NOVARTIS

Global Clinical Development - General Medicine

KAF156

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A Phase 2 interventional, multicenter, randomized open-label study to determine the effective and tolerable dose of KAF156 and Lumefantrine Solid Dispersion Formulation in combination, given once daily for 1, 2 and 3-days to adults and children with uncomplicated *Plasmodium falciparum* malaria

Statistical Analysis Plan (SAP) Addendum

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Document History – Changes compared to previous final version of SAP

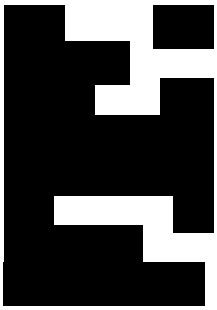
Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
28-May-2017	final in CREDI	N/A	N/A - First version	N/A
02-Jul-2018	Amendment 1	Updates during Mock shell finalization	Tail of KM plots	Section 2.1.1
			Definition of treatment failure and ACPR: Only P. falciparum asexual form is used	
			Subgroup categories defined in one section only	Section 2.2.1, 2.7.2.6
			Weight categroies define for each part separately. Body temperature using other than axilarry	Section 2.3.2
			Censoring rule for Patients reinfected with other species than P. falciparum added	Section 2.5.4.2
			Shift tables of LAB are deleted	Section 2.8.2
			[redacted]	
			Worst assessment will be selected for efficacy if multiple assessment within a visit window	Section 5.1.4
09-Aug-2018	Amendment 2	Updated prior to interim dry run	Make axillary equivalent temperature by subtracting 0.5^0C from a value and cut off as 38.0 ^{0}C for different routes	All applicable section
			Closest assessment will be selected for efficacy variables	Section 5.1.4 Section 2.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
15-Oct-18		No direct SAS procedure is available for calculating the treatment difference and 95% CI for K-M estimate	Clarified PPS - Valid PCR assessment required for late treatment failures between Day 8 and Day 29 Clarification is added	Section 2.5.4.2 is updated
6-Nov-18		Tables using summary of change from baseline in ECG variables is removed		
		To consider the partial dosing for calculating the compliance		Section 2.8.3
6-Nov-18		Handling Lab values beyond detection limit		
		Length exceeds the limit		Section 2.4.1
3-Jan-19		To be consistent with conversion of body temperature from axillary to other routes		
		Compliance is on full doses	Note is added	Section 2.8.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
7-1-2019				Section 2.1.1
			Section 2.1.1 is updated for the treatment header for PK run in cohort	
			Section 2.3.2 is updated for Body temperature categories	Section 2.3.2
				Sction 2.4.1
			Compliance definition is further clarified	
11-01-2019		LAB notable abnormality criterion to matched with standard templates	Table 2-2 updated to include additional notable criterion	Section 2.8.2
13-02-2019	Post Dry run 2	To allow the possibility for patients with late parasite clearance or missing data on Days 8, 9, or 15 to be classified as cured (clinical success)	Removed the condition that the parasite must be cleared by Day 7. Accordingly, changed the condition for the analyses of recrudescence and reinfection at Days 15, 29, and 43 from “parasite clearnce by Day 7” to “parasite clearance before Day 15”.	Sections 2.1.1, 2.5.4, 2.7.2
20-02-2019	Post Dry run 2	Due to the multiple assessments/day in treatment	Study day calculation is based on dosing date and time during treatment period	Section 2.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		period the study day calulcation is updated		
26-02-2019	Post dry run 2	PD ID INCL01B corresponds to ascent form for adolescent patients have been retired	PD ID is removed from the criterion for exclusion from the randomized set	Section 5.7
5-03-2019	Post dry run 2	Ngeative PCR results for positive blood smear sample	Negative PCR will categorize the patient as PCR corrected responder	2.1.1.2
10-03-2019	Post dry run 2	Exclude the patients from PPS received non antimalarial drugs which may impact on efficacy. Exclude patients having compliance <80% from PK set	Definition of PPS/PK SET and criterion for patients exclusion from PPS/ PKSET is updated 5-<10 kg category removed Average daily dosage = sum of actual doses taken in mg / planned number of days of treatment.	2.2, 5.7
27-03-2021	Before final DBL		Section deleted Table 5-10 is updated to clarify	2.3.2 Patient demographics and other

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				baseline characteristics
			Age category of <12 years is added	2.4.1 Study treatment / compliance
		All patients are >=10 Kgs. 5-<10 Kg category is not applicable		
		Formula for average daily dose is revised using planned number of days	[redacted]	5.13.1 and 5.1.3.2 Prior and post therapies dates imputation
			Sensitivity analysis is added	
		Imputation of missig prior/post therapies dates is combined with the concomitant medication dates	Sensitivity analysis is added	5.7 Rule of exclusion criteria of analysis sets
20-08-21				Section 2.3.2 Patient demographics and other baseline characteristics
30-Oct-21	Post final DBL	Anti malarial drugs between Day1 and Day 29 should be changed prior to Day 29 to include Day 1		Section 2.2.1, Subgroup of interest
		In Part A, 4 patients with		Section 2.3.2 Patient demographics and other baseline characteristics

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		age <12 years were recruited Replace patients with patients  To assess the impact of administration non-study antimalarial drugs on the PCR uncorrected response rate at D29 To assess the impact of new infections on the PCR corrected ACPR rate at D29		 2.7.2.2 Treatment failure related parameters 2.5.4 Supportive analyses

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List of abbreviations

AE	Adverse event
ACPR	Adequate clinical and parasitological response
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Data base lock
ETF	Early treatment failure
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IVR	Interactive Voice Response
IWR	Interactive Web Response
LCF	Late clinical failure
L.O.S.	Level of significance
LPF	Late parasitalogical failure
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
PK	Pharmacokinetics
PPS	Per-Protocol Set
qd	Qua'que di'e / once a day
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The purpose of Statistical Analysis Plan (SAP), is to describe the implementation of the statistical analysis which is planned in the protocol. The study has three parts: PK Run-in Part, Part A, and Part B. A single database for run-in part and Part A will be locked after the last patient last visit (LPLV) in Part A and before the first patient first visit (FPFV) in Part B. The interim assessment in Part A will be performed and is outlined in section 2.15 below. The clinical study report will be prepared after the final database lock (DBL) at the end of Part B on the basis of this SAP. This single SAP will be used for the analysis of data collected for the run-in part, Part A, Part B, and the pooled analysis of Part A and Part B together. A separate analysis plan will be prepared and executed by [redacted] for DMCs based on this SAP.

1.1 Study design

This will be a multicenter, open-label, randomized, parallel-group study in adults and children with confirmed and uncomplicated *P. falciparum* malaria.

The study has a PK Run-in Part and two subsequent parts: Part A and Part B.

PK Run-in Part:

Male and female adult/adolescent patients (≥ 12 years old and ≥ 35.0 kg) will be enrolled in the PK Run-in Part. 12 patients will be dosed with a single dose of 200 mg KAF156 and 960 mg LUM-SDF. Study procedures and assessments are the same as in the 1-day cohorts in Part A with rich PK.

Interim assessment after PK Run-in Part

For the patients in the PK Run-in KAF156 200 mg/LUM-SDF 960 mg cohort, PK analyses will be performed on the samples collected in the first 24 hours. The results will trigger the start of Part A with dosing as planned, or lead to a dose adaptation in Part A in case an interaction is shown between LUM-SDF and KAF156.

Part A:

Approximately 325 male and female adult/adolescent patients (≥ 12 years old and ≥ 35.0 kg) will be enrolled in Part A of the study.

At screening, eligible patients will be randomized into one of the seven cohorts, i.e., six KAF156 and LUM-SDF dose combinations and a control arm (see Figure 1-1), in 2:2:2:2:2:2:1 ratios:

- Cohort 1: KAF156 400 mg and LUM-SDF 960 mg once daily (QD) for 1 day
- Cohort 2: KAF156 800 mg and LUM-SDF 960 mg QD for 1 day
- Cohort 3: KAF156 400 mg and LUM-SDF 960 mg QD for 2 days
- Cohort 4: KAF156 200 mg and LUM-SDF 480 mg QD for 3 days
- Cohort 5: KAF156 400 mg and LUM-SDF 480 mg QD for 3 days
- Cohort 6: KAF156 400 mg and LUM-SDF 960 mg QD for 3 days

- Cohort 7: Coartem® twice a day (BID) for 3 days (dosing as per product label)

Randomization will be stratified by country in Part A.

Patients will be admitted to the hospital on Day 1. They will be dosed on either a) Day 1 alone or b) Days 1 and 2 or c) Days 1, 2 and 3 depending on the assigned study arm, and will remain in the hospital under close supervision until they are discharged by the investigator or designee on Day 4. At the discretion of the investigator, patients may stay additional days if needed. The patients will then be followed up at Days 5, 8, 15, 29 (primary analysis time point), and 43. Visits to assess safety and efficacy will be scheduled during the follow-up period as described in the schedule of assessments tables (Table 6-1, through Table 6-4) in the protocol. If malaria symptoms re-emerge outside the scheduled study visits, patients will be instructed to contact the investigator.

Rich pharmacokinetic (PK) sampling will be done in 6 patients each in Cohorts 1-4 and 6, and in 12 patients in Cohort 5 (see protocol Table 6-3), and sparse PK sampling will be done in the rest of the patients as well as in Cohort 7 (see protocol Table 6-4).

Interim assessment after Part A:

Upon completion of Part A, all the dosing groups will be evaluated in an interim assessment (IA) to determine the effective and tolerated KAF156/LUM-SDF dose combination for 3 days and for 1 to 2 days. The IA will be performed on selected endpoints which include, Polymerase Chain Reaction (PCR) corrected and uncorrected adequate clinical and parasitological response (ACPR) at Day 29, KAF156 and LUM-SDF blood exposures, incidence of adverse events (AEs), QTc, laboratory abnormalities, serious adverse events (SAEs), or any other endpoints that are deemed important for the IA. Dosing regimen and dosages in Part B will be informed by results from Part A.

Part B:

Approximately up to 175 children (2 to < 12 years old and ≥ 10.0 kg) with uncomplicated *P. falciparum* malaria will be randomized to up to three KAF156 and LUM-SDF dose combinations and the control arm in 2:1 ratios (2 patients for each KAF156 and LUM-SDF dose combination and 1 patient for control) depending on the outcome of the interim assessment in Part A.

Randomization will be stratified by country and age category at screening in Part B (2 to < 6, 6 to < 12 years).

Eligible patients will be enrolled into one out of the up to four dosing cohorts, i.e., up to three investigational drug dosing arms and a control arm (see protocol Figure 1-1). Dosing will be adjusted based on children's body weight similar to the adjustment of Coartem®.

