including but not limited to medical advice and/or treatment, nor is it intended to substitute for the users relationships with their own health care providers. To that extent, by use of this website and the information it contains, the user affirms the understanding of the purpose and releases AZCERT, Inc. from any claims arising out of his/her use of the website and its lists. The absence of drugs from these lists should not be considered an indication that they are free of risk of QT prolongation or TdP. Many medicines have not been tested for this risk in patients, especially those with congenital long QT syndrome.

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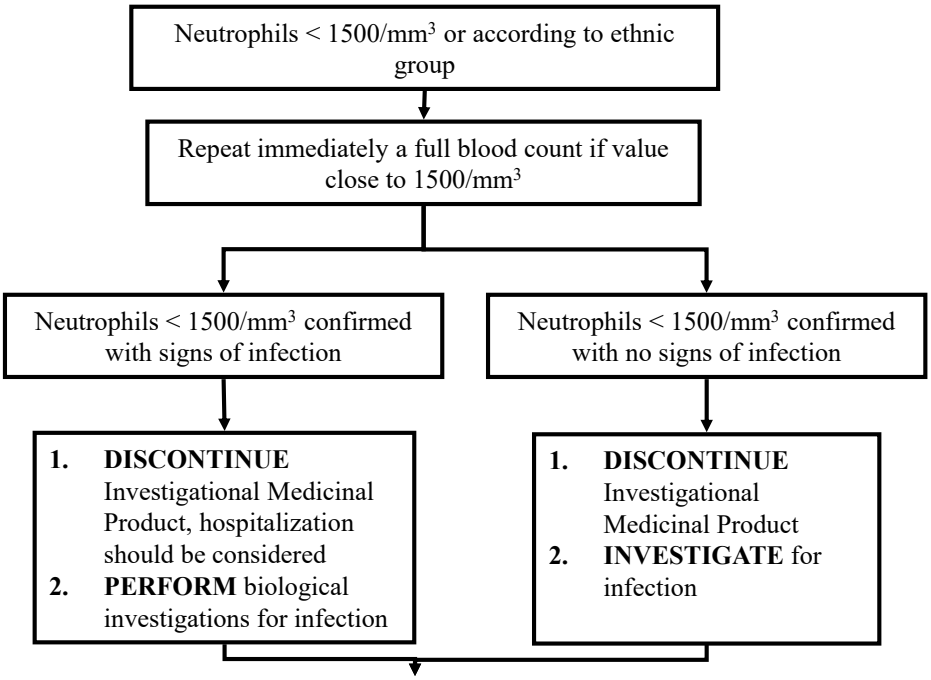
Or https://www.crediblemeds.org/pdftemp/pdf/CombinedList.pdf

Appendix D General Guidance for the follow-up of laboratory abnormalities by Sanofi

NEUTROPENIA



3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

Note:
•The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
•For individuals of African descent, the relevant value of concern is <1000/mm3