- KAF156 and LUM-SDF: up to 3 cohorts selected depending on the outcome of Part A
- Coartem® BID for 3 days

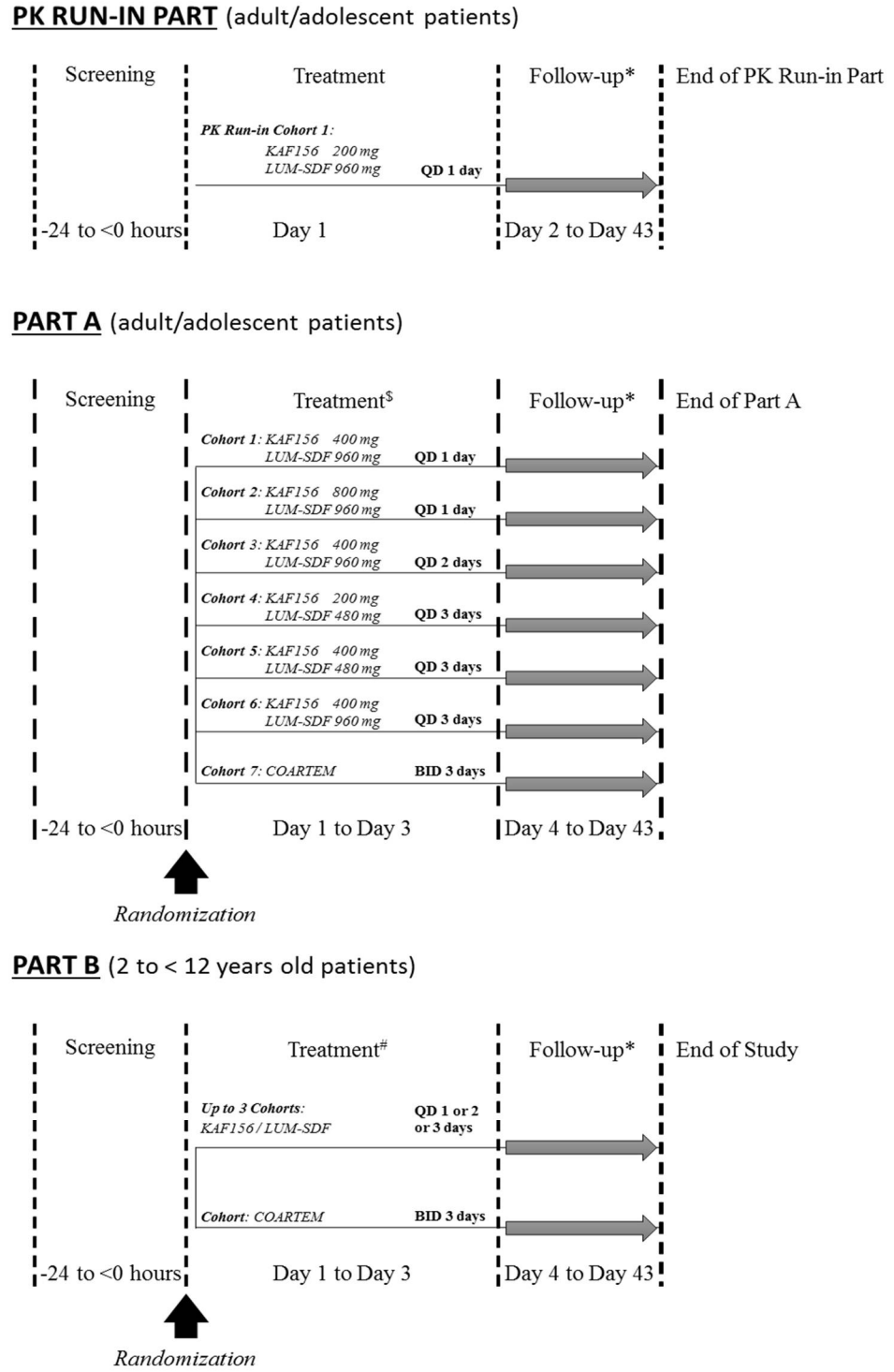
Before fully enrolling patients in Part B, 4-6 children in the age range of 6 to < 12 years will be enrolled first in Part B to confirm that KAF156 and LUM-SDF PK/drug exposure is consistent

with Part A and that the assumption in dosing is correct in these cohorts. Following confirmation of drug exposure in these children, the additional patients will be included in Part B of the study.

Study design, procedures and assessments are the same in Part A and Part B as described in Section 6 in the protocol.

The safety of entire study will be monitored by an Independent Data Monitoring Committee (DMC).

Figure 1-1 Study design



$ Dosages of KAF156 in Part A might be adapted based on PK Run-in results

Dosages and regimen of dosing in Part B will be informed by results from Part A

* During the follow-up period, rescue medication will be local standard at the discretion of the Investigator

QD: once daily; BID: twice a day

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints (PK Run-in Part, Part A and Part B)

Objective(s)	Endpoint (s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To determine the effective doses of KAF156 combined with LUM-SDF given daily over 1, 2 or 3 days for treatment of uncomplicated malaria caused by *P. falciparum*.	• PCR-corrected adequate clinical and parasitological response (ACPR) at Day 29 (i.e., 28 days post-dose) in Parts A and B. • Assessments of KAF156 exposure in the PK Run-in cohort to understand the impact of LUM-SDF on KAF156 exposure.
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the safety and tolerability of KAF156/LUM-SDF.	• Standard safety/tolerability assessments: AE incidence and severity, liver and kidney function tests and electrocardiogram (ECG) abnormalities.
• To further assess the effect of treatment with KAF156/LUM-SDF by assessing uncorrected ACPR and corrected ACPR at additional time points, as well as fever- and parasite clearance times.	• PCR-Uncorrected ACPR at Days 15, 29 and 43 (i.e., 14, 28 and 42 days post-dose). • PCR-corrected ACPR at Days 15 and 43 (i.e., 14 and 42 days post-dose). • Incidence rate of recrudescence and new infection at Days 15, 29 and 43. • Parasite Clearance time and Fever Clearance Times (PCT and FCT). • Proportion of patients with parasitemia at 12, 24, and 48 hours after treatment.
• To assess the key PK parameters of KAF156 and lumefantrine.	• PK assessments.

[redacted]

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by Novartis for the interim assessment and after final DBL using SAS version 9.4 according to the data analysis presented in section 9 of the study protocol which is also available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

Statistical analyses for PK run-in cohort, Part A, and Part B will be performed separately. For key efficacy and safety outcomes, pooled analysis will be performed by pooling Part B with corresponding cohorts in Part A to determine which KAF156 and LUM-SDF dose combination can be carried forward to Phase 3 studies. Unless described separately otherwise, the same statistical method will be used for separate analysis and pooled analysis.

For each cohort in Part B, a corresponding cohort in Part A will exist with matching dose and regimen. For statistical analyses and clinical study reporting, treatment group name (see Section 2.1.1), instead of cohort number, will be used for both parts and the pooled analysis which will include only those treatment groups with patients in both parts.

Data analyses required for the study Data Monitoring Committee (DMC) will be analyzed by the third party vendor [redacted]. The outline of the DMC analysis plan is presented in the DMC charter and will be detailed in a separate SAP based on this SAP.

Information on visit windowing, imputation rules and the methods of efficacy and safety analyses is given in the sections to follow and details will be provided, as applicable, in Appendix 16.1.9 of the CSR. This SAP covers the methods for: DMC meetings, planned interim analysis, and the final analysis.

Unless otherwise stated, summary tables/figures/listings will be on all patients included in the population under consideration.

Categorical data will be presented as frequencies and percentages. For continuous data, n, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented. Additionally, geometric mean will be presented for PK parameters which may be better described using the lognormal distribution.

Unless otherwise stated, p-values will be provided for two-sided alternative hypotheses and presented up to 4 significant digits after decimal place; confidence intervals will be presented up to 2 significant digits after decimal place.

Although randomization is stratified by country in part A and stratified by country and age category in part B, statistical analysis will not be stratified accordingly due to small sample sizes in each country/age category. For pooled analyses, study part (part A, part B) will be used as stratum.

2.1.1 General definitions

Study treatment: KAF156, Lumefantrine solid dispersion formulation (LUM-SDF), and Coartem®. KAF156 and LUM-SDF are part of investigation treatments whereas Coartem® will be served as control. They are referred to as study treatments in the document.

Treatment group name, instead of cohort number, will be used in statistical analyses and outputs. The following abbreviated treatment groups will be used as the headers in the CSR outputs:

- KAF200 mg/LUM960 mg-1D (for PK run-in part) or KAF200 mg/LUM960 mg-1D in case the description is too long
- KAF400 mg/LUM960 mg-1D
- KAF800 mg/LUM960 mg-1D
- KAF400 mg/LUM960 mg-2D
- KAF200 mg/LUM480 mg-3D
- KAF400 mg/LUM480 mg-3D
- KAF400 mg/LUM960 mg-3D
- Coartem

Baseline: The last measurement made prior to administration of the first dose of study treatment. Note this may include measurements taken on the day of randomization (e.g. lab, ECG, vitals). If a patient did not receive any dose of study treatment then the date at randomization date will be used as the date of first dose of study treatment.

Study day: Study day will be calculated with respect to the first dose of study treatment. The first day of administration of study treatment (first dose) is defined as Day 1. Day -1 will be the day before Day 1. Day 0 does not exist. Due to the multiple assessments collecetd more than once for a day in the treatment phase for some variables, the study day calulcation is based on the treatment start date and time.

For the assessments that are performed more than once for a day:

On or after Day 1 up to Day 3, study day =Integer (datetime of assessment – datetime of first dose of study treatment)/(60*60*24) + 1.

For assessments collected after Day 3, study day =date of assessment – date of first dose of study treatment + 1.

For assessments that are performed once for a day: study day =date of assessment – date of first dose of study treatment + 1.

For assessments collected prior to Day 1, study day = date of assessment - date of first dose of study treatment.

Tail of KM plots: Since the tail of KM plots after the day of last planned assessment is not reliable due to small numbers of patients at risk, the time to event will be reset to planned last day regardless of censoring.

2.1.1.1 Definition of treatment failures

Early Treatment Failures (ETF)

Patient will be classified as ETF upon meeting any of the following criterion

- Development of danger signs or severe malaria on Day 2, Day 3, Day 4 in the presence of parasitemia.
- Parasitemia on Day 3 higher than Day 1 count irrespective of axillary temperature.
- Parasitemia on Day 4 with axillary temperature ≥ 37.5°C.
- Parasitemia on Day 4 equals to or more than 25% of count on Day 1.

Late Clinical Failure (LCF)

Patient will be classified as LCF upon meeting any of the following criterion

- Development of danger signs or severe malaria on any day from Day 5 to Day 43 in the presence of parasitemia without previously meeting any of the criteria of early treatment failure.
- Presence of parasitemia and axillary temperature ≥ 37.5ºC on any day from Day 5 to Day 43 without previously meeting any of the criteria of Early Treatment Failure.

Late Parasitological Failure (LPF)

- Presence of parasitemia on any day from Day 8 to Day 43 and axillary temperature < 37.5ºC without previously meeting any of the criteria of Early Treatment Failure or Late Clinical Failure. Missing body temperature assessment in presence of parasitemia will be classified as LCF.

Note: If the temperature is measured using other routes, such as oral/tympanic/rectal, the corresponsding threshold for fever is 38.0ºC. Danger signs or severe malaria is recorded as adverse events. The adverse event start date of danger signs or severe malaria will be used in the determination of ETF and LCF. Only *P. Falciparum* asexual form is used for parasitemia/parasite in the assssments of treatment failure and ACPR in Section 2.1.1.2 below. The body temperature assessment closest to the blood smear assessment date will be used.

2.1.1.2 Definition of ACPRs

Uncorrected ACPR at Day X where X=15, 29, or 43

- A patient is considered as non-responder at Day X if the patient experiences an ETF, LCF from Day 5 to Day X, or LPF from Day 8 to Day X.
- A patient is also considered as non-responder if the parasite is not cleared by Day X unless the patient discontinues the study prior to Day X without ETF or LCF or LPF, in which case the response is considered as missing.
- A patient is considered as responder (Uncorrected ACPR) at Day X if the patient is not classified as a non-responder at Day X and the patient has a malaria blood film showing absence of parasite at Day X or later if Day X is missing.
- The response for a patient is considered as missing/undertermined if the patient is not classified as a non-responder and the malaria blood film result at Day X is missing and not followed by a subsequent negative result.

PCR-corrected ACPR at Day X where X=15, 29, or 43

- A patient is considered as non-responder at Day X if the patient experiences an ETF or LCF from Day 5 to Day 7.
- A patient is also considered as non-responder if the parasite is not cleared by Day X unless the patient discontinues the study prior to Day X without ETF or LCF or LPF, in which case the response is considered as missing,
- A patient is considered as non-responder at Day X if the patient has a parasite recrudescence from Day 8 to Day X
- A patient is considered as responder (corrected ACPR) at Day X if the patient is not classified as a non-responder by Day 7 and has a new infection or negative results from Day 8 to Day X based on PCR genotyping unless that the patient did not have parasites cleared prior to the new infection, in which case the patient is considered as non-responder.
- A patient is considered as responder at Day X if the patient is not classified as a non-responder at Day X and the patient has a malaria blood film showing absence of parasite at Day X or later if Day X is missing.
- The response for a patient is considered as missing/undertermined if
  - The patient, not classified as non-responder at Day X, has parasite present from Day 8 to Day X for which the PCR genotyping of recrudescence or new infection is not determined.
  - The patient is not classified as a non-responder at Day X and the malaria blood film result at Day X is missing and not followed by a subsequent negative result.

Note - The outcome of PCR-corrected ACPR and uncorrected ACPR at a given day is categorized as responder or non-responder to distinguish from failure used in early treatment

failure, late clinical failure or late parasitological failure. With this notation, ACPR rate is the proportion of responders.

Recurrence of parasitemia after 7 days is considered as non-responder for uncorrected ACPR. We reclassify such patient as responder for PCR-corrected ACPR if recurrence of parasitemia after 7 days is due to new infection. Whether the recurrence of parasitemia after 7 days is due to recrudescence or new infection is determined and provided by the central laboratory. Negative PCR will catgeorize the patient as PCR corrected responder.

The above defintions of ACPRs are purely based on the malaria blood film and PCR results without consideration for taking concomitant anti-malaria drugs. In statistical analyses, some responses may be overriden for patients who take concomitant anti-malaria drugs (see Sections 2.5 and 2.7).

Fever Clearance is defined (in patients with axillary temperature of >= 37.5°C at baseline) as the time of the first measurement of at least 2 consecutive axillary temperatures of < 37.5°C (or < 38.0°C for alternative routes) measured at least 24 hours apart.

Time to parasite clearance (PCT) is defined as time from the first dose until the first total and continued disappearance of asexual parasite forms which remained at least a further 48 hours

2.2 Analysis sets

Randomized set

All patients who are enrolled in the PK run-in cohort or randomized in Parts A and B. Unless otherwise specified, misrandomized patients will be excluded from the randomized set. For the PK run-in part, this set includes all patients with informed consent and treated with study medication.

Misrandomized patients, if identified from IRT, include patients who are screen-failures, but have been randomized by the investigator before eligibility was finally assessed or mistakenly, and have not been treated. If patients were re-screened and successfully randomized, they will be included in the randomized set according to the treatment assigned in the last randomization.

Note: There is no randomization in the PK run-in cohort. For this cohort, the more appropriate terminology is “Enrolled set”. However, ‘Randomized set’ is used for simplicity.

Full analysis set (FAS)

FAS will be comprised of all patients from Randomized set who take at least one dose of study treatment during the treatment period and whose baseline *P. Falciparum* asexual parasitemia count is greater than 0. Following the intent-to-treat principle, patients will be analyzed according to the treatment group assigned to at randomization.

Safety set (SAF)

Safety set includes all patients who take at least one dose of study drug during the treatment period. Patients will be analyzed according to treatment received. In particular, patient will be

analyzed in the same treatment group as randomized if s/he receives at least one dose of the study medication of that group.

Per-protocol set (PPS)

Per-protocol set will be comprised of patients in FAS who

- did not have any important protocol deviations
- took at least 80% of randomized study medication(s). If a patient vomited the original dose but did not vomit the replacement dose, the patient is considered as taking the dose of study medication. Since a partial compliance, such as 83%, etc., can be calculated based on the actual dosage taken (see Section 2.4.1), this allows patients assigned to KAF156 and LUM-SDF arms to take partial dosages which slightly deviates from the protocol.
- did not take non-study drug antimalarial medications prior to Day 29 unless experiencing any treatment failure (ETF, LCF, LPF) (e.g new infections between Day 8 and Day 29), and
- met at least one of the following criteria: (a) classified as treatment failure (including parasite not cleared) before Day 8 (see Section 2.1.1), (b) absent from parasitemia at Day 29 or later, (c) had valid PCR evaluations at baseline and at the time point with parasitemia using malaria blood film if parasitemia is present between Day 8 and Day 29, or (d) had parasitemia present on Day 8 or later without parasite clearance before Day 8.

Important protocol deviations for exclusion from PPS are specified in Table 5-9 and will be identified by the clinical team before database lock for each part.

PK analysis set

All patients in the safety analysis set who had evaluable pharmacokinetic parameter data and with at least 80% compliance to study medication and did not receive the concomitant prohibited medication which found to be change in the exposure that impacts interaction in PK parameters.

2.2.1 Subgroup of interest

The following subgroups will be used for descriptive summary of the selected efficacy and safety analyses . The details will be provided in the corresponding sections.

- Age groups as per section 2.3
- Baseline weight groups as per section 2.3
- Sex (male vs female)
- Region

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Medical history

Any condition entered on the *Relevant medical history / current medical conditions* CRF will be coded using the MedDRA dictionary. They will be summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary. Summary will also be provided on medical conditions that were active at the time of screening.

Medical conditions that are present after informed consent has been signed are collected in the Adverse event panel and will be summarized separately from adverse events.

The Medical History conditions captured on the eCRF "Protocol solicited medical history or medical history possibly contributing to liver dysfunction" will be tabulated separately.

History of use of alcohol will also be provided.

Unless otherwise specified, analyses will be based on the randomized set.

2.3.2 Patient demographics and other baseline characteristics

Demographic data and baseline disease characteristics will be descriptively presented and tabulated per treatment group, as well as overall, using randomized set and PPS. If many patients are excluded from randomized set, summary will also be provided for the FAS.

Following demographic variables will be summarized

- Age and age categories (for Part B: 2 to <6, 6 to <12 ; for PK run-in cohort and and Part A: <12, 12 to <18, 18 to <65, and ≥ 65, <18 vs ≥18 yrs)
- Sex (male, female)
- Patient child bearing status (able to bear children, premenarche, post menopausal, sterile of child bearing age)
- Race (Caucasian, black, Asian, native american, pacific islander, unknown, other)
- Ethnicity
- Body weight and weight categories (<35, 35 to <75 and >=75 kg for Part A and PK run-in cohort); (10 to <15, 15 to <25, 25 to <35 and >= 35 kg for Part B);(<15 , 15 to <25, 25 to <35, 35 to 75, >75 kg for Parts A+B)
- Body height (cm)
- BMI and BMI categories (<16, 16 to 25, >25) (Kg/m^2)

Following disease characteristics at baseline will be summarized

- Body temperature and categories (<37.5, 37.5 to <39, ≥39) (°C) for *(axillary)* and < 38.0°C, 38.0 to 39.5, ≥ 39.5 for other routes)

- Falciparum species: (P. Falciparum asexual forms, P. Falciparum gametocytes, P. Vivax, P. Ovale, P. malariae, P. Knowlesi, and Mixed-infection , n (%))
- P. falciparum density per micro ltr. and its categories (<1,000, 1,000 to <2,000, 2,000 to <5,000, 5,000 to <15,000, 15,000 to <50,000, 50,000 to <100,000, 100,000 to <150,000, >=150,000 parasites/μL; <100,000 /μL, ≥100,000 parasites /μL)
- Gametocytes counts /μL.

2.3.3 Patient disposition

The number of patients who screened and screening failures will be presented. In addition, the reasons for screen failures will be provided. The number and percent of patients who completed each epoch (treatment and follow up) and who discontinued each epoch prematurely (including the reason for discontinuation) will be presented for each treatment group and overall.

For each protocol deviation, the number and percent of patients for whom the deviation applies will be tabulated.

Randomized set will be used.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Number and percent of doses taken will be presented by treatment group and drug (KAF156, LUM-SDF, or Coartem®). The percentage will be calculated based on the planned number of doses per treatment group.

Planned number of doses in a treatment group= planned number of days of dosing x number of doses to be administered per day in that treatment group.

For example, planned number of doses is 3 for 'KAF156 400 mg and LUM-SDF 480 mg QD for 3 days' group, 6 for Coartem, etc.

In the percent calculation for KAF156/LUM-SDF based treatment groups, patient is considered to be dosed if s/he took any study drug regardless of vomiting or not.

Percent of doses taken (i.e. compliance) on a day will be calculated as actual dose administered /planned dose x 100% capped at 100% (if a compliance on a given day exceeds 100%, use 100%). Average compliance for a study drug will be calcualted as sum of the compliance for all days and divide by the number of day's. For KAF/LUM, compliance for combined dose will be the average compliance of both drugs.

In addition, percent of full doses taken will be calculated as actual number of full doses administered /planned number of doses x 100% where a patient is considered to be fully dosed if s/he took all study drug(s) in full dose.

Compliance will be categorized by < 80 % and >=80 % of full doses taken and summarized by treatment group.

Number and percent of patients with study drug vomiting and dose replacement will be presented by treatment group.

Average daily dosage and total dosage (in mg) of each study drug (KAF156, LUM-SDF, Artemether, Lumefantrine) will be summarized by treatment group. If a patient vomited the original dose and took a replacement dose, the replacement dose will be used to calculate the average.

Average daily dosage = sum of actual doses taken in mg / planned number of days of treatment.

For Coartem, the tablets taken by the patient are converted into mg based on the strength of tablet.

Note- If a patient vomited the original dose but did not vomit the replacement dose, the patient is considered as fully dosed. If a patient vomited the original dose and did not have a replacement dose or vomited both the original dose and the replacement dose, the patient is not considered as fully dosed.

Safety set will be used.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medications will be summarized in separate tables by treatment group.

Concomitant rescue and other anti-malarial medications will also be summarized by treatment group.

Note – rescue medications and non-study antimalarial drugs are the same. If they are used after discontinuation of study drug due to early treatment failure, late clinical failure or late parasitological failure then they should be considered as resue medications, otherwise, they are considered as other non-study drug antimalarial medications. Rescue medications will be captured along with other concomitant medications by the investigators under rescue medication category.

Prior medications are defined as drugs taken and stopped prior to first dose of study medication. Any medication given at least once between the day of first dose of study medication and the last day of study visit will be a concomitant medication, including those which were started pre-baseline and continued into the treatment period.

Prior and concomitant medications will be coded according to the latest version of WHO Drug Reference List dictionary which employs the ATC. The number and percentage of patients taking prior and concomitant medications will be summarized for each treatment by ATC class and preferred term (PT).

Number and percentages of the patients received prohibited prior and concomitant drugs will be summarized

Safety set will be used.

2.5 Analysis of the primary objective

The PK Run-in Part will be separately analyzed. The primary objective for the part is to investigate the pharmacokinetic interaction potential between KAF156 and LUM-SDF. The analyses of PK parameters of KAF156 and LUM-SDF are detailed in Section 2.9.

The primary efficacy objective in Part A is to determine the effective dose of KAF156 combined with LUM-SDF given daily over 1, 2, 3 days for treatment of uncomplicated malaria caused by *P. falciparum* in adults/adolescents. If there are multiple KAF156 and LUM-SDF dose combinations that are effective, tolerable and safe, the most effective dose combination(s) in the less frequent 1 to 2 days regimen and the most effective dose combination(s) in the 3 days regimen will be carried over to Part B. Up to 3 KAF156 and LUM-SDF dose combinations may be carried over to Part B.

The primary efficacy objective in Part B is to determine if the selected dose combination regimens (adjusted for body weight) from Part A are effective in children down to 2 years.

2.5.1 Primary endpoint

The primary efficacy variable is the PCR corrected Adequate Clinical and Parasitological Response (ACPR) at Day 29 (see Section 2.1).

2.5.2 Statistical hypothesis, model, and method of analysis

The statistical null hypothesis is that the ACPR rate at Day 29 is at most 80% with the alternative hypothesis that the ACPR rate at Day 29 is greater than 80%. The statistical hypothesis will be evaluated using the lower limit of 2-sided 95% exact confidence interval (CI) (Pearson-Clopper method) for the ACPR rate at Day 29. If the lower limit of 2-sided 95% exact confidence interval for the ACPR rate at Day 29 is greater than 80%, the null hypothesis will be rejected. The statistical hypothesis testing will be evaluated separately for each KAF156 and LUM-SDF combination in each part based on the PPS. There is no adjustment for multiplicity since this is an exploratory study.

2.5.3 Handling of missing values/censoring/discontinuations for primary endpoint analysis

Parasite assessments obtained within the protocol specified visit window for Day 29 (Day 25 to Day 33) will be considered as the assessment for Day 29.

No missing data are expected for the primary efficacy analysis based on PPS since patients who are not evaluable for the primary efficacy variable are excluded from PPS. See Section 2.5.4 for missing data handling for the supportive analysis using FAS.