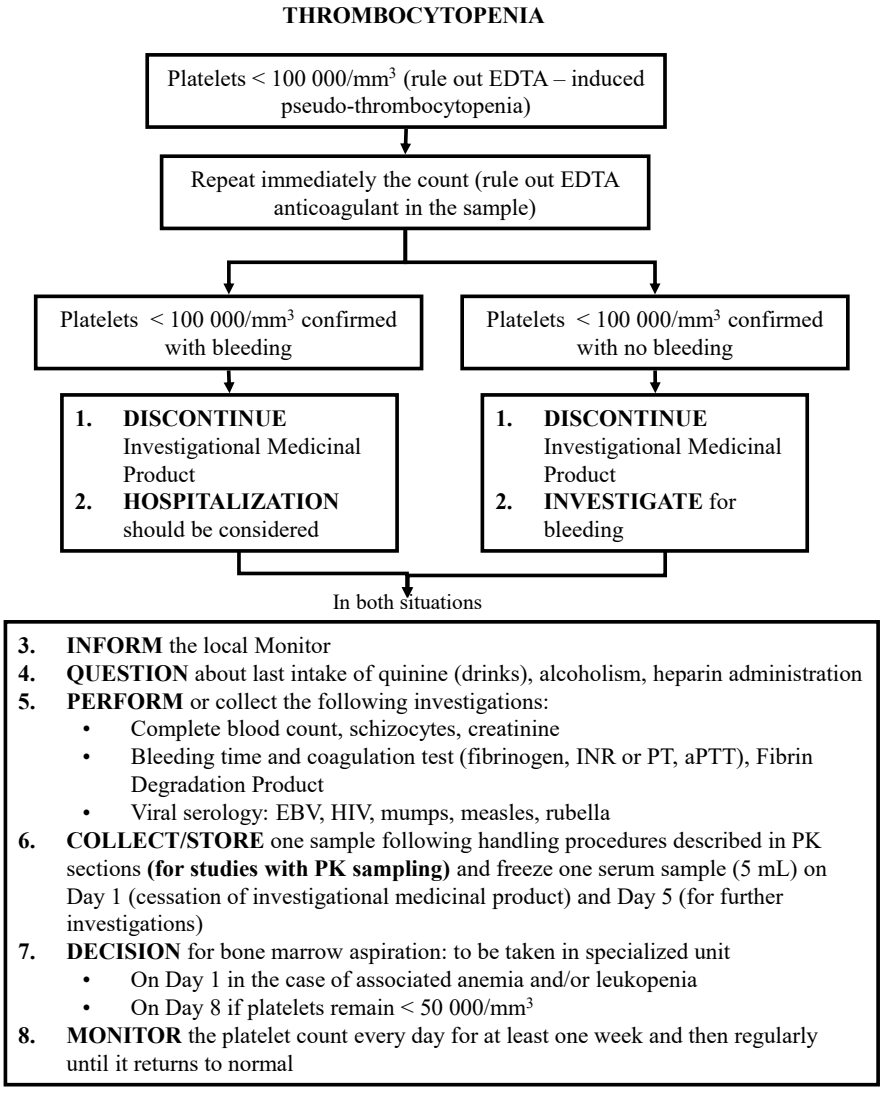
Neutropenia is to be recorded as AE only if at least one of the criteria listed in the General guidelines for reporting adverse events in Section 10.4.2 is met.

Neutropenia is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met

Due to single dose regimen, instructions regarding IMP discontinuation/resumption do not apply.