2.5.4 Supportive analyses

The primary efficacy variable will be performed based on the FAS using the statistical method specified in Section 2.5.2.

Primary efficacy variable will be handled additionally for those patients who are excluded from the PPS as follows:

- Presence of parasitemia which cannot be determined to be recrudescent or reinfection due to missing PCR data will be counted as non-responders (from the day of test)
- Missing/undertermined responses at Day 29 due to missing blood smear data at the visit will be counted as non-responders unless there is a later blood smear test indicating no parasitemia
- Patients who received non rescue anti-malarial medication will be considered in the analysis as if they had not taken the antmalarial drug.
  - Note: These patients did not experience any treatment failure (ETF, LFT, or LPF). In case that non-PPS patients who experienced treatment failure, they will be included as non-responders if they received rescue medication for the treatment of P. falciparum malaria due to recrudescent or as responder for PCR corrected ACPR if they received rescue medication for treatment of a new infection on Day 8 or later.

For exploratory purpose, 2-sided 95% confidence intervals for the difference in ACPR at Day 29 between each KAF156/LUM-SDF treatment group and Coartem® will be constructed using the Wilson uncorrected method.

Let

a = # patients with responders in investigational arm

c = # non-responders in investigational arm

m = sample size of investigational arm (a+c)

b = # responder in control arm

d = # in control arm

n = sample size of control arm (b+d)

$\theta = \pi_1 - \pi_2$ is the treatment difference

$\hat{\theta} = {}^{a}/_{m} - {}^{b}/_{n}$ is estimated treatment difference

Method based on the Wilson score method for the single proportion, without continuity correction:

$L = \hat{\theta} - \delta$, $U = \hat{\theta} + \varepsilon$ where

$$\delta = \sqrt{\{(a/m - l_1)^2 + (u_2 - b/n)^2\}} = z\sqrt{\{l_1(1 - l_1)/m + u_2(1 - u_2)/n\}}$$

$$\varepsilon = \sqrt{\{(u_1 - a/m)^2 + (b/n - l_2)^2\}} = z\sqrt{\{u_1(1 - u_1)/m + l_2(1 - l_2)/n\}}$$

l_1 and u_1 are the roots of $|\pi_1 - a/m| = z\sqrt{\{\pi_1(1 - \pi_1)/m\}}$, and l_2 and u_2 are the roots of $|\pi_2 - b/n| = z\sqrt{\{\pi_2(1 - \pi_2)/n\}}$.

where z is the standard normal deviate associated with 5% level of significance (l.o.s.) two sided.

In planned analysis of PCR corrected ACPR at Day 29, PCR corrected ACPR rate at Day 29 was to be calculated by considering patients with new infections prior to Day 29 as PCR corrected ACPR. In order to assess the impact of new infections on the PCR corrected ACPR rate, two sensitivity analysis will be performed. In the first analysis, PCR corrected ACPR rate will be recalculated by excluding the patients with new infections occurring prior to Day 27. It is seen that new infections were reported more on Day 29 visit compared to prior to Day 29 visit. In another sensitivity analysis, patients with new infections occurring up to Day 29 will be excluded and PCR corrected ACPR rate will be recalculated in the remaining patients. Analyses will be based on Per-protocol set for PK Run-in, Part A and B.

2.5.4.1 Analysis of PCR-corrected ACPR rate using Kaplan-Meier method

For the FAS, the proportion of patients with PCR-corrected ACPR at Day 29 and 95% CI will be also estimated using the Kaplan-Meier method (Stepniewska and White 2006 and WHO 2015)

Event = PCR-corrected non-responder during the study (same as at Day 15, Day 43, See Section 2.1). The event time is the first time when the patient becomes a non-responder based on PCR-correction. If a patient parasite is not cleared at all, Day 7 is considered as the event time.

The PCR-corrected responder rate at Day 29 is estimated by the survivor function at Day 29 using the Kaplan-Meier method.

Rule for censoring:

The following censoring rules will be applied to the patients who were not non-responder

- Patients who had a new infection (i.e., reinfection) with *P. falciparum* or other species without *P. falciparum* recrudescence on or after Day 8 will be censored at the first time of the PCR that indicate the infection or blood smear with other species;
- Patients who received non-rescue antimalaria medication for other infections, such as *P. falciparum* gametocytes, will be censored at the first time of antimalaria medication;
- Patients who have parasites at Day 8 or later but cannot be determined as recrudescence or new infection due to missing PCR genotyping will be censored at the time of the first malaria blood film with presence of parasites on or after Day 8.
- other patients not classified as non-responder will be censored at the time of last parasitemia assessment.

A two-sided 95% CI for the difference in proportion of responders between each KAF156/LUM-SDF combination treatment group and Coartem® will be calculated based on the variance of individual proportion using the Greenwood formula.

2.5.4.2 Analysis of uncorrected ACPR rate using Kaplan-Meier method

For the FAS, the proportion of patients with uncorrected ACPR at Day 29 and 95% CI will be also estimated using the Kaplan-Meier method (Stepniewska and White 2006 and WHO 2015)

Event = PCR-uncorrected non-responder during the study (same as at Day 15, Day 43, See Section 2.1). The event time is the first time when the patient becomes a non-responder without PCR-correction. If a patient parasite is not cleared at all, Day 7 is considered as the event time.

The uncorrected ACPR rate at Day 29 is estimated by the survivor function at Day 29.

Rule for censoring:

The following censoring rules will be applied to the patients who were not non-responders

- Patients who cleared the initial infection by Day 7 and are re-infected with species different than *P. Falciparum* will be censored at the time of re-infection.
- Patients who received non-rescue anti-malaria medication will be censored at the first time of anti-malaria medication;
- other patients will be censored at the time of last parasitemia assessment.

An asymptotic two-sided 95% CI for the difference in proportion of responders between each KAF156/LUM-SDF combination treatment group and Coartem® will be calculated from the z-test statistic distribution based on the variance of individual proportion using the Greenwood formula.

The confidence interval will be constructed as: $(r_k - r_C) \pm Z_{\alpha/2} * SE_d$,

where,

r_T = Kaplan-Meier estimate for the investigational group at time t,

r_C = Kaplan-Meier estimate for the control group at time t,

$SE_d = \sqrt{(SE_k^2 + SE_C^2)}$,

SE_T = estimated standard error for the investigational group based on Greenwood's formula,

SE_C = estimated standard error for the control group based on Greenwood's formula,

$Z_{\alpha/2}$ = z-statistic = probit(1- α /2) from a normal distribution function,

α = 0.05.

2.6 Analysis of the key secondary objective

There is no key secondary objective in this study.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

Secondary efficacy variables include:

1. PCR-corrected ACPR at Days 15 and 43;
2. Uncorrected ACPR at Days 15, 29, and 43;

3. Proportion of patients with parasitemia at 12, 24, and 48 hours after treatment;
4. Time to parasite clearance (PCT), defined as time from the first dose until the first total and continued disappearance of (*P. Falciparum)* asexual parasite forms which remained at least a further 48 hours;
5. Time to fever clearance (FCT), defined as time from the first dose until the first time the axillary body temperature decreased below and remained below 37.5°C axillary or 38.0°C oral/tympanic/rectal for at least a further 24 hours;
6. Proportion of patients with early treatment failure (ETF);
7. Proportion of patients with late clinical failure (LCF);
8. Proportion of patients with late parasitological failure (LPF);
9. Incidence rate of recrudescence and reinfection at Days 15, 29 and 43.

Analyses of ACPRs (PCR corrected or uncorrected) will be based on the FAS and PPS. Analyses of other secondary efficacy variables will be based on the FAS.

2.7.2 Statistical hypothesis, model, and method of analysis

There are no pre-specified hypotheses for secondary endpoints. Model, method of analysis, and handling of missing values/censoring/discontinuations are presented in the following sub-sections by topic.

2.7.2.1 PCR-corrected ACPR and uncorrected ACPR

At each visit, the ACPR rate with 95% confidence intervals will be provided using Pearson-Clopper method for each treatment group.

Handling of missing values/censoring/discontinuations

Data will be handled as follows for ACPRs (PCR corrected or uncorrected):

- Presence of parasitemia which were determined to be reinfection on Day 8 or later will be counted as responders for PCR corrected ACPR and as non-responder for PCR uncorrected ACPR from the day of test
- Presence of parasitemia which cannot be determined to be recrudescent or reinfection due to missing PCR data will be counted as non-responders from the day of test
- Missing/undertermined responses at a visit due to missing blood smear data at the visit will be counted as non-responders (PCR corrected or uncorrected) unless there is a later blood smear test indicating no parasitemia
- Patients who received non rescue anti-malarial medication will be considered in the analysis as if they had not taken the antmalarial drug

In addition, PCR-corrected and uncorrected ACPR rate will be calculated and plotted using the Kaplan-Meier method for each treatment group in the FAS (see Section 2.5.4).

2.7.2.2 Treatment failure related parameters

For the following parameters, 95% confidence intervals will be provided for each treatment group using the Pearson-Clopper method:

- proportion of patients with parasitemia at 12, 24, and 48 hours after treatment
- proportion of patients with early treatment failure (ETF)
- proportion of patients with late clinical failure (LCF)
- proportion of patients with late parasitological failure (LPF)

The above parameters will be determined using the uncorrected asexual parasite counts.

In addition, patients whose outcome status cannot be determined due to incomplete/missing data will be excluded from analysis. Especially, the denominator is the number of patients who experience treatment failure or have malaria blood film result at Day 43 for LCF and LPF.

In planned analysis of PCR uncorrected ACPR at Day 29, administration of non-study antimalarial drugs without treatment failures was not considered. A sensitivity analysis will be performed to assess the impact of administration non-study antimalarial drugs on the PCR uncorrected response rate. Proportion of patients with PCR uncorrected ACPR at Day 29 with 95% CI will be re-calculated by considering the patients receiving non-study antimalarial drugs if received before Day 29 without being treatment failures as non-responder using FAS for PK Run-in, Part A and B. Patients who received concomitant prohibited non-malaria medications with potential impact on efficacy/antimalarial activity (PROH01b) before the Day 29 visit without being treatment failures will be considered as as non-responder also.

2.7.2.3 Parasite clearance time (PCT) and fever clearance time (FCT)

Descriptive statistics (mean, standard error, median, quartiles) will be presented using the Kaplan-Meier method. Kaplan-Meier curves will be provided.

PCT will be calculated based on uncorrected asexual parasite counts. Patients without parasite clearance for whatever reason will be censored at the time of last parasite assessment. Patients who were enrolled on the basis of history of fever and did not subsequently have a fever at pre-dose will not be included in the analysis of FCT. Patients without fever clearance for whatever reason will be censored at the time of last temperature assessment. Patients who received any antimalarial medication (including rescue medication) before (parasite or fever) clearance will be censored at the first use of antimalarial medication. The difference between each test group and control will be evaluated using a log-rank test. Patients who did not experience a clearance will be censored at the time of last relevant assessment (parasite or fever). For the pooled analysis, the log-rank test will be stratified by Part.

2.7.2.4 Time to event analysis for Recrudescence

Recrudescence is defined as 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 PCR analysis.

Incidence rates of recrudescence at Days 15, 29 and 43 will be estimated by the Kaplan-Meier method based on the subset of FAS patients who have clearance of initial infection before Day 15.

Time to event (recrudescence) will be calculated from the time of first study medication to the date of first event if a patient experience the event and be censored at the time of last parasite assessment if a patient does not experience the event.Undertermined treatment failures due to missing PCR data will be considered as censored at the time of treatment failure.

2.7.2.5 Time to event analysis for reinfection

Reinfection is defined as appearance of asexual parasites after clearance of initial infection with a genotype different from those parasites present at baseline. Reinfection must be confirmed by PCR analysis.

Incidence rates of reinfection at Days 15, 29 and 43 will be estimated by the Kaplan-Meier method based on the subset of FAS patients who have clearance of initial infection before Day 15.

Time to event (reinfection) will be calculated from the time of first study medication to the date of first event if a patient experiences the event and be censored at the time of last parasite assessment if a patient does not experience the event. Indetermite treatment failures due to missing PCR data will be considered as censored at the time of treatment failure.

2.7.2.6 Pooled efficacy analyses

PK run-in part will not be pooled in the pooled efficacy analysis. The following additional analyses will be performed on pooled Part A and Part B (and pooled PK run-in cohorts, if available):

- For PCR corrected and uncorrected ACPR rates, the treatment differences versus control will be evaluated using a Mantel-Haenszel estimate of the common risk difference stratified by Part (see SAS manual version 13.2 Pages 2681-2682, 2014).
- For PCT and FCT, the difference between each test group and control will be evaluated using a stratified log-rank test (stratified by part).
- In addition, between treatment differences among the following KAF156 and LUM-SDF combinations will be evaluated to support the contribution of individual component for Part A:
    - KAF800 mg/LUM 960 mg-1D vs KAF400 mg/LUM 960 mg-1D
    - KAF200 mg/LUM 480 mg-3D vs KAF400 mg/LUM 480 mg-3D
    - KAF800 mg/LUM 960 mg-1D vs KAF400 mg/LUM 960 mg-2D
    - KAF400 mg/LUM 960 mg-3D vs KAF400 mg/LUM 480 mg-3D

PCR corrected/uncorrected ACPRs at Day 29, PCT, and FCT will be summarized descriptively by the following subgroups

- Age groups as per section 2.3
- Baseline Weight groups as per section 2.3
- Sex (male vs female)
- Region

2.8 Safety analyses

All safety analyses will be performed using the safety set. Safety data for PK run-in cohort will be summarized separately. Part A and Part B will be pooled for selected safety analysis.

2.8.1 Adverse events (AEs)

The number and percent of patients with treatment emergent adverse events will be presented. The treatment emergent adverse events (events started on or after the first dose of study medication or events present prior to the first dose of study medication but increased in severity based on preferred term) will be summarized by primary System Organ Class (SOC) and Preferred Term (PT).

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having at least one AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity (Toxicity grade) and for study treatment related AEs. If a patient reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

The MedDRA version used for reporting the adverse events will be described in a footnote.

The most common adverse events reported (≥ z % in any group for each preferred term in the table by SOC and PT) will be presented in the clinical study report by descending frequency according to its incidence in overall group starting from the most common event. Here threshold value z is set to 5 (%) but it may be updated following review of the dry run outputs.

Separate summaries will be provided for deaths, serious adverse events, severe malaria, other significant adverse events leading to treatment discontinuation and adverse events leading to dose adjustment.

Serious adverse events in screening phase will be flagged in data listing due to rare frquency.

Patients who experienced a grade 3 or grade 4 AE will be summarized.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

Number of deaths resulting from SAEs suspected to be related to study treatment and number of deaths resulting from SAEs irrespective of causality will be provided.

The adverse events and SAEs pooled from Parts A and B will be summarized overall and for the following subgroups.

- Age groups as per section 2.3
- Baseline Weight groups as per section 2.3
- Sex (male vs female)
- Region

Algorithms for date imputations is provided in Appendix 5.

2.8.1.1 Adverse events of special interest / grouping of AEs

The adverse events of special interest are defined in the Case retrieval Sheet (CRS) which is updated for each MEDDRA dictionary. The CRS data are stored in RDCRS SAS dataset corresponding to a subset of eCRS SAS view for which the following filtering criteria are applied

-Drug code = KAF156

-the latest version of MedDRA at the time of final database lock.

-End date is null (this means this is the latest CRS version). Potential risks based on the current CRS are listed in Table 2-1.

The number and percent of patients with these special AEs will be summarized. In addition, listings of related arverse events will be provided.

Newly occurring liver enzyme abnormalities and QTcF abnormalities will be summarized (see Sections 2.8.2 and 2.8.3.1)

Table 2-1 List of safety topics of interest

Safety Topic Of Interest	SOC	Search Criteria Details	MedDRA Code	MedDRA Term	MedDRA Level	MedDRA Qualifier
Gastrointestinal tolerability	Gastrointestinal disorders		20000140	Gastrointestinal nonspecific symptoms and therapeutic procedures (SMQ)	MQ2	BROAD
Bradycardia	Cardiac disorders		90003924	Bradycardia [KAF156] (CMQ)	NMQ1	
Gastrointestinal bleeding and ulceration	Gastrointestinal disorders		90003929	Gastrointestinal bleeding and ulceration [KAF156] (CMQ)	NMQ1	
Renal tubular necrosis	Renal and urinary disorders		90003925	Renal tubular necrosis [KAF156] (CMQ)	NMQ1	
Thyroid hypertrophy and hyperplasia	Endocrine disorders		90003926	Thyroid hypertrophy and hyperplasia [KAF156] (CMQ)	NMQ1	
Hepatotoxicity (GenMed)	Hepatobiliary disorders	ALT/AST > 3 ULN; ALP > 2 ULN; TBL>1.5 ULN; ALP >3 ULN and TBL>2 ULN; ALT/ AST > 3 ULN and TBL>2 ULN; ALT/AST > 3 ULN and TBL >= 2 ULN and ALP <2 ULN'	20000006	Drug related hepatic disorders – comprehensive search (SMQ)	MQ2	BROAD
QTc prolongation	Cardiac disorders	Number of pts with notable QTcF, those with QTcF>500 msecs, or increase by >=60 msecs over baseline. Sustained ventricular tachycardia lasting 30 sec or more, or ventricular fibrillation	20000001	Torsade de pointes/QT prolongation (SMQ)	MQ1	BROAD

Hematological disorders	Blood and lymphatic system disorders		20000027	Haematopoietic cytopenias (SMQ)	MQ1	BROAD
Antimalarial drug resistance	Infections and infestations		90003928	Anti-malarial drug resistance [KAF156] (CMQ)	NMQ1	
Drug – Drug Interactions	General disorders and administration site conditions		90000024	Interactions (PSUR) [STANDARD] (NMQ)	NMQ1	

2.8.2 Laboratory data

Descriptive statistics will be generated for all clinical laboratory tests performed (actual values and changes from baseline) for three groups of laboratory tests (hematology, clinical chemistry and urinalysis) by laboratory test and treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value

The following laboratory parameters will be analyzed for hematology test group: hemoglobin, platelets, white blood cell count, Reticulocytes, Haptoglobin, hematocrit, red blood cell (RBC) count, lymphocytes, lymphocytes (%), monocytes, monocytes (%), eosinophils eosinophils (%), neutrophils, neutrophils(%) , basophils, and basophils (%) .

The following laboratory parameters will be analyzed for Biochemistry test group: creatinine, total bilirubin (TBL), direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose, blood urea nitrogen (BUN). Sodium, potassium, calcium, creatinine, uric acid, gamma glutamyltransferase (GGT), magnesium, phosphate, chloride, and total protein, albumin, INR, Thyroid Stimulating hormone (TSH), Thyroxine Free T4.

Box plot for direct platelet count normalized using ULN (upper limit of normal) will be provided by timepoint and treatment group. Similarly, box plot for biochemistry parameters will also be provided by timepoint and treatment group. These Box plots will be presented using normalized values based on ULN and LLN (lower limit of normal) for all parameters with the exception of GGT, ALT, ALP, AST, BUN, direct bilirubin, total bilirubin Creatinine, and Urate, which are normalized using ULN only.

For liver enzymes (ALT, AST, etc.), the shift table of CTCAE grades relative to baseline will be provided. Summary with frequency and percentage of patients with liver related events as defined in Table 2-2 will be provided by treatment:

Table 2-2 Liver-related events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN; > 20XULN
AST	>3xULN; >5xULN; >8xULN >10xULN; >20XULN
ALT or AST	>3xULN; >5xULN; >8xULN >10xULN>20XULN
ALT or AST and TBL	ALT or AST > 3 × ULN and TBL > 2 x ULN ALT or AST > 5 × ULN and TBL > 2 x ULN ALT or AST > 10 × ULN and TBL > 2 x ULN
TBL	>1.5xULN, >2xULN, >3XULN
ALP	>2xULN, >3xULN
ALP & TBL	ALP >3xULN & TBL >2xULN
(ALT or AST) & TBL & ALP	ALT or AST >3xULN & TBL >2xULN & ALP <2xULN (**Hy's Law**)

Listing of patients with the following renal related laboratories will be provided:

- Serum creatinine increase 25 – 49% compared to baseline

- Serum creatinine increase ≥ 50% compared to baseline
- New dipstick proteinuria ≥ 1+
- New dipstick hematuria ≥ 1+

For urinalysis, frequency tables will be presented. Number and percent of patients in each category will be presented for each visit.

Urine pregnancy data will be summarized by visit.

Laboratory measurements, which are recordred as below the assay detection limits, will be imputed as half of the detection limit; and that above the detection limit will be impued as detection limit, for the summary statistics.

2.8.3 Other safety data

2.8.3.1 ECG and cardiac imaging data

The following quantitative variables will be summarized for averaged triplicate ECG: heart rate, RR interval, PR interval, QRS interval, QT interval, QTcB (QT interval corrected for heart rate according to Bazett) and QTcF (QT interval corrected for heart rate according to Fredericia).

Descriptive summary statistics for the change from baseline for each post-baseline visit will be performed by ECG parameters and treatment group.

Patients with notably high QT, HR and fever (≥37.5 °C for *axillary* or ≥ 38.3°C for other routes) will be provided.

To assess the temporal correlations mean change of QTcF over time, mean change of ECG HR over time, mean change of temperature over time, and PK concentration of KAF156 and lumefantrine over time will be plotted with all panels aligned on the x-axis (Time after dosing).

QTc will be summarized categorically by computing the number and percentage of patients at each time point and at the maximum post baseline value with following:

- QT, QTcF, or QTcB
  - > 450 and ≤ 480 ms
  - > 480 and ≤ 500 ms
  - > 500 ms
  - Increase from Baseline of ≥ 30 ms to < 60ms
  - Increase from Baseline of ≥ 60 ms
- HR for age ≥18 years
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- HR for age <18 years
  - > upper limit of normal (ULN) defined in Table 2-3
  - < lower limit of normal (LLN) defined in Table 2-3
- PR

- Increase from baseline >25% and to a value > 200 ms
- New value of > 200 ms

- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - > 120 ms

Table 2-3 Normal heart rates (resting) by age

Age (years)	Normal range bpm
1 - ≤ 3	70 - 110
3 - ≤ 6	65 -110
6 - ≤12	60 -95
>12	55 -85

Source: Nelson Textbook of Pediatrics, 18th Edition

A line plot by patient (Spaghetti plot) will be provided by visit and treatment group.

In addition, shift tables comparing baseline ECG results (normal, abnormal, not available, total) with the post-baseline results will be provided by visit and at the worst post-baseline result (normal, abnormal, not available, total).

A listing of all newly occurring or worsening abnormalities as compared with baseline will be provided, as well as a by-patient listing of all quantitative ECG parameters.

2.8.3.2 Vital signs

The following quantitative variables will be summarized: Weight (kg), Temperature (°C), Pulse (beats/min), Supine systolic blood pressure (mmHg) and Supine diastolic blood pressure (mmHg).

Analysis in vital sign measurement using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed by vital sign and treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline values and will be calculated as:

Change from baseline = post-baseline value – baseline value

As body temperature is being measured using different routes, in order to harmonize all temperature values, for summaries a correction will be made to methods other than axillary as follows.

Body temperature (axillary equivalent) = value (oral/tympanic/rectal) - 0.5 degrees (°C).

The number and percentage of patients with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in Table 2-4 below.

Table 2-4 Criteria for notable vital sign abnormalities

Vital sign (unit)	Notable abnormalities
Systolic blood pressure (mmHg) for age ≥18 years	≥ 180 mmHg/≤ 90 mmHg with increase/decrease from baseline of ≥ 20 mmHg
Systolic blood pressure (mmHg) for age <18 years	> ULN or < LLN defined in Table 2-5
Diastolic blood pressure (mmHg) for age ≥18 years	≥ 105 mmHg/≤ 50 mmHg with increase/decrease from baseline of ≥ 15 mmHg
Diastolic blood pressure (mmHg) for age <18 years	> ULN or < LLN defined in Table 2-5
Pulse (beats/min) for age ≥18 years	≥ 120 bpm/≤ 50 bpm with increase/decrease from baseline of ≥ 15 bpm
Pulse (beats/min) for age <18 years	> ULN or < LLN defined in Table 2-3
Temperature (°C)	>=37.5 (axillary) or >=38.0 (other routes)
Weight	decrease > 7% from Baseline increase > 7% from Baseline

A listing of all newly occurring or worsening abnormalities as compared with baseline will be provided, as well as a by-patient listing of all vital signs.