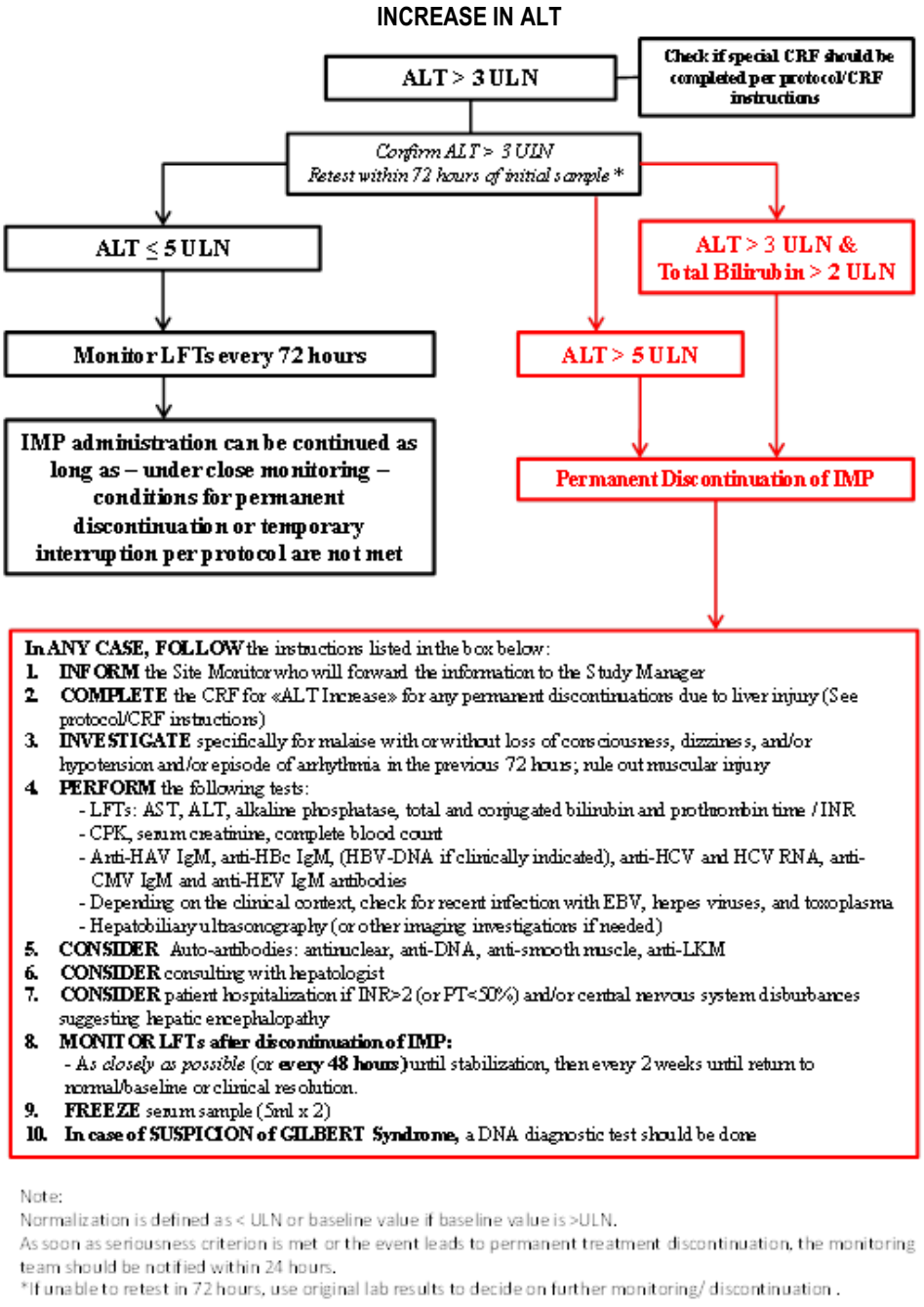
For patients with low platelets count (Platelets <100 000/ mm^3), after immediately repeating the count (rule out EDTA anticoagulant in the sample), the instructions from point 2 to 8 must be followed, if at least one of the following situations is present:

- If the confirmed decrease (repeat measure) is deemed by the investigator larger than expected due to underlying disease
- 50 000 ≤Platelets <100 000/ mm^3 confirmed with bleeding
- Platelets <50 000/ mm^3 confirmed



Thrombocytopenia is to be recorded as AE only if at least one of the criteria listed in the General guidelines for reporting adverse events in Section 10.4.2 is met.

Due to single dose regimen, instructions regarding IMP discontinuation/resumption do not apply.