Table 2-5 Normal blood pressure by age

Age (years)	Normal range systolic (mmhg)	Normal range diastolic (mmhg)
1 - ≤ 3	90-105	55-70
3 - ≤ 6	95-110	60-75
6 - ≤12	100-120	60-75
>12 - <18	110-135	65-85

Source: Nelson Textbook of Pediatrics, 18th Edition

2.9 Pharmacokinetic endpoints

PK concentrations below the limit of quantification will be treated as zero in summary statistics and for the calculation of pharmacokinetic parameters by non-compartmental analysis. Descriptive statistics of pharmacokinetic parameters will include arithmetic and geometric (means, standard deviation (SD), median, minimum and maximum, etc). In the study rich PK data will be collected from subset of patients whereas all other patient will provide sparse PK samples. A separate PK analysis will be performed for patients providing rich PK data. Parameters such as AUCinf, AUClast, AUC0-t, Cmax and Tmax may be reported for the patients with rich PK data using non-compartmental method of analysis (using Phoenix 6.4 or higher). 2-sided 90% confidence intervals for $AUC_{0\text{-}24h}$, Cmax and Tmax PK parameters of KAF156 and lumefantrine will be calculated by part and treatment group using normal or log-normal approximation as applicable. Non-compartmental PK analysis for patients with sparse data will also be conducted and feasible PK parameters will be reported. A descriptive statistics for concentration at nominal time point of 168 hours post dose or any other time point identified

critical for the cure may also be reported for all the patients. These PK parameters/ PK concentration may also be explored graphically.

All the PK data may be pooled for population pharmacokinetics analysis across studies and the broad principles outlined in the Food and Drug Administration (FDA) Guidance for Industry: Population Pharmacokinetics would be followed.

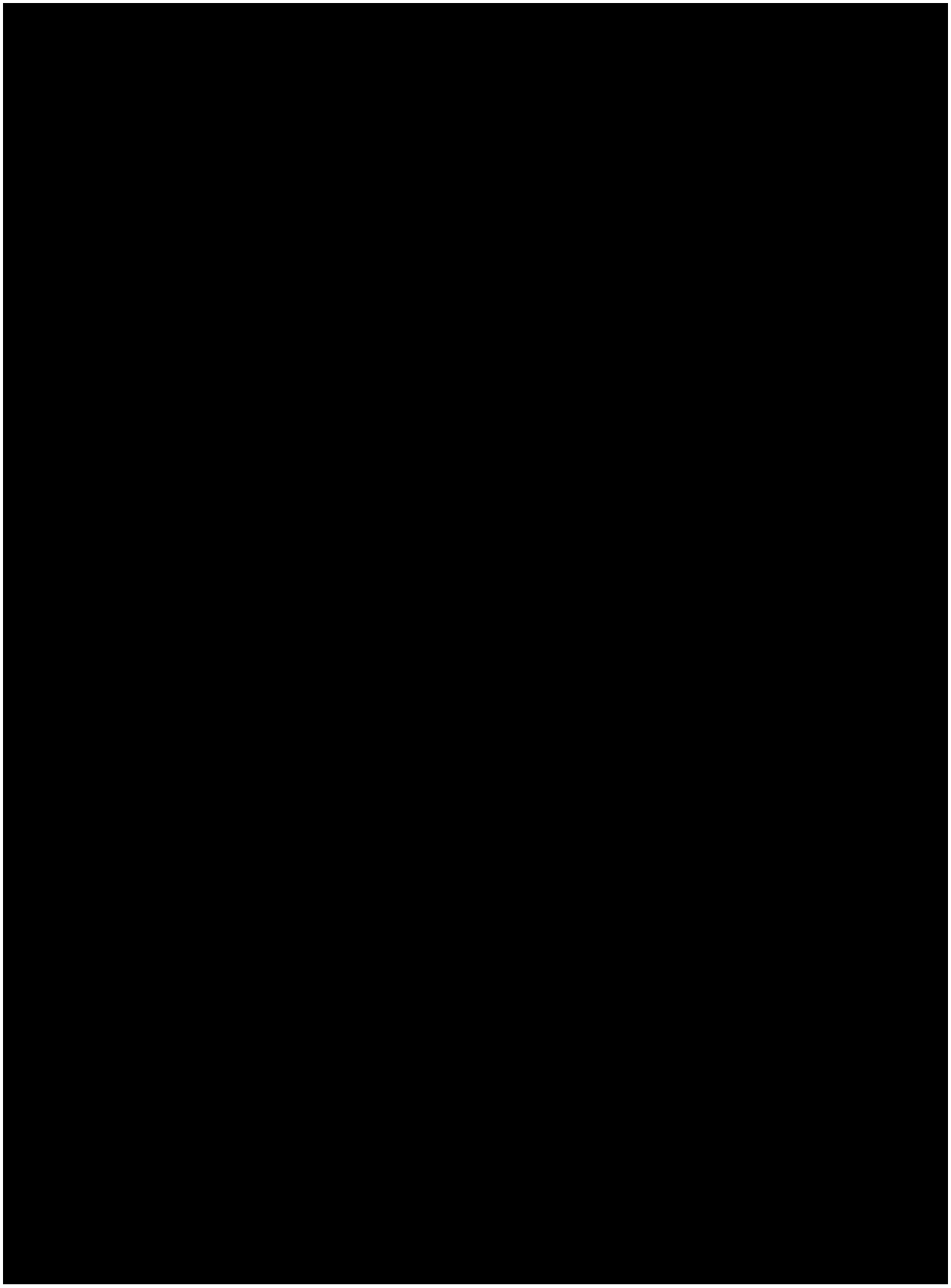
[redacted]

2.11 Patient-reported outcomes

NA

[redacted]

[redacted]



2.14 Overview of analysis methods

An overview of statistical analyses and methods applied to efficacy variables and safety variables are given in Table 2-6 and Table 2-7.

Table 2-6 Overview of analysis methods for baseline data and efficacy variables

Variable(s)	Summary statistics for binary/ categorical data	Listings	Between treatment comparison	95% CI for each treatment group	Summary statistics for continuous data	Time-to-event data analysis K-M	Graphs	Pooled analysis (Part A +Part B)
Medical history	X	X	-	-	-	-	-	-
Demogrpahics and baseline characteristics	X	X	-	-	-	-	-	X
Patient disposition	X	X	-	-	-	-	-	X
Prior medication use	X	X	-	-	-	-	-	-
Concomitant medication use	X	X	-	-	-	-	-	-
Concomitant rescue medication use	X	X	-	-	-	-	-	-
Concomitant Non-study drug antimalarial medication use	X	X	-	-	-	-	-	-
Prior other prohibited medications use	X	X	-	-	-	-	-	-
Concomitant other prohibited medications use	X	X	-	-	-	-	-	-
PCR-corrected Response at Day 29	X	X	X	X	-	X	X	X
PCR-corrected response at Days 15 and 43	X	X	X	X	-	X	X	X
Uncorrected ACPR response at Days 15, 29, and 43	X	X	X	X	-	X	X	X
Proportion of patients with parasitemia at 12, 24, and 48 hours after treatment;	X	X		X	-	-	-	-
Time to parasite clearance (PCT)		X	X	-	-	X	X	X
Time to fever clearance (FCT)		X	X	-	-	X	X	X
Proportion of patients with early treatment failure	X	X	-	X	-	-	-	-

Variable(s)	Summary statistics for binary/ categorical data	Listings	Between treatment comparison	95% CI for each treatment group	Summary statistics for continuous data	Time-to-event data analysis K-M	Graphs	Pooled analysis (Part A +Part B)
Proportion of patients with late clinical failure	X	X	-	X	-	-	-	-
Proportion of patients with late parasitological failure (LPF)	X	X	-	X	-	-	-	-
Incidence rate of recrudescence at Days 15, 29 and 43	X	-	-	-	-	X	X	-
Incidence rate of reinfection at Days 15, 29 and 43	X	-	-	-	-	X	X	-
[redacted]								
Proportion of infected mosquitoes	-	-	-	-	X	-	-	-

Table 2-7 Overview of analysis methods for safety/PK variables

Variable(s)	Summary statistics for binary/ categorical data	Listings	Summary statistics for continuous data	Graphs	Pooled analysis (Part A +Part B)
AE	X	X	-	-	X
SAE	X	X	-	-	X
severe malaria	X	X	-	-	
Adverse events of special interest	X	X	-	-	X
Hematology change from baseline	-	X	X	X	X
Biochemistry change from baseline	-	X	X	X	X
Liver abnormalities	X	X	-	-	X
ECG abnormality	X	X	-	-	X
Vital signs change from baseline	-	X	X	-	X
Notable vital signs abnormality	X	X	-	-	X
Drug concentrations	-	X	X	-	-

2.15 Interim analysis

PK Run-in Part: For the patients in the PK Run-in KAF156 200 mg/LUM-SDF 960 mg cohort, PK analyses will be performed on the samples collected in the first 24 hours. AUC_{0-24}, for KAF156 and lumefantrine will be calculated and compared with the expected values when one drug was given alone. Dosing in Part A will subsequently proceed according to the algorithm specified in protocol, Table 3-1.

End of Part A: After the last patient has completed the last visit in Part A, the clinical database will be cleaned and locked.

An interim assessment will be performed to evaluate if any KAF156 and LUM-SDF combination is effective and safe and which KAF156 and LUM-SDF dose regimen(s) will be carried forward in Part B. Only the primary efficacy endpoint, selected secondary efficacy (uncorrected ACPR at Day 29, PCT, and FCT), PK, and safety endpoints (all adverse events, serious adverse events and laboratory results) will be analyzed by the study biostatistics team. Other efficacy and safety endpoints will be analyzed if deemed necessary.

The results will be communicated to relevant internal and external people who will contribute to the selection of effective and safe dose regimen.

DMC reports: At selected time points during the study, DMC reports will be provided by a CRO team not involved in the study conduct. The unblinded DMC reports will be reviewed by the DMC.

Additional ad-hoc safety review may be requested by DMC or Novartis if needed. Only the decision or information needed for planning/modifying the trial (such as continuation of study, dosing information for new patients, etc.) will be communicated to the blind clinical trial team involved in trial conduct. No further dissemination of DMC reports should occur.

Below is the outline of the data required for the DMC review.

Table 2-8 Specification of data outputs for DMC data review

Output	Analysis set	Periodic safety review	End of Part A interim analysis
Baseline			
Patient disposition	Randomized	Yes	Yes
Recruitment by country and center	Randomized	Yes	Yes
Demographic characteristics	Randomized	Yes	Yes
Background disease characteristics	Randomized	Yes	Yes
Safety			
Concomitant medications/significant non-drug therapies	Safety	Yes	Yes
All adverse events and Serious adverse events (including narratives)	Safety	Yes	Yes
General, liver, and renal specific safety laboratories (categorical analysis)	Safety	Yes	Yes
ECG (Categorical analysis)	Safety	Yes	Yes
Vital signs (clinical notable)	Safety	Yes	Yes
Early treatment failures	Safety	Yes	Yes
Efficacy			
PCR corrected and uncorrected cure rates at Day 29	Per-Protocol	No	Yes
PCR corrected and uncorrected cure rates at Day 43	Per-Protocol	No	Yes
PCT, FCT	FAS	No	Yes
KAF156 and LUM-SDF PK	PK	No	Yes

3 Sample size calculation

Sample size for PK run-in cohort

The objective of this part is to assess the effect of LUM-SDF in the exposure of KAF156 in patients and to see if the current planned dosages for KAF156 in Part A should be modified or how to modify KAF156 dosages in Part A. Therefore, the sample size is calculated/justified based on the precision of estimating KAF156 exposure. The key variables for exposure of KAF156 are $AUC_{0\text{-}24h}$ and Cmax. It's well known that the distribution of AUC or Cmax is best described by log normal distribution. The half width of 2-sided 90% confidence interval for the log $AUC_{0\text{-}24h}$ or log Cmax is the target for sample size calculation. The relevant historical data for sample size calculation are the standard deviations of log $AUC_{0\text{-}24h}$ and log Cmax, which are usually invariant to the dosage.

In POC Study X2202, the standard deviation for log $AUC_{0\text{-}24h}$ was 0.26 and 0.27 for 10 *P. falciparum* patients treated with KAF156 400 mg QD 3 days and for 18 *P. falciparum* patients

treated with KAF156 800 mg QD, respectively. The corresponding standard deviation for log Cmax was 0.205 and 0.215, respectively.

Table 3-1 Sample size and width of 2-sided 90% CI for log AUC_{0_24h} and log Cmax

Standard deviation (in log)	n	Target half width of 2-sided 90% CI	Probability that observed half width of 2-sided 90% CI is ≤ the target
0.21	9	0.153	0.80
0.21	12	0.126	0.80
0.21	10	0.150	0.80
0.26	9	0.200	0.80
0.26	12	0.155	0.80
0.26	13	0.150	0.80
0.26	12	0.150	0.70
0.27	9	0.200	0.80
0.27	12	0.161	0.80
0.27	14	0.150	0.80
0.27	12	0.150	0.68

Based on nQuery Table MOC1-1.nqa.

A sample size of 12 patients will provide 80% probability that the observed half width of 2-sided 90% CI for log AUC_{0_24h} is ≤0.155. A sample size of 12 patients will provide 80% probability that the observed half width of 2-sided 90% CI for log Cmax is ≤0.126.

Part A

The primary efficacy objective for this part is to determine the effective dose(s) of KAF156 combined with LUM-SDF for treatment of uncomplicated malaria caused by *P. falciparum* in adolescents and adults. The primary efficacy endpoint is the PCR corrected ACPR rate at Day 29 based on the per-protocol analysis set. The statistical null hypothesis is that the ACPR rate is at most 80% with the alternative hypothesis that the ACPR rate is greater than 80%. The statistical hypothesis will be evaluated using the lower limit of 2-sided 95% exact confidence interval for the ACPR rate. If the lower limit of 2-sided 95% exact confidence interval for ACPR rate is greater than 80%, the null hypothesis will be rejected.

Rejecting the null hypothesis of at most 80% ACPR rate is equivalent to showing non-inferiority to a ACPR rate of 90% with a non-inferiority margin of 10%. 90% is specified in the 2015 WHO guidelines as the ACPR rate cutoff-threshold for a change in treatment policy and a 10% non-inferiority margin is considered as acceptable for early-phase trials (Held, et al 2015).

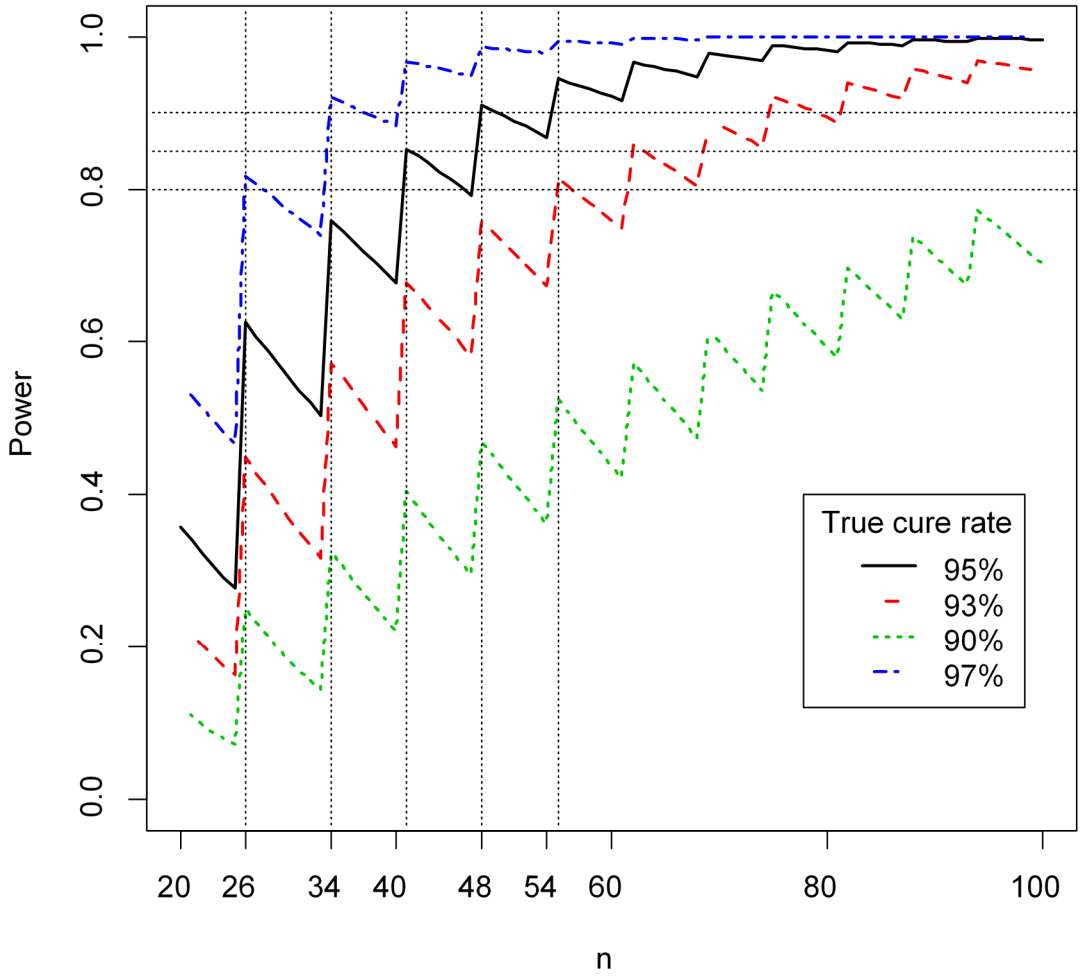
Figure 3-1 plots the power to reject the null hypothesis of at most 80% ACPR rate versus sample size by various true ACPR rates (90%, 93%, 95%, and 97%). Due to the discrete property of binomial distribution, the power increases zigzag with jump at 26, 34, 41, 48, 55, 62, and 68 as the sample size increases. When the sample size is at least 41, the power to reject the null hypothesis of at most 80% ACPR rate is about 80% or higher if the true rate is 95% or higher.

Since there is a 2:1 ratio among different treatment groups, the sample size in the per-protocol analysis set will be targeted to be 42 patients for each KAF156/LUM-SDF dose combination

group and 21 patients for the comparator (Coartem®) cohort. This sample size will provide at least 80% power to reject the null hypothesis of at most 80% ACPR rate for the 6 KAF156 dose combinations if the true ACPR rate is at least 95%. If there are multiple KAF156/LUM-SDF dose combinations that are all effective, the less frequent or/and highest KAF156/LUM-SDF dose combination(s) that is tolerable may be selected for further evaluation. The PK/PD modeling may be used to assist the selection of appropriate dose combination(s) for Part B.

Assuming that about 16% of patients will be excluded from the per-protocol analysis set, about 325 patients (50:50:50:50:50:50:25) will be randomized to yield 42 patients for each KAF156/LUM-SDF dose combinations and 21 patients for the Coartem® cohort in the per-protocol analysis set.

Figure 3-1 Power to reject adequate clinical and parasitological response (ACPR) rate less than or equal to 80% based on 2-sided 95% CI by true rate



Part B

The primary objective for this part is to assess the safety and efficacy of the selected KAF156/LUM-SDF dose combination(s) adjusted for body weight in pediatric patients. For the primary efficacy variable of PCR corrected ACPR rate at Day 29 based on the per-protocol analysis set, a sample size of at least 41 patients will provide about 80% power or higher to reject the null hypothesis of at most 80% ACPR rate based on the lower limit of 2-sided 95% exact confidence interval if the true rate is 95% or higher for a KAF156/LUM-SDF dose combination. Since there is a 2:1 ratio between a KAF156/LUM-SDF dose combination group and the Coartem® cohort, the sample size in the per-protocol analysis set will be targeted to be 42 patients for each KAF156/LUM-SDF dose combination group and 21 patients for the Coartem® cohort. Assuming that 16% of patients will be excluded from the per-protocol analysis set, about 50 pediatric patients will be randomized to yield 42 patients for each KAF156 and LUM-SDF combination and 21 patients for the Coartem® cohort in the per-protocol analysis set.

4 Change to protocol specified analyses

None

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The study drug administatrtion date should be complete since it's taken in the hospital. In case missing or partial, the visit date will be used as the study drug administatrtion date.

5.1.2 AE date imputation

The following missing dates will not be imputed

- Missing AE start dates
- AE start dates missing the year
- Partial/missing AE end dates

For other type of partial missing start dates, rules specified in Tables 5-1 to 5-3 will be used

Table 5-1 AE/Treatment Date Abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

Table 5-2 describes the possible combinations and their associated imputations. The upper text indicates the imputation (NC, A, B, C etc.) and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-2 Imputation algorithm

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	NC Uncertain	NC Uncertain	NC Uncertain	NC Uncertain
AEY < TRTY	(D) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD
AEY = TRTY	(B) Uncertain	(C) Before TRTSTD	(B) Uncertain	(A) After TRTSTD
AEY > TRTY	(E) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD

The legend to the above table is shown in Table 5-3.

Table 5-3 Imputation algorithm legends

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation calculation	
NC / Blank	No convention/imputation
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

Few examples are shown in Table 5-4.

Table 5-4 Example scenarios

Partial AE start date	Treatment start date	Relationship with TRTSTD	Imputation Calculation	Imputed Date
12mmyyyy	20OCT2001	Uncertain	NC	<blank>
ddmmm2000	20OCT2001	Before	(D)	01JUL2000
ddmmm2002	20OCT2001	After	(E)	01JAN2002
ddmmm2001	20OCT2001	Uncertain	(B)	21OCT2001
ddSEP2001	20OCT2001	Before	(C)	15SEP2001
ddOCT2001	20OCT2001	Uncertain	(B)	21OCT2001
ddNOV2001	20OCT2001	After	(A)	01NOV2001

5.1.3 Concomitant medication/non-drug therapy date imputation

Missing concomitant dates will be imputed similar as to AE dates.

5.1.3.1

5.1.3.2 Other imputations

NA

5.1.4 Visit windows

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the Day *4* visit of a patient is delayed and occurs on Day 7, say, it will be re-aligned to visit window Day *8*. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a patient may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

- Of note, patients are allowed to have gaps in visits. All data collected will be displayed in listings.
- Lower limit and upper limit of the Day 29 visit is set to be Day 25 and Day 33 respectively, according to the protocol visit schedule since this is the primary analysis timepoint.
- The following rules are used to determine the window for other visits post baseline:
  - "Lower limit" = "upper limit of prior applicable visit" + 1.
  - "Upper limit" = "target day of current visit" + integer part of ("target day of next applicable visit" – "target day of current visit")/2 with the exception of Day 29
  - No upper limit for Day 43 visit
  - Upper limit of Day 15 is one day before the lower limit of Day 29

For assesments that are scheduled to be performed only once on a day, Table 5-5 describes the analysis windows mapping to visits (not just scheduled visits) based on study days alone. For the assessments that may be performed on multiple timepoints on a day, Table 5-6 describes the analysis windows mapping to visits based on study day and time. Repeat and/or unscheduled visits (which will be numbered in the database according to new NCDS standards) will be mapped for analysis purposes in the same way. If there are multiple measurements within an analysis window, the conventions defined in Table 5-7 will be used to determine the appropriate measurement to be selected for analysis.

The mapped visits will be used in the by visit analyses. However, the listings will show the collected data regardless of used in the by visit analyses.