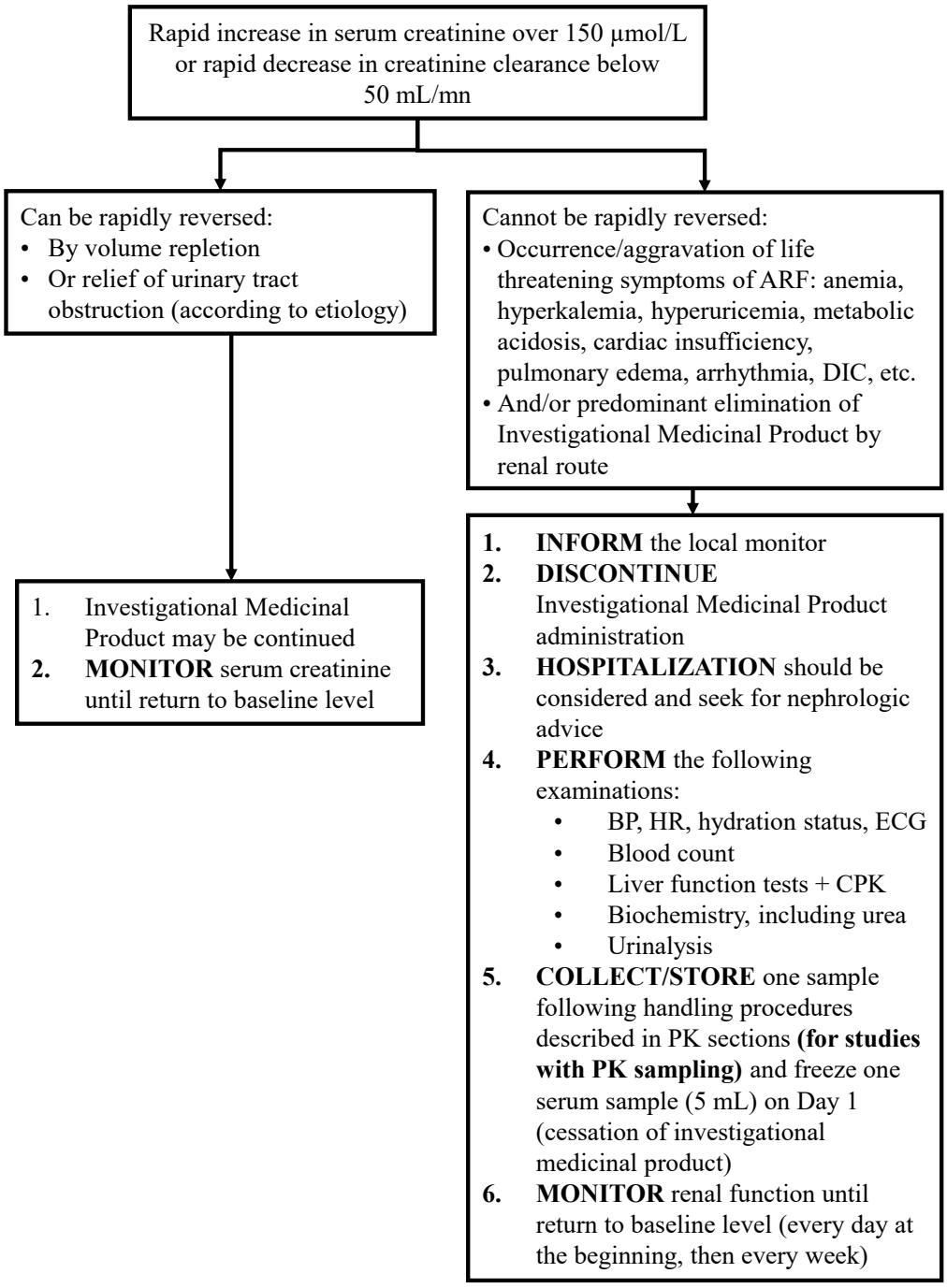


NOTE: ALT ≥3 ULN (IF BASELINE ALT <LN) OR ALT ≥2 TIMES THE BASELINE VALUE (IF BASELINE ALT ≥ULN) SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM (SEE SECTION 10.4.1.4, SECTION 10.4.5).

IN ADDITION, IF ALT < 3 ULN MEETS A SERIOUSNESS CRITERION, THE EVENT SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM.

Due to single dose regimen, instructions regarding IMP discontinuation/resumption do not apply.