Table 5-5 Analysis visit windows based on study days alone

Analysis Visit	Target Day	Analysis window for assessment group		
		Vital signs/ Chemistry/ Hematology/ Urinalysis	Thyroid function	Membrane feed assay/ pregnancy
Baseline	1	Up to Day 1	Up to Day 1	up to day 1
Day 2	2	Day 2	NA	NA
Day 3	3	Day 3	NA	NA
Day 4	4	Day 4	NA	NA
Day 5	5	Days 5 - 6	NA	NA
Day 8	8	Day 7 - 11	NA	NA
Day 15	15	Day 12 - 24	Day 2 - 29	NA
Day 29	29	Day 25 - 33	NA	NA
Day 43/End of study	43	Day 34 and above	Day 30 and above	Day 2 and above

Table 5-6 Analysis visit windows based on study day and time

Analysis Visit	Analysis timepoint	Analysis window for assessment group			
		Temperature	Parasite count	ECG	Rich and Sparse PK
Baseline	0 hrs	up to 0 hrs	up to 0 hrs	up to 0 hrs	up to 0 hrs
Day 1	1 hrs	NA	NA	NA	> 0 - 2 hrs
	3 hrs	NA	NA	>0 - 4 hrs	> 2 - 4 hrs
	6 hrs	>0 - 9 hrs	>0 - 9 hrs	>4 - 12 hrs	>4 - 9 hrs
	8 hrs	NA	NA	NA	NA
	12 hrs	>9 - 15 hrs	>9 - 18 hrs	NA	>9 - 15 hrs
	18 hrs	>15 - 21 hrs	NA	>12 - 21 hrs	>15 - 21 hrs
Day 2	24 hrs	>21 - 27 hrs	>18 hrs to 30 hrs	>21 - 25 hrs	>21 - 25 hrs
	27 hrs	NA	NA	>25 – 28 hrs	>25 - 28 hrs
	30 hrs	>27 - 33 hrs	NA	>28 - 39 hrs	>28 - 33 hrs
	36 hrs	>33 - 42 hrs	>30 - 42 hrs	NA	>33 - 42 hrs
Day 3	48 hrs	>42 - 60 hrs	>42 - 60 hrs	>39 – 49 hrs	>42 - 49 hrs
	51 hrs	NA	NA	>49 – 52 hrs	>49 - 52 hrs
	54 hrs	NA	NA	>52 – 61 hrs	>52 - 63 hrs
	60 hrs	NA	NA	NA	NA
	68 hrs	NA	NA	>61 – 70 hrs	NA
Day 4	72 hrs	>60 hrs to Day 4	>60 hrs to Day 4	>70 hrs to Day 5	>63hrs to Day 4
Day 5	NA	Day 5 - 6	Day 5 - 6	NA	Day 5 - 6
Day 8	NA	Day 7 – 11	Day 7 – 11	Day 6 -25	Day 7 – 11
Day 15	NA	Day 12 - 24	Day 12 - 24	NA	Day 12 and above
Day 29	NA	Day 25 - 33	Day 25 - 33	NA	NA
Day 43/End of study	NA	Day 34 and above	Day 34 and above	Day 26 and above	NA

Table 5-7 Rules for flagging variables

Timing of measurement	Type of data	Rule
Baseline	All data	The last measurement made prior to administration of the first dose of study treatment – note this may include measurements taken on the day of randomization. If a patient did not receive any dose of study treatment then the randomization date will be used.
Post-baseline efficacy	parasite count and temperature	The measurement closest to the target day/time will be used. In the event two measurements are taken equally apart, the first one will be used.()
Post-baseline safety	Summary visit information (e.g. lab, ECG, etc.)	The measurement closest to the target day/time will be used. In the event two measurements are taken equally apart, the first one will be used.
Post-baseline safety	Notable abnormalities (e.g. lab, ECG, VS)	The most extreme measurement in the window will be used. Note this means a patient can have a notably high and notably low measurement within a window

5.2 Non-study drug antimalarials

Table 5-8 Table of non-study drug antimalarials with respective ATC codes

Non-study drug antimalarials	ATC code	ATC name
Aminoquinolines	P01BA01	Chloroquine
	P01BA02	Hydroxychloroquine
	P01BA03	Primaquine
	P01BA06	Amodiaquine
Biguanides	P01BB01	Proguanil
	P01BB02	Cycloguanil embonate
	P01BB51	Proguanil, combinations
Methanolquinoline	P01BC01	Quinine
	P01BC02	Mefloquine
Diaminopyridimidines	P01BD01	Pyrimethamine
	P01BD51	Pyrimethamine, combinations
Artemisinin and derivatives, plain	P01BE01	Artemisinin
	P01BE02	Artemether
	P01BE03	Artesunate
	P01BE04	Artemotil
	P01BE05	Artenimol
Artemisinin and derivatives, combinations	P01BF02	Artesunate and mefloquine
	P01BF03	Artesunate and amodiaquine
	P01BF04	Artesunate, sulphamethopyrazine and pyrimethamine
	P01BF05	Artenimol and piperaquine
	P01BF06	Artesunate and pyronaridine
Other Antimalarials	P01BX01	Halofantrine
	P01BX02	Arterolane and Piperaquine
Coartem*	P01BF01	Artemether and lumefantrine

*in case used by patients receiving KAF156/Lum-SDF

5.3 Prohibited medications

Table 5-9 Prohibited medication with respective ATC codes

Prohibited medication	ATC code	ATC name
ANALGESICS	N02CC06	Eletriptan
	N02CA01	Dihydroergotamine
	N02CA02	Ergotamine
	N02AB03	Fentanyl
ANESTHETICS	N01AH02	Alfentanil
	N01AH02	Alfentanil
	N01AH01	Fentanyl
ANTIARRHYTHMICS	C01BD07	Dronedarone
	C01BC04	Flecainide
	C01BA01	Quinidine
	N06AA01	Desipramine
	N06AX16	Venlafaxine
	N06AX12	Bupropion
	N06AA02	Imipramine
	N06AA09	Amitriptyline
	N06AA04	Clomipramine
ANTIEMETICS AND ANTINAUSEANTS	A04AD12	Aprepitant
ANTIEPILEPTICS	N03AB02	Phenytoin
ANTIHISTAMINES FOR SYSTEMIC USE	R06AX11	Astemizole
	R06AX12	Terfenadine
ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS	M01AH01	Celecoxib
ANTINEOPLASTIC AGENTS	L01CD01	Paclitaxel
ANTIPSYCHOTICS	N05AB03	Perphenazine
	N05AE05	Lurasidone
	N05AH04	Quetiapine
	N05AC02	Thioridazine
	N05AG02	Pimozide
	N05	Neuroleptics
ANTITHROMBOTIC AGENTS	B01AA03	Warfarin
ANXIOLYTICS	N05BE01	Buspirone
BETA BLOCKING AGENTS	C07AB02	Metoprolol
	C07AB12	Nebivolol
	C07AB02	Metoprolol
CALCIUM CHANNEL BLOCKERS	C08CA02	Felodipine
	C08CA07	Nisoldipine
CORTICOSTEROIDES	R01AD08	Fluticasone
COUGH SUPPRESSANTS	R05DA09	Dextromethorphan
DIRECT ACTING ANTIVIRALS	J05AE10	Darunavir
	J05AE02	Indinavir
	J05AR10	Lopinavir
	J05AX09	Maraviroc

	J05AE01	Saquinavir
	J05AE09	Tipranavir
	J05AG03	Efavirenz
DIURETICS	C03DA04	Eplerenone
	C03XA01	Tolvaptan
DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	A03FA02	Cisapride
HYPNOTICS AND SEDATIVES	N05CD08	Midazolam
	N05CD05	Triazolam
IMMUNOSUPPRESSANTS	L04AA18	Everolimus
	L04AA10	Sirolimus
	L04AD01	Ciclosporin
	L04AA10	Sirolimus
	L04AD02	Tacrolimus
INTESTINAL ANTIINFLAMMATORY AGENTS	A07EA06	Budesonide
LIPID MODIFYING AGENTS	C10AA02	Lovastatin
	C10AA01	Simvastatin
	C10AA03	Pravastatin
OTHER ANTIHYPERTENSIVES	C02KX01	Bosentan
OTHER ANTINEOPLASTIC AGENTS	L01XE06	Dasatinib
	L01XE10	Everolimus
	L01XX33	Celecoxib
OTHER BLOOD GLUCOSE LOWERING DRUGS	A10BX02	Repaglinide
OTHER DERMATOLOGICAL PREPARATIONS	D11AH01	Tacrolimus
OTHER DIURETICS	C03XA02	Conivaptan
OTHER OPHTALMOLOGICALS	S01XA18	Ciclosporin
	S01XA23	Sirolimus
PSYCHOSTIMULANTS	N06BA09	Atomoxetine
UROLOGICALS	G04BD07	Tolterodine
	G04BD10	Darifenacin
	G04BE03	Sildenafil
	G04BE09	Vardenafil

5.4 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology. AEs are assessed by investigators according to the most current Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

5.5 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (specify version used in the

RAP). The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.0 at the time of analysis will be used.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

5.6 Statistical models

5.6.1 Primary analysis

The primary analysis of ACPR at Day 29 is detailed in Section 2.

SAS procedure FREQ with EXACT statement for one-way tables will be used to estimate the proportion of responders (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – *two-sided alpha level*)) two-sided Clopper- Pearson CI [Clopper and Pearson 1934].

5.6.2 Key secondary analysis

NA

5.6.3 Other secondary [redacted] analysis

Kaplan-Meier estimates

An estimate of the survival function in each treatment group will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survivor function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

Difference in responder rates stratified by part using Mantel-Hanszel estimate

For PCR corrected and uncorrected ACPR rates, the treatment differences versus control will be evaluated using a Mantel-Haenszel estimate of the treatment difference in responder rates stratified by Part using PROC FREQ with RISKDIFF(COMMON) option in the TABLES statement).

Difference in responder rates using the Wilson uncorrected method

For PCR corrected and uncorrected ACPR rates, the treatment differences versus control will be evaluated using a Wilson uncorrected method using PROC FREQ with RISKDIFF (CL= WILSON) option in the TABLES statement.

5.7 Rule of exclusion criteria of analysis sets

Table 5-10 Protocol deviations and non-PD criteria leading to exclusion from analysis sets

Analysis Set	PD (Description and ID) that causes Patients to be excluded	Non-PD criteria that cause Patients to be excluded
Randomized	• Informed Consent for study participation or parental consent not obtained and patient entered trial (INCL01) •	• Not randomized (Parts A and B) • Misrandomized if identified from IRT (Parts A and B) • Not treated with study medication (PK run-in part)
FAS	NA	• Not in Randomized set; • Baseline parasitemia count is 0 or missing • No study drug taken
PPS	• Parasite specie is other than Plasmodium falciparum OR mixed infection (INCL04) • Baseline plasmodium falciparum parasite count <1000/uL or >=150000/uL at screening visit (INCL05) • No fever within the past 24 hours at baseline (INCL07) • Prohibited non-antimalarial medications that may have effect on efficacy (PROH01b) if received before the Day 29 visit without being treatment failures	• Not in FAS; • <80% of randomized study medication taken • Received non-study concomitant antimalarial drugs prior to Day 29 without experiencing treatment failure • Not classified as non-responder before Day 8, no positive blood smear parasite on Day 8 onwards, and blood smear parasite result is missing at Day 29 and later (early discontinued) • Not classified as non-responder before Day 8, have at least one positive blood smear parasite result between Day 8 and Day 29 which cannot be determined as recrudescent or new infection based on PCR genotyping and have parasites cleared prior to the positive blood smear parasite;

		• Not classified as non-responder before Day 8, no positive blood smear parasite before Day 29, blood smear parasite result is missing at Day 29, and blood smear parasite result is not negative at Day 43 (intermediate missing)
SAF	NA	• Not in Randomized set; • No study drug taken
PK	Patients who received concomitant prohibited medication which found to be change in the exposure that impacts interaction in PK parameters; will be reviewed case by case for exclusion from the PK set	• Not in SAF • No evaluable pharmacokinetic parameter data • Compliance is <80% of randomized study medication taken

6 Reference

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SAS/STAT ® 9.1 User's Guide. Cary, NC: SAS Institute Inc.