ACUTE RENAL FAILURE

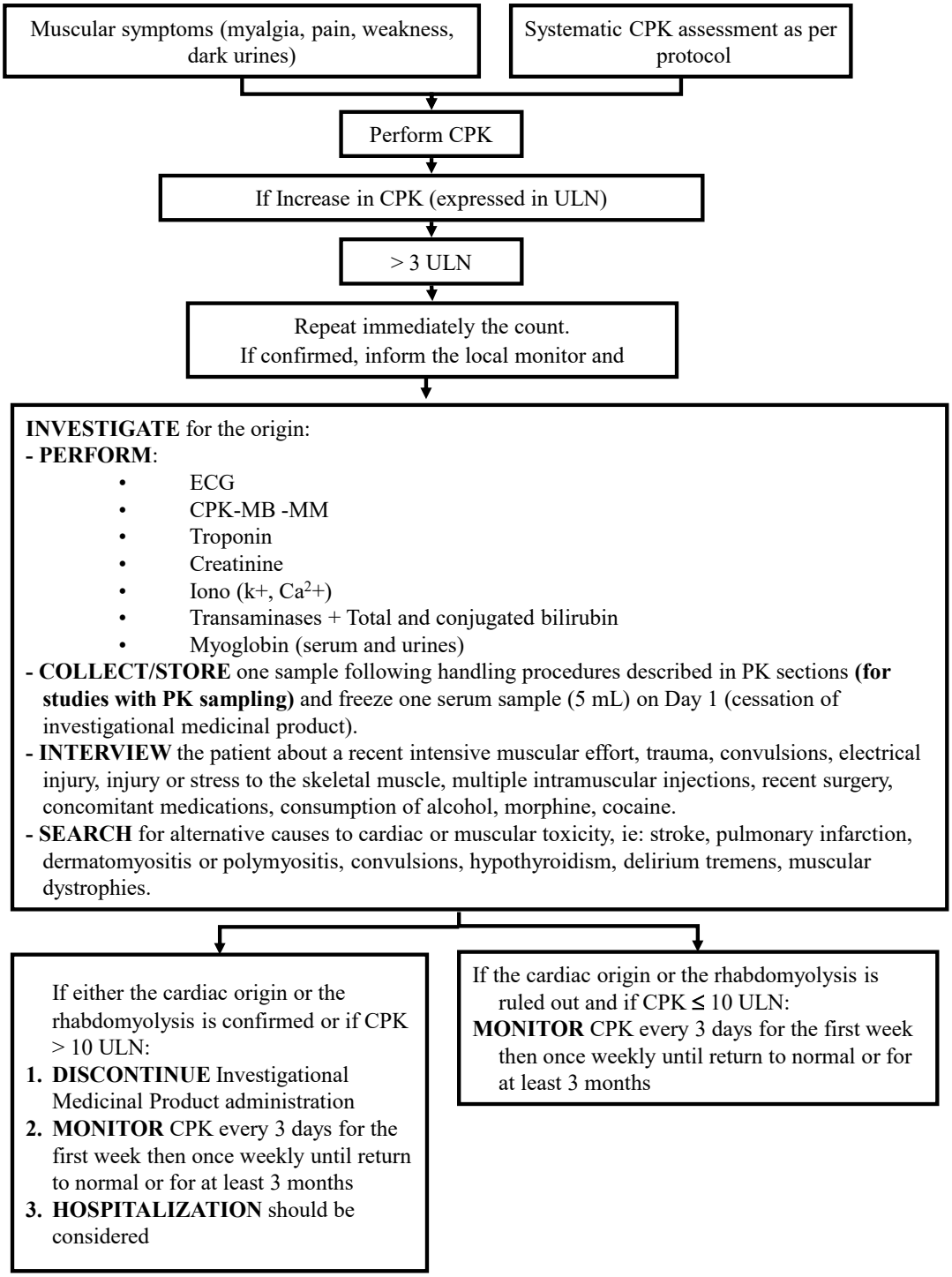


Acute renal failure is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met

Acute renal failure is to be recorded as AE only if at least one of the criteria listed in the General guidelines for reporting adverse events in Section 10.4.2 is met.

Due to single dose regimen, instructions regarding IMP discontinuation/resumption do not apply.

SUSPICION OF RHABDOMYOLYSIS



Suspicion of rhabdomyolysis is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met.

Suspicion of rhabdomyolysis is to be recorded as AE only if at least one of the criteria listed in the General guidelines for reporting adverse events in Section 10.4.2 is met.

Due to single dose regimen, instructions regarding IMP discontinuation/resumption do not apply.

